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# 1,3-Oxazine Derivatives

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# I. Introduction

The continuous interest in the chemistry of 1,3-oxazines, manifested by numerous papers and patents, may be attributed to further evidence of the biological activity<sup>1</sup> of tetrahydro-1,3-oxazines, to the synthetic utility of 5,6-dihydro-4*H*-1,3-oxazines (due mainly to Meyers<sup>2.3</sup> and Schmidt<sup>4</sup>), and to the discovery that some antibiotics contain the 1,3oxazine ring, e.g., Oxazinomycin (1)<sup>5</sup> (see also Section V,A,1).

It was also of interest that the antibiotic Indolmycin (from *Strepto-myces albus*) on acid degradation furnished an indolyl derivative of 1,3-oxazine-2,4-dione (2).<sup>6</sup> The continuation of the work of Kjaer *et al.*<sup>1,7</sup> led to the finding that enzymatic hydrolysis of some naturally



occurring glucosinates produced isothiocyanates that readily undergo spontaneous or base-induced cyclization to tetrahydro-1,3-oxazine-2thiones.

- <sup>1</sup> Z. Eckstein and T. Urbański, Ad. Heterocycl. Chem. 2, 311 (1963).
- <sup>2</sup> A. I. Meyers, "Heterocyclics in Organic Synthesis." Wiley, New York, 1974.
- <sup>3</sup> E. W. Collington, Chem. Ind. (London), 987 (1973).
- <sup>4</sup> R. R. Schmidt, Synthesis, 333 (1972).
- <sup>5</sup> T. Haneishi, T. Okazaki, T. Hata, C. Tamuta, M. Namura, A. Naito, I. Seki, and M. Arai, J. Antibiot. 24, 797 (1971).
- <sup>6</sup> M. Schach v. Wittenau and H. Els, J. Am. Chem. Soc. 83, 4678 (1961).
- <sup>7</sup> A. Kjaer and A. Schuster, Acta Chem. Scand. 24, 1631 (1970).

The present review deals with the chemistry of 1,3-oxazine derivatives from 1962 until 1975. The literature up to 1962 was covered by our previous review.<sup>1</sup> Some papers published before 1962 but omitted therein are also quoted. We apologize for any work overlooked in the present review.

# II. Methods of Preparation of 1,3-Oxazine Derivatives

Schmidt<sup>4</sup> systematically classified methods of synthesis of some unsaturated 1,3-oxazines. We use the same system for all 1,3-oxazines.

#### A. TETRAHYDRO-1,3-OXAZINES

# 1. Methods of Cyclization

The main ring syntheses of tetrahydro-1,3-oxazine derivatives are summarized by diagrams a to d (Fig. 1). Two additional methods comprise the cyclization of six-membered chains, and the hydrogenation or



FIG. 1. Diagram of ring closure to form tetrahydro-1,3-oxazines.

other additions to unsaturated 1,3-oxazines.

a. *Ring Closure* **a**. The ring closure of 3-aminopropanol derivatives with aldehydes and ketones has become a conventional method of forming tetrahydro-1,3-oxazines of general formula **3**.



Many papers and patents cover the formation of tetrahydro-1,3oxazines from 3-aminopropanols and aldehydes or ketones.<sup>7-34</sup> Aliphatic, aromatic, or heterocyclic aldehydes introduced the corresponding

<sup>10</sup> W. J. Croxall, (Miles Labs. Inc.) French Patent 1,221,977 [Chem. Zentr., 6209 (1962)].

<sup>&</sup>lt;sup>8</sup> A. L. Morrison and H. Rinderknecht, J. Chem. Soc., 1510 (1950).

<sup>&</sup>lt;sup>9</sup> J. S. Eden, U.S. Patent 2,911,294 [CA 54, 3842 (1960)].

substituents in position 2. The reaction is usually carried out in an organic solvent in the presence of a catalytic quantity of a mineral acid, and water formed in the course of the reaction is removed by azeotropic distillation.

3-Aminopropanol derivatives also cyclized with reactive compounds containing a heteroatom to introduce the latter into position 2 of the ring. Thus, from 2-alkyl-3-amino-5-nitropropanol and bis(dialkylamino)-dimethylsilane, 5-nitrotetrahydro-2,1,3-silaoxazine (4)<sup>35</sup> was formed [Eq. (1)].



- <sup>11</sup> Miles Labs., British Patent 889303 [CA 58, 1347 (1963)].
- <sup>12</sup> A. S. Orahovats, Monatsh. Chem. 96, 1446 (1965).
- <sup>13</sup> G. Fodor, J. Stefanowsky, and B. I. Kurtev, Chem. Ber. 98, 705 (1965).
- <sup>14</sup> G. Fodor, J. Stefanowsky, and B. I. Kurtev, Chem. Ber. 100, 3069 (1967).
- <sup>16</sup> Z. Horii, T. Inoi, S-W. Kim, Y. Tamura, A. Suzuki, and H. Matsumoto, *Chem. Pharm. Bull.* 13, 1151 (1965).
- <sup>16</sup> L. Turbanti, G. Cerbai, C. Bramanti, P. Bianchi, and N. Tellini, *Chem. Therap.* 2, 354 (1967) [*CA* 69, 36048 (1968)].
- <sup>17</sup> J.-M. Lehn, P. Linscheid, and F. G. Ridell, Bull. Soc. Chim. Fr., 1172 (1968).
- <sup>18</sup> F. G. Ridell and J. M. Lehn, J. Chem. Soc. B, 1224 (1968).
- <sup>19</sup> Z. Horii and T. Inoi, Japanese Patent 18,465 [CA 69, 10449 (1968)].
- <sup>20</sup> Eastman Kodak Co., French Patent 1,504,886 [CA 70, 57863 (1969)].
- <sup>21</sup> Krewel-Leuffen G.m.b.H., British Patent 1,059,666 [Chem. Zentr. 14, 1404 (1969)].
- <sup>22</sup> Dynamit Nobel A. G., British Patent 1,152,560 [CA 71, 49951 (1969)].
- <sup>23</sup> K. Thewalt and G. Reuckhoff (Dynamit Nobel A.G.), French Patent 1,560,931 [CA 72, 66929 (1970)].
- <sup>24</sup> L. D. Taylor, P. McLaughlin, and M. Bach, Org. Prep. Proc. 2, 33 (1970).
- <sup>25</sup> H. Booth and R. U. Lemieux, Can. J. Chem. 49, 777 (1971).
- <sup>26</sup> R. A. Y. Jones, A. R. Katritzky, and D. L. Trepanier, J. Chem. Soc. B, 1300 (1971).
- <sup>27</sup> K. Eites, K. F. Hebenbrock, and M. Plempel, Ger. Offen. 2,035,797 [CA 76, 127001 (1972)].
- <sup>28</sup> Farbenfabriken Bayer A.G., French Patent 2,082,275 [CA 77, 101629 (1972)].
- <sup>29</sup> O. P. Boiko, Yu. F. Malina, and B. V. Unkowskii, *Khim. Tehnol. Tr. Yubileinoi Konf.* p. 161 (1972) [CA 81, 49532 (1974)].
- <sup>30</sup> C. Fauran, C. Douzon, G. Huguet, G. Raynaud, and T. Bailly (Delalande S.A.), Ger. Offen. 2,221,408 [CA 78, 58435 (1973)].
- <sup>31</sup> C. Fauran, C. Douzon, G. Raynaud, and N. Dorme, French Demande 2,131,888 [CA 78, 124603 (1973)].
- <sup>32</sup> Yu. Yu. Samitov, B. V. Unkovskii, I. P. Boiko, O. I. Zhuk, and Yu. F. Malina, Zh. Org. Khim. 9, 193 (1973).
- <sup>33</sup> I. P. Boiko, Yu. E. Kazantsev, Yu. F. Malina, O. I. Zhuk, Yu. Yu. Samitov, and B. V. Unkovskii, *Khim. Geterotsikl. Soedin.*, 467 (1973).

Sec. II.A.1]

In a similar way, dinitro-4-azaheptane-1,7-diols reacted with phenylboronic acid to yield isomeric cis- and trans-substituted diptychs with condensed 5-nitrotetrahydro-2,1,3-boraoxazine rings (5)<sup>36,37</sup> [Eq. (2)].



b. Ring Closure b. This method has been particularly successful for preparation of 5-nitro-tetrahydro-1,3-oxazines (6), by reacting 2-nitro-propane-1,3-diol with primary amines or ammonia and formalde-hyde.<sup>1.37-58</sup> This work has been summarized by Urbański.<sup>37</sup>



- <sup>34</sup> A. Rassat and P. Rey, *Tetrahedron* **30**, 3315 (1974); French Demande 2,219,146 [*CA* **82**, 156335 (1975)].
- <sup>35</sup> M. Szretter-Szmid and T. Urbański, Tetrahedron Lett., 2131 (1967).
- <sup>36</sup> W. Daniewski and T. Urbański, Tetrahedron, Suppl. 8 (Part II), 663 (1966).
- <sup>37</sup> T. Urbański, Synthesis, 613 (1974).
- <sup>38</sup> T. Urbański, D. Gürne, R. Koliński, H. Piotrowska, A. Jończyk, B. Serafin, M. Szretter-Szmid, and M. Witanowski, *Tetrahedron* 20, Suppl. 1, 195 (1964).
- <sup>39</sup> D. Gürne, L. Stefaniak, T. Urbański, and M. Witanowski, *Tetrahedron* 20, Suppl. 1, 211 (1964).
- <sup>40</sup> Z. Eckstein, P. Gluziński, and T. Urbański, Bull. Acad. Pol. Sci., Sér. Sci. Chim. 12, 623 (1964).
- <sup>41</sup> T. Urbański, D. Gürne, B. Orłowska, and M. Mordarski, Polish Patent 5,1812 (1966); British Patent 1,098,759 (1968); Swedish Patent 314,374 (1969).
- <sup>42</sup> T. Urbański, D. Gürne, I. Szczerek, and M. Mordarski, Polish Patent 54,007 (1967).
- <sup>43</sup> T. Urbański, D. Gürne, I. Szczerek, and M. Mordarski, Polish Patent 54,033 (1967).
- <sup>44</sup> T. Urbański, D. Gürne, I. Szczerek, and M. Mordarski, Polish Patent 54,035 (1967).
- <sup>45</sup> T. Urbański, D. Gürne, M. Mordarski, and B. Orłowska, German (East) Patent 50,833 (1967) [Chem. Zentr. 48, 1689 (1968)].
- <sup>46</sup> I. Szczerek and T. Urbański, *IUPAC Congr.*, 21st, 1967 Abstr. Papers N-36; Carbohydr. Res. 7, 357 (1968).
- 47 R. A. Koliński and T. Urbański, J. Chem. Soc. C, 1004 (1970).
- <sup>48</sup> A. Schmidt-Szałowska and T. Urbański, Bull. Acad. Pol. Sci., Ser. Sci. Chim. 18, 73 (1970).
- <sup>49</sup> H. Piotrowska, T. Urbański, and K. Wejroch-Matacz, Bull. Acad. Pol. Sci., Ser. Sci. Chim. 19, 359 (1971).

Using ammonia and formaldehyde as cyclizing agents, a fast reaction between them yields hexamethylenetetramine which gives an addition complex with 2-nitro-1,3-propanediol.<sup>53</sup> The components are here linked by hydrogen bonding.<sup>37</sup> The hexamethylenetetramine acts as a source of both formaldehyde and ammonia in a relatively slow reaction forming the tetrahydro-1,3-oxazine. There is a similarity with the mechanism described previously<sup>1</sup> for formation of 5-nitrotetrahydro-1,3-oxazines from 2-nitropropane-1,3-diol, formaldehyde, and primary amines through hexahydro-*s*-triazine intermediates.<sup>1,37</sup>

A compound formerly reported<sup>53</sup> with an eight-membered oxazocine ring proved to contain a 2-nitrotetrahydro-1,3-oxazine ring, being a diastereoisomer of 5-ethyl-5-nitro-3-(2-nitrobutyl)tetrahydro-1,3-oxazine.<sup>1,37,47</sup>

c. Ring Closure c. Mannich and Wieder<sup>54</sup> reacted isobutyraldehyde with formaldehyde and lower primary amines to give bicyclic compounds with two fused 1,3-oxazine rings (7). Johnson *et al.*<sup>55,56</sup> modified the reaction conditions and obtained a high yield of **8** by reacting isobutyral-dehyde with two molecules of formaldehyde and methylamine hydrochloride in an alcohol (ROH) in the presence of an acid.



d. *Ring Closure* d. This method, described previously,<sup>1</sup> consists in reacting olefins with formaldehyde and ammonium chloride. Recently, new compounds have been obtained.<sup>57</sup>

- <sup>50</sup> H. Piotrowska, T. Urbański, and K. Wejroch-Matacz, *Rocz. Chem.* 45, 1267, 2107 (1971).
- <sup>51</sup> H. Piotrowska, T. Urbański, and W. Sienicki, Rocz. Chem. 47, 193 (1973).
- <sup>52</sup> B. Kamieński, Tetrahedron 30, 2777 (1974).
- <sup>53</sup> E. L. Hirst, J. K. N. Jones, S. Minahan, F. W. Ochynski, A. T. Thomas, and T. Urbański, J. Chem. Soc., 924 (1947).
- <sup>54</sup> C. Mannich and H. Wieder, Chem. Ber. 65, 385 (1932).
- <sup>55</sup> P. Y. Johnson, R. B. Silver, and M. M. Davis, J. Org. Chem. 38, 3753 (1973).
- <sup>56</sup> P. Y. Johnson and R. B. Silver, J. Heterocycl. Chem. 10, 1029 (1975).
- <sup>57</sup> R. Quelat and A-M. Touzin, Ann. Chim. 1, 14, 107 (1966) [Chem. Zentr. 5, 1026 (1968)].
- 58 C. N. C. Drey and R. J. Ridge, J. Chem. Soc., Chem. Commun., 948 (1975).

# 2. Hydrogenation or Other Addition to the Double Bond of Unsaturated 1,3-Oxazines

Numerous tetrahydro-1,3-oxazines have been prepared by Meyers *et al.*<sup>2,3</sup> by reducing 5,6-dihydro-4*H*-1,3-oxazines with sodium borohydride. Catalytic hydrogenation of 5,6-dihydrooxazine-6-one failed to produce the tetrahydro derivative, as ring opening occurred.<sup>58</sup>

Additions to the double bond of dihydro-1,3-oxazines can also produce bicyclic derivatives of tetrahydro-1,3-oxazines, such as  $9^{59}$  [Eq. (3)]. Phthaloylglycyl chloride and dihydro-1,3-oxazines in the presence



of triethylamine give the bicyclic system 10.60



3. Quaternary Salts: N-Oxides and Nitroxides

A number of diastereoisomeric pairs of quaternary salts of 5-nitrotetrahydro-1,3-oxazine derivatives (**11a** and **11b**) were prepared by the action of *n*-alkyl bromides or iodides on 5-nitrotetrahydro-1,3-oxazines.<sup>61</sup> The products contained at the 3-equatorial position the *n*-alkyl derived from the alkyl bromide (or iodide), **6a** and **6b** [Eqs. (4) and (5)].



<sup>59</sup> R. Feinauer and W. Seeliger, Ann. Chem. 698, 174 (1966).

<sup>60</sup> J. C. Sheehan and M. Dadić, J. Heterocycl. Chem. 5, 779 (1968).

<sup>61</sup> D. Gürne, T. Urbański, M. Witanowski, B. Karniewska, and L. Stefaniak, *Tetrahe*dron 20, 1173 (1964).

(6)



A few perchlorates of quaternary tetrahydro-1,3-oxazines were also described.<sup>62</sup> Quaternary chlorides were prepared by direct cyclization of 3-dimethylaminopropanols with formaldehyde in hydrochloric acid.<sup>23</sup>

A number of N-oxides have been obtained by oxidizing 5-nitrotetrahydro-1,3-oxazines (6) with peracetic acid.<sup>63</sup> Rassat and Rey<sup>34</sup> prepared nitroxides (12) from tetrahydro-1,3-oxazines with an NH group and *m*chloroperbenzoic acid [Eq. (6)].



#### 4. Other N-Substituted Derivatives

N-Nitroso compounds (13) have been obtained by the action of nitrous acid<sup>64-66</sup> on tetrahydrooxazines (3;  $R^3 = H$ ). Compounds 13



- 62 B. C. Cossar and D. D. Reynolds, J. Heterocycl. Chem. 2, 430 (1965).
- <sup>63</sup> M. Mordarski, B. Chylińska, and T. Urbański, Arch. Immunol. Ther. Exp. 18, 679 (1970).
- <sup>64</sup> K. Eiter, British Patent 1,276,623 [CA 77, 88515 (1972)].
- 65 Farbenfabriken Bayer A.G., French Patent 2,082,275 [CA 77, 101629 (1972)].
- <sup>66</sup> K. Eiter, U.S. Patent 3,709,882 [CA 78, 72166 (1973)].

gave other N-substituted tetrahydro-1,3-oxazines,<sup>67</sup> e.g., 14 and 15, using phosgene, chloroformic esters, oxalyl chloride, and similar halogen compounds [Eq. (7)].

Urea derivatives (16) were obtained from 3-unsubstituted tetrahydro-1,3-oxazines and aryl isocyanates.<sup>68</sup>



Amides (3;  $R^3 = COR^4$ ) were prepared by acylating 3 ( $R^3 = H$ ) with acid chlorides<sup>69</sup> and also by cyclizing N-acylated 3-aminopropanols with aldehydes or ketones.<sup>70</sup>

N-Unsubstituted tetrahydro-1,3-oxazines (3;  $R^3 = H$ ) take part in Mannich-type reactions, e.g., 3-(2-nitrobutyl)-tetrahydro-1,3-oxazine<sup>1.37,47,53</sup> and the corresponding bicyclic compound<sup>1,37</sup> were thus obtained. A reaction with paraformaldehyde and acetophenone derivatives yields 3 ( $R^1 = H$ , alkyl, or Ph,  $R^2 = CH_2CH_2COPh$ ).<sup>71,72</sup>

# B. OXO AND THIONO DERIVATIVES OF TETRAHYDRO-1,3-OXAZINE

# 1. Methods of Cyclization

a. *Monooxo Compounds*. Cyclization to the oxo derivatives are similar to those for preparing tetrahydro-1,3-oxazines.

The most general method of preparing 2-carbonyl derivatives is to react 3-aminopropanols with difunctional derivatives of carbonic acid.<sup>1</sup> 2-Oxo derivatives of tetrahydro-1,3-oxazine being both  $\delta$ -lactams and  $\delta$ -lactones differ in their chemical properties from those of tetrahydro-1,3-oxazines.

- <sup>69</sup> L. Turbanti, G. Cerbai, G. Bramanti, P. Bianchini, and N. Tellini, Chim. Ther. 2, 354 (1967) [CA 69, 36048 (1968)].
- <sup>70</sup> K. Thewalt and G. Renckhoff, Fette, Seifen, Anstrichm. 70, 648 (1968) [CA 71, 30425 (1969)].
- <sup>71</sup> K. Kormendy, P. Sohár, and L. Torkos, Acta Chim. Acad. Sci. Hung. 40, 333 (1964) [Chem. Zentr. 22, 1089 (1968)].
- <sup>72</sup> F. Hoffmann-La Roche A.G., Austrian Patent 251,598 [Chem. Zentr. 42, 1442 (1969)].

<sup>&</sup>lt;sup>67</sup> K.-F. Hebenbrock and K. Eiter, Ann. Chem. 765, 78 (1972).

<sup>&</sup>lt;sup>60</sup> G. R. Haynes and D. D. Phillips, U.S. Patent 3,558,615 [CA 75, 63639 (1971)].

*N*-Alkyl derivatives of 3-aminopropanol react readily with phosgene<sup>73-75</sup> to yield **17** [Eq. (8)]; with  $R^1 = H$  the reaction proceeds more readily.<sup>13,76</sup> Ethyl chloroformate has also been used for cyclization.<sup>77</sup>

2-Oxo analogs of 17 have been prepared similarly,<sup>78,79</sup> and also from 3-halogenopropyl chloroformates and amines.<sup>80</sup> Meyers and Shaw<sup>81</sup>



obtained a more complex system (18) from a long-chain ketochloroformate and ammonia [Eq. (9)].



Simple oxo compounds (17) and their derivatives have also been prepared from 3-aminopropanols and carbonate esters: ethylene carbonate at  $100^{\circ}C^{82}$  or diethyl carbonate in the presence of alkali.<sup>83,84</sup>

- <sup>73</sup> W. Tuszko and T. Urbański, Int. Symp. Nitro Compounds, 1963 Abstr. p. 116; Tetrahedron 20, Suppl. 1, 325 (1964).
- <sup>74</sup> C. P. Fauran, C. Douzon, G. M. Raynaud, and M. Y. Sergant (Delalande S.A.), U.S. Patent 3,821,215 [CA 82, 125412 (1975)].
- 75 K. C. Murdoch, J. Org. Chem. 33, 1367 (1968).
- <sup>76</sup> A. Schmidt-Szałowska and T. Urbański, Bull. Acad. Pol. Sci. Ser. Sci. Chim. 24, 447 (1976).
- <sup>77</sup> E. H. White, M. C. Chen, and L. A. Dolak, J. Org. Chem. 31, 3038 (1966).
- 78 K. Schmidt, Ger. Offen. 1,257,147 [CA 69, 10447 (1968)].
- <sup>79</sup> J. Maillard, M. Vincent, G. Remoud, Vo-Van Tri, and M. Rapin, *Chem. Ther.* 3, 321 (1968) [CA 70, 68280 (1969)].
- <sup>80</sup> R. G. Haber (ABIC Chemical Labs., Ltd.), Canadian Patent 697,720 [Chem. Zentr. 43, 2771 (1966)].
- <sup>81</sup> A. I. Meyers and Chia-Cheng Shaw, Tetrahedron Lett., 717 (1974).
- <sup>82</sup> H. K. Hall and A. K. Schneider, J. Am. Chem. Soc. 80, 6409 (1958).
- 83 Krewel-Leuffen G.m.b.H., British Patent 931,571 [Chem. Zentr. 29, 2646 (1965)].
- <sup>64</sup> Krewel-Leuffen G.m.b.H., Austrian Patent 231,454 (1964).

3-Hydroxy-*n*-propylhydrazine (3-hydrazylpropanol) was cyclized with ethyl carbonate to yield 17 ( $R = NH_2$ ). The reaction was followed by treatment with isocyanate, RNCO, to form a urea derivative 19.<sup>85</sup>



Carbamate esters also produced 2-oxo compounds, e.g., the esters of 3-aminopropanol<sup>86</sup> and of 3-halogenopropanol.<sup>87</sup> A few compounds have thus been prepared from carbamates, e.g., **20**, with an aromatic substituent<sup>88</sup> [Eq. (10)] or a heterocyclic one.<sup>89</sup> Ethyl *N*-(3-hydroxy-propyl) urethanes cyclize to 2-oxo compounds with sodium methoxide.<sup>78</sup> An interesting novel approach was to react an *N*-(chloromethyl)-carbamate with olefins to yield **21**<sup>90</sup> [Eq. (11)].



2-Oxo derivatives of 17 can be obtained via a Curtius degradation by the action of nitrous acid on  $\gamma$ -hydroxycarboxylic hydrazides, e.g., Eq. (12).<sup>91,92</sup>

- <sup>85</sup> E. K. W. Wat (du Pont de Nemours and Co.), U.S. Patent 3,859,301 [CA 82, 140151 (1975)].
- <sup>86</sup> K. Schmidt, Ger. Offen. 1,257,147 [CA 69, 10447 (1968)].
- <sup>87</sup> Norwich Pharmacal Co., British Patent 944,594 [Chem. Zentr. 36, 1783 (1966)].
- <sup>88</sup> P. J. Stoffel and A. J. Speziale, J. Org. Chem. 27, 3079 (1962).
- <sup>89</sup> Norwich Pharmacal Co., Austrian Patent 233,000 [Chem. Zentr. 46, 1853 (1965)].
- <sup>90</sup> R. Merten and J. Müller, Angew. Chem. 74, 866 (1962).
- <sup>91</sup> E. D. Nicolaides, J. Org. Chem. 32, 1251 (1967).
- <sup>92</sup> J. M. Sullivan and H. F. Efner, J. Org. Chem. 33, 2134 (1968).



3-Chloropropanol was also used to prepare 17 (R = H) by reaction with potassium cyanate in dimethylformamide [Eq. (13)].<sup>93</sup>

$$\begin{array}{c} H_2 \\ H_2 C \xrightarrow{C} Cl \\ I \\ H_2 C \xrightarrow{} OH \end{array} (17) + Cl^- (13)$$

Breslow<sup>94</sup> introduced an interesting method of forming 2-oxo compounds, which was based on his earlier work.<sup>95</sup> Thermolysis of *n*octadecyl azidoformate gives some tetrahydro-1,3-oxazin-2-one (23) [Eq. (14)].



A new route to mono- and dioxo derivatives of 1,3-oxazine was given by Martin *et al.*<sup>96,97</sup>: addition of 2 moles of ketene to the C—N of azomethines. (This reaction was described by Staudinger<sup>98-100</sup> in 1906, but piperidinedione structures were assigned to these compounds.) When the Schiff's base PhCH—NEt reacted with 2 moles of dimethylketene a good yield of a derivative of 2-isopropylidenetetrahydro-1,3-

- <sup>93</sup> B. L. Phillips and P. A. Argabright, J. Heterocycl. Chem. 3, 84 (1966)].
- 94 D. S. Breslow and G. A. Ward, J. Org. Chem. 38, 4205 (1973).
- <sup>95</sup> D. S. Breslow, T. J. Prossner, A. P. Marcantonio, and C. A. Genge, J. Am. Chem. Soc. 89, 2384 (1967).
- 96 J. C. Martin, V. A. Hoyle, and K. C. Brannock, Tetrahedron Lett., 3589 (1965).
- <sup>97</sup> J. C. Martin, K. C. Brannock, R. D. Burpitt, P. G. Grott, and V. A. Hoyle, J. Org. Chem. 36, 2211 (1971).
- 98 H. Staudinger and H. W. Klever, Chem. Ber. 39, 968 (1906); 40, 1149 (1907).
- 99 H. Staudinger, Chem. Ber. 39, 3062 (1906); 40, 1145 (1907).
- <sup>100</sup> H. Staudinger, H. W. Klever, and P. Kober, Ann. Chem. 374, 1 (1910).

oxazin-6-one (24) resulted [Eq. (15)]. The formation of  $\beta$ -lactams competes,<sup>96</sup> and this is favored by solvents of low polarity.



A similar reaction with diphenylketene<sup>101</sup> yields an analog of **24**. Diphenylketene also cycloadds to some heterocycles containing a C=N bond<sup>102</sup> to form fused 1,3-oxazine rings. 1,3-Oxazin-4-one is also formed by condensation of a  $\beta$ -propiolactone with *p*-nitrobenzylideneaniline at 130° to 135°C in the presence of sodium acetate.<sup>103</sup>

Enlargement of an isoxazolidine ring is also a method of forming 1,3-oxazin-4-ones.<sup>104</sup> A derivative (25) of the antibiotic cycloserine with methyl  $\alpha$ -bromoisovalerate yielded two diastereoisomers, namely, 26a and b [Eq. (16)], probably by ring cleavage of 25 as shown, followed by recylization.



Farrissey and Nashu<sup>105</sup> reported that the reaction of an epoxide with phenyl isocyanate, which previously had been claimed to yield a tetrahydro-1,3-oxazin-2-one,<sup>1,106</sup> produced, in fact, a 2-oxazolidone derivative.

- <sup>103</sup> F. I. Luknitskii and B. A. Vovsi, USSR Patent 195,457 [CA 68, 114582 (1968)].
- <sup>104</sup> R. B. Morin, J. R. Lake, and E. M. Gordon, Tetrahedron Lett., 2979 (1974).
- <sup>108</sup> W. J. Farrissey and A. M. Nashu, J. Heterocycl. Chem. 7, 331 (1970).
- <sup>106</sup> Y. Iwakura and Y. Taneda, J. Org. Chem. 24, 1992 (1959).

<sup>&</sup>lt;sup>101</sup> R. Huisgen, B. A. Davis, and M. Morikawa, Angew. Chem. 80, 802 (1968); Angew. Chem., Int. Ed. Engl., 7, 826 (1968).

<sup>&</sup>lt;sup>102</sup> M. J. Haddadin and A. Hassner, J. Org. Chem. 38, 2650 (1973).

b. Dioxo Compounds.  $\beta$ -Hydroxy acids<sup>1</sup> have continued to be a source of 2,4-dioxotetrahydro-1,3-oxazines.<sup>107-109</sup> A modification consists in reacting  $\beta$ -hydroxypropiolactone with cyanic acid.<sup>110-112</sup> Hydrolysis of 2-imino-4-oxotetrahydro-1,3-oxazine also produced the 2,4-dioxo compound.<sup>113</sup> As mentioned already, the product of the acid degradation of the antibiotic Indolmycin contains a 1,3-oxazine-2,4-dione unit.<sup>6</sup>

 $\beta$ -Amino acids and phosgene were used, as previously reported,<sup>1</sup> for the preparation of 2,6-dioxo derivatives.<sup>114</sup> Reaction of dialkylmalonyl chloride with *N*-methylisobutyramide to yield **27** [Eq. (17)] is a general method of forming 4,6-dioxo derivatives of tetrahydro-1,3-oxazine, as reported by Martin *et al*.<sup>115</sup>



A diamide and malonyl chloride gave a compound with two dioxotetrahydro-1,3-oxazine rings.<sup>116</sup> Diacylamines were also used to produce tetrahydro-1,3-oxazine-4,6-dione.<sup>117</sup>

c. Trioxo Compounds. The only trioxo derivative of tetrahydro-1,3oxazine (28) was described recently.<sup>118</sup> It was obtained by condensing a  $\beta$ -aminoacrylic ester with N-methyl bis(carbamyl chloride).

- <sup>107</sup> E. Testa (Lepetit S.p.A.), Austrian Patent 212,323 [Chem. Zentr., 12764 (1962)].
- <sup>108</sup> E. Testa, Ger. Offen. 1,105,418 [CA 57, 3454 (1962)].
- <sup>109</sup> Lepetit S.p.A., Indian Patent 69,607 [Chem. Zentr. 14, 1589 (1964)].
- <sup>110</sup> S. Ozaki and T. Kato, J. Polym. Sci., Part C, 695 (1966).
- <sup>111</sup> Y. Miyake, S. Ozaki, and T. Kato, Japanese Patent 6808,278 [CA 69, 106719 (1968)].
- <sup>112</sup> S. Ozaki and K. Kato, Japanese Patent 6,927,807 [CA 72, 43701 (1970)].
- <sup>113</sup> F. I. Luknitskii, B. A. Vovsi, and D. O. Taube, USSR Patent 222,394 [CA 70, 11705 (1969)].
- <sup>114</sup> E. Testa, G. Cignarella, and G. Pifferi (Lepetit S.p.A.), Ger. Offen. 1,179,207 [Chem. Zentr. 30, 1834 (1965)].
- <sup>115</sup> J. C. Martin, K. C. Brannock, and R. H. Meen, J. Org. Chem. 31, 2966 (1966).
- <sup>118</sup> J. C. Martin and K. C. Brannock, U.S. Patent 3,373,159 [CA 69, 59254 (1968)].
- <sup>117</sup> H. W. Wittmann, A. Wohlkönig, H. Stark, and E. Ziegler, *Monatsh. Chem.* 101, 296 (1970).
- <sup>118</sup> J. Grohe, Ger. Offen. 2,311,704 [CA 82, 4266 (1975)].



d. Thiono Compounds. A simple 2-thiono derivative (29) of tetrahydro-1,3-oxazine was obtained<sup>119</sup> from carbon disulfide and 3aminopropanol [Eq. (18)].



Kjaer and Schuster<sup>7</sup> described the cyclization of the derivative of 3-hydroxypentyl isothiocyanate found in the seeds of *Erysimum hieracifolium* L. to a levorotatory tetrahydro-1,3-oxazine-2-thione (30) [Eq. (19)].



A novel method was recently reported of preparation of 2-thiones<sup>120</sup> by treating the pyridinium salt 31 with hydrogen sulfide.



<sup>119</sup> M. Menard, A. W. Wringley, and F. L. Chub, *Can. J. Chem.* **39**, 273 (1961). <sup>120</sup> A. Krantz and B. Hoppe, *Tetrahedron Lett.*, 695 (1975).

e. Iminotetrahydro-1,3-oxazine Derivatives. Carbodiimides produce 2-imino derivatives of tetrahydro-1,3-oxazine (32), for instance when condensed with propane-1,3-diol<sup>121</sup> [Eq. (20)] or its cyclic ethers.<sup>122</sup>



Carbodiimides with trimethyleneoxide and triethylamine<sup>123</sup> should produce compounds **32**.

Other methods include condensing N-(dichloromethylene)carbamides with 3-aminoalcohols<sup>124</sup> [Eq. (21)] from thioureas to give  $33^{124}$  [Eq. (22)]; some imino compounds were prepared similarly.<sup>124,126</sup>



According to Ignatova *et al.*,<sup>125</sup> 2-iminotetrahydro-1,3-oxazines are tautomeric with 2-amino-5,6-dihydro-4H-1,3-oxazines [Eq. (23)].



A novel method consists in reacting a  $\beta$ -propiolactone with S-alkyl isothiouronium salts<sup>127</sup> to give 2-imino-4-oxotetrahydro-1,3-oxazines.

- <sup>121</sup> E. Schmidt, E. Däbritz, K. Thulke, and E. Crassmann, Ann. Chem. 685, 161 (1965).
- <sup>122</sup> E. Däbritz, Angew. Chem. 78, 483 (1966).
- <sup>123</sup> S. H. Metzger, U.S. Patent 3,479,351 [CA 72, 21699 (1970)].
- <sup>124</sup> J. Burkhardt and K. Hamann, Chem. Ber. 100, 2569 (1967).
- <sup>125</sup> L. A. Ignatova, A. E. Gekhman, P. L. Ovechkin, and V. B. Unkovskii, *Khim. Geterotsikl. Soedin.*, 354 (1974).
- <sup>126</sup> Farbenfabrik Bayer A.G., French Patent 1,555,972 [CA 73, 14861, 45496 (1970)].
- <sup>127</sup> F. I. Luknitskii, B. A. Vovsi, and D. O. Taube, USSR Patent 222,393 [CA 70, 11706 (1969)].

# C. 5,6-DIHYDRO-4H-1,3-OXAZINES

As mentioned already, the interest in 5,6-dihydro-4H-1,3-oxazines is considerably increased by their use in the synthesis of aldehydes, ketones, and carboxylic acids.<sup>2-4</sup> They are also useful protecting groups for reactions involving Grignard reagents.

# 1. Methods of Cyclization

Schmidt<sup>4</sup> recently systematized existing syntheses of 5,6-dihydro-4H-1,3-oxazines into four general methods of ring closure (see diagrams **a**, **b**, **c**, and **d** of Fig. 2).



FIG. 2. Diagram of ring closure to form 5,6-dihydro-4H-1,3-oxazines.

a. The oldest method, condensing 3-halopropylamines with carboxylic acid chlorides<sup>1</sup>, was extended<sup>128</sup> [Eq. (24)]. Further derivatives



(34) have since been obtained.<sup>129,130</sup> Methacryloyl chloride gave 35,<sup>129</sup> which is suitable for further polymerization.



<sup>128</sup> S. Gabriel, Ann. Chem. 409, 305 (1915).

- <sup>120</sup> L. S. Luskin and P. La Roche de Benneville (Rohm & Hass Co.), Ger. Offen. 1,067,437 [Chem. Zentr., 19785 (1963)].
- <sup>130</sup> C. Fauran, C. Douzon, G. Raynaud, and Y. Bailly (Delalande S.A.), French Demande 2,158,143 [CA 79, 126509 (1973)].



**b.** The method consists in treating an ester of 3-aminopropanol with alkali<sup>5</sup> or 3-aminopropanol with a carboxylic acid derivative, as previously described<sup>1</sup> [Eq. (25)].



Cyclization of *N*-acylated 3-aminopropanol derivatives<sup>131,132</sup> and of urea derivatives<sup>133</sup> belongs to the same category of reactions as do cyclization of isothioureas<sup>134</sup> and a novel cyclization followed by Claisen rearrangement of **37** into **38**<sup>135</sup> [Eq. (26)].



c. Nitriles cycloadd to propane-1,3-diol in the presence of a strong mineral acid<sup>1,136</sup> [Eq. (27)]. Amides react similarly.<sup>1</sup> The mechanism of

- <sup>131</sup> M. H. Litt, R. B. Lund, J. Vitrone, J. L. Herz, and F. C. O'Donnel, U.S. Patent 3,681,333 [CA 77, 1,011,633 (1972)].
- <sup>132</sup> C. Fauran, C. Douzon, G. Raynaud, and B. Pourrias (Delalande S.A.), French Demande 2,215,223 [*Ref. Zh. Khim.* 170,103 P (1975)].
- <sup>133</sup> A. Noriaki, J. Pharm. Soc. Jpn 82, 1547 (1962) [Chem. Zentr. 33, 0977 (1966)].
- <sup>134</sup> L. A. Ignatova, P. L. Ovechkin, M. Z. Branzburg, A. E. Gekhman, and B. V. Unkovskii, *Zh. Geterotsikl. Soedin.*, 1037 (1972).
- <sup>135</sup> R. E. Ireland and A. K. Willard, J. Org. Chem. 39, 421 (1974).
- <sup>136</sup> Yu. M. Portiyagin and T. M. Pavel, Zh. Org. Khim. 11, 649 (1975).

the formation of 36 involves intermediate carbocation formation, e.g., 39a [Eq. (28)].



3-Aminopropanol in the presence of salts of divalent metals<sup>137,138</sup> similarly yields 5,6-dihydro-4H-1,3-oxazines.

An alternative route, to form the 2-amino compounds, by Meschino and Bond<sup>139</sup> used cyanogen bromide to cyclize aminopropanol [Eq. (29)] (see also Meschino and Poos<sup>140</sup>).



Acrylonitrile took part in the cyclization to form  $36 (R = CH=CH_2)$ , which could be polymerized.<sup>141</sup> Cyano- and chlorocyanoacetylene were also used in the modified Ritter nitrile cycloaddition to produce 2-ethynyl- and 2-chloroethynyl-5,6-dihydro-4*H*-1,3-oxazines.<sup>142</sup>

Unsaturated alcohols, e.g.,  $CH_2 = C(CH_3)CH_2CH_2OH$ , cyclize with R-CN in the presence of concentrated sulfuric acid.<sup>143</sup>

Meyers *et al.*<sup>144</sup> gave an ingenious method of forming a 5,6-dihydro-4H-1,3-oxazine with the ultimate aim of producing azasteroids: nitriles react with cyclopentenyl-*t*-butanol (41) in the presence of sulfuric acid

- <sup>138</sup> J. E. Kmiecik and H. Schulze, U.S. Patent 3,741,961 [Ref. Zh. Khim, 10N, 161P (1974)].
- <sup>139</sup> J. A. Meschino and C. I. Bond, J. Org. Chem. 28, 3129 (1963).
- <sup>140</sup> J. A. Meschino and G. J. Poos (McNeil Lab., Ind.), U.S. Patent 3,115,494 [Chem. Zentr. 32, 1686 (1966)].
- <sup>141</sup> M. A. Perry, J. B. Dickey, and A. G. Robinson (Eastman Kodak Co.), U.S. Patent 2,968,657 [*Chem. Zentr.* 46, 2541 (1966)].
- <sup>142</sup> T. Sasaki, S. Eguchi, and S. Shoji, Bull. Chem. Soc. Jpn. 46, 540 (1973) [CA 78, 124525 (1973)].
- Laboratories Dausse, French Patent 1,241,140 [Chem. Zentr. 13, 1576 (1964)].
- A. I. Meyers, J. Schneller, and N. K. Ralhan, J. Org. Chem. 28, 2944 (1963).

<sup>&</sup>lt;sup>137</sup> H. Witte and W. Seeliger, Ger. Offen. 2,127,776 [CA 78, 97627 (1973)].

to yield 42 [Eq. (30)]. Nitriles can also react with 3-aminopropanol to yield 5,6-dihydro-4H-1,3-oxazines with elimination of ammonia.<sup>145</sup>

Isocyanates also cyclize with 3-chloropropylamine<sup>146</sup> and isothiocyanates with 3-aminopropanol<sup>134</sup> to yield derivatives of **36**.



d. The method involves Diels-Alder-type addition of N-acylimines with olefins. N-Acylimines are rather unstable compounds,  $^{4,144}$  but they possess electrophilic character and react with nucleophilic dienophiles, such as enamines,  $^{147-149}$  yielding 43 [Eq. (31)].



Subsequently it was shown that *N*-acylimines with their increased electrophilicity cycloadd to simple olefins,<sup>150–164</sup> as predicted.<sup>4</sup>

- <sup>145</sup> H. Witte and W. Seeliger, Angew. Chem. 84, 343 (1972).
- <sup>146</sup> H. J. Pander and H. Kiefer, Ger. Offen. 2,049,160 [CA 77, 19655 (1972)].
- <sup>147</sup> R. R. Schmidt and E. Schlipf, Chem. Ber. 103, 3783 (1970).
- 148 N. P. Gambaryan and Yu. V. Zeifman, Izv. Akad. Nauk. SSSR 2059 (1969).
- <sup>149</sup> H. E. Zaugg, Synthesis, 49 (1970).
- <sup>150</sup> R. R. Schmidt, Chem. Ber. 98, 334 (1965).
- <sup>151</sup> R. R. Schmidt, Angew. Chem. 81, 576 (1969); Angew. Chem. Int. Ed. Engl. 8, 602 (1969).
- <sup>162</sup> R. R. Schmidt and R. Machat, Angew. Chem. 82, 322 (1970); Angew. Chem., Int. Ed. Engl. 9, 311 (1970).
- <sup>153</sup> W. Seeliger and W. Diepers, Ann. Chem. 697, 171 (1966).
- <sup>164</sup> W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Thier, and H. Hellmann, Angew. Chem. 78, 913 (1966); Angew. Chem., Int. Ed. Engl. 5, 87 (1966).
- <sup>155</sup> Chemische Werke Huels A.G., French Patent 1,478,076 [CA 68, 78296 (1968)].
- <sup>156</sup> K. Bott, *Tetrahedron Lett.*, 4185, 4301 (1970).
- <sup>157</sup> R. R. Schmidt, Chem. Ber. 103, 3242 (1970).
- <sup>158</sup> Chemische Werke Huels A.G., French Patent 1,585,475 [CA 74, 42365 (1971)].
- <sup>159</sup> C. Giordano, G. Ribaldone, and G. Borsotti, Synthesis, 92 (1971).
- <sup>160</sup> B. A. Arbuzov, N. N. Zobova, F. B. Balabanova, and M. F. Tarasova, Izv. Akad. Nauk SSSR, Ser. Khim., 2324 (1972).

Sec. II.C.21

N-Hydroxymethyl amides are potential acylimines<sup>152–154</sup> and react in a strongly acid medium (usually acetic and sulfuric acids) at ca. 10°C, probably as a carbonium-immonium ion:

$$\text{RCONHCH}_2\text{OH} \xrightarrow{+\text{HX}, \text{H}_2\text{O}} [\text{RCONH} - \overset{\cdot}{\text{CH}_2} \leftrightarrow \text{RCONH} = \text{CH}_2]X^{-1}$$

A modification consists of reacting amides with aldehydes and olefins. 157-158

Another general method, mentioned in our earlier review,<sup>1</sup> of formation of 5,6-dihydro-4H-1,3-oxazines is the reaction of 3-azidopropanol and aromatic aldehydes.

Also cyclization of a six-membered chain has been reported. By brominating nonconjugated allylic amides, McManus et al. 165,166 obtained 5,6-dihydro-1,3-oxazine derivative in addition to two other compounds (a five-membered ring and the brominated amide) [Eq. (32)].



# 2. Ring Enlargement

Recently the tetrahydrofuran ring of a hemiacetal (45) was enlarged<sup>167</sup> by inserting nitrogen from hydrazoic acid to obtain 36 [Eq. (33)]. This method was used for the formation of a 5,6-dihydro-4H-1,3-oxazine steroid.



- <sup>161</sup> A. D. Sinitsa, B. S. Drach, and A. A. Kisilenko, Zh. Org. Khim. 9, 685 (1973).
- <sup>162</sup> M. Pánková and M. Tichý, Coll. Czech. Chem. Commun. 39, 1447 (1973).
- <sup>163</sup> Yu. A. Arbuzov, E. I. Klimova, N. D. Antonova, and Yu. V. Tomilov, Zh. Org. Khim. 10, 1164 (1974).
- <sup>164</sup> R. R. Schmidt and A. R. Hoffman, Chem. Ber. 107, 78 (1974).
- <sup>165</sup> S. P. McManus and R. A. Hames, *Tetrahedron Lett.*, 4549 (1973).
- <sup>166</sup> S. P. McManus and D. W. Ware, *Tetrahedron Lett.*, 4271 (1974).
- <sup>167</sup> C. Monneret, P. Choay, and O. Khuong-Huu, *Tetrahedron* 31, 575 (1975).

# 3. Reactions of 2-Thione Derivatives

Tetrahydro-1,3-oxazine-2-thione reacts with rearrangement to yield **46** and a thiazine<sup>168</sup> [Eq. (34)].



Thione derivatives can be S-methylated. Thus the tetrahydro-1,3oxazine-2-thione with methyl iodide yielded 2-methylthio-5,6-dihydro-4H-1,3-oxazine (47).



# D. OXO DERIVATIVES OF 5,6-DIHYDRO-4H-1,3-OXAZINES

Of the new methods of preparation of oxo derivatives of the 5,6dihydro-4*H*-1,3-oxazines, the most important is that developed by Martin and co-workers:<sup>169</sup> the reaction of acylisocyanates with enol ethers at room temperature under nitrogen yields **48** [Eq. (35)] (see also Arbuzov *et al.*<sup>170,171</sup>) together with an isomeric azetidinone. The



<sup>168</sup> R. C. Clapp and L. Long, J. Heterocycl. Chem. 7, 1357 (1970).

<sup>169</sup> J. L. Chitwood, P. G. Gott, and J. C. Martin, J. Org. Chem. 36, 2228 (1971).

- <sup>170</sup> B. A. Arbuzov, N. N. Zubova, and F. B. Balabanova, *Izv. Akad. Nauk SSSR*, Ser. *Khim.*, 2086 (1972).
- <sup>171</sup> B. A. Arbuzov, N. N. Zubova, and I. I. Adrianova, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1566 (1974).

product  $(R = CCl_3)$  is extremely hygroscopic and subject to ring opening under acid conditions.

By reacting an acylisocyanate with dimethylketene, 4,6-dioxo derivatives of 1,3-oxazine (49) were obtained<sup>172</sup> [Eq. (36)]. The reaction is exothermic and the temperature was kept below 40°C.



An earlier work of Barker<sup>173</sup> described the formation of 5,6-dihydro-4-methyl-6-oxo-2,4-diphenyl-1,3-oxazine through dehydration of  $\beta$ benzamido-β-phenylbutyric acid with acetic anhydride.

Steglich et al.<sup>174</sup> obtained 5,6-dihydro-4H-1,3-oxazin-6-one by pyrolysis (270°C) of ethyl  $\beta$ -acylaminocrotonate. Ethanol is evolved and a ketene is formed as an intermediate.

# E. 3,4-DIHYDRO-2H-1,3-OXAZINES

By a method similar to one previously described,<sup>1</sup> a new 2-spiro derivative of 3,4-dihydro-2H-1,3-oxazine was obtained<sup>175</sup> by the cyclization of phenylcyanopyruvic ester with cyclohexanone. Also a 3,4dihydro derivative was found as a by-product in the formation of a 5,6dihydro derivative.33

## F. Oxo Derivatives of 3,4-Dihydro-2H-1,3-oxazines

A relatively large number of papers has described the preparation of oxo derivatives of 3,4-dihydro-2H-1,3-oxazine. The previously reported<sup>1</sup> use of diketene as a cyclizing agent has found wider application. Gunar et al.<sup>176</sup> described the reaction of diketene with ammonium thiocyanate. It passes through an intermediate acetoacetyl isothiocyanate to a 2thiono derivative, which, on oxidation, yields 50 [Eq. (37)].

<sup>&</sup>lt;sup>172</sup> J. C. Martin, R. D. Burpitt, P. G. Gott, M. Harris, and R. H. Meen, J. Org. Chem. 36, 2205 (1971).

<sup>&</sup>lt;sup>173</sup> C. C. Barker, J. Chem. Soc., 317 (1954).

W. Steglich, E. Buschmann, and O. Hollitzer, Angew. Chem. 86, 596 (1974).

<sup>&</sup>lt;sup>176</sup> P. Cordier, L. Jung, and R. Hug, Ger. Offen. 2,241,271 [*CA* 78, 159,632 (1973)].

<sup>&</sup>lt;sup>176</sup> V. I. Gunar, L. F. Ovechkina, and S. I. Zavyalov, *Izv. Akad. Nauk SSSR*, 1076 (1965).

They also described the reaction of diketene with N,N-dimethylurea in acetic acid, yielding **50** (see also Ahmed *et al.*<sup>177</sup>). Gunar *et al.*<sup>178</sup> used diketene in the reaction with cyanic acid (see also Ozaki<sup>179</sup>), thiocyanic acid, ethyl urethane, and N,N'-disubstituted ureas in acetic acid medium to obtain **50**. When a 2-thiono derivative was obtained from thiocyanic acid, as in Eq. (37), they desulfurized it with mercuric acetate.



The reaction of diketene with aryl isocyanates in an acid medium furnished derivatives of  $50^{.180,181}$  It was also found that acetoacetic and benzoylacetic esters react with unsymmetrical dimethylurea to yield 50 and 51, respectively [Eq. (38)].



Diketene reacts with Schiff's bases<sup>182</sup> to yield a monooxo product (52) [Eq. (39)]. Acetoacetamide reacts similarly.<sup>182</sup>



 <sup>177</sup> S. Ahmed, R. Lofthouse, and G. Shaw, J. Chem. Soc. Chem. Commun., 959 (1974).
 <sup>178</sup> V. I. Gunar, I. A. Mikhailopulo, L. F. Ovechkina, and S. I. Zavyalov, Kh. Geterotsikl. Soedin., 48 (1967).

<sup>179</sup> S. Ozaki, Japanese Patent 69 12735 [CA 71, 91490 (1969)].

<sup>180</sup> S. Ozaki, Japanese Patent 70 21663 [CA 74, 53811 (1971)].

<sup>181</sup> S. Ozaki, Japanese Patent 70 37018 [CA 74, 64251 (1971)].

182 T. Kato and T. Sakamoto, Yakugaku Zasshi 87, 1322 (1967) [CA 68, 114524 (1968)].

[Sec. II.F

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A novel approach to the reaction of diketene with compounds possessing a C=N bond was given by Suzuki et al.<sup>183</sup> They treated diketene with N-trimethylsilyl(diphenylmethylene)amine. "Demetallation" with methanol eventually yielded 52 [Eq. (40)].



Monosubstituted malonyl chlorides can also be used to obtain 3,4-dihydro-1,3-oxazine-2,4-diones. Ziegler et al.<sup>184</sup> reported the formation of 53 by heating benzylmalonyl chloride with phenyl isocyanate [Eq. (41)]. By carrying out the reaction in the presence of stannic chloride, the temperature can be considerably lowered.<sup>185</sup> Mono-



substituted malonyl chlorides react with carbodiimides to form imino derivatives (54)186 [Eq. (42)].



<sup>183</sup> H. Suzuki, I. Matsuda, K. Itoh, and Y. Ishii, Bull. Chem. Soc. Jpn. 47, 2736 (1974). <sup>184</sup> E. Ziegler, G. Kleineberg, and H. Meindl, Monatsh. Chem. 94, 544 (1963); 97, 10 (1966). <sup>185</sup> H. Disselnkoetter, Ger. Offen. 1,940,368 [CA 74, 88003 (1971)].

<sup>186</sup> G. Kleineberg and E. Ziegler, Monatsh. Chem. 94, 502 (1963).

Aromatic ketones ( $R^1COCH_2R^2$ ) can undergo electrophilic addition of chlorosulfonyl isocyanate (ClSO<sub>2</sub>NCO) yielding eventually 55.<sup>187</sup>



*N*-Acetoacetyl urethanes (56) can be cyclized by concentrated sulfuric acid to yield 1,3-oxazine-2,4-dione derivatives.<sup>188</sup>



A novel approach to the preparation of 3,4-dihydro derivatives was described recently.<sup>189</sup> It consists in heating 1,3-dioxin-4-one with isocyanates [Eq. (43)].



A fluorinated 2-oxo derivative of 3,4-dihydro-2H-1,3-oxazine (58) was obtained, along with a 2,3-dihydro derivative (59) and an azetidinone, from perfluoromethacryloyl fluoride and cyclohexyl isocyanate<sup>190</sup> [Eq. (44)].

- <sup>187</sup> A. Hassner and J. R. Rasmussen, J. Am. Chem. Soc. 97, 1451 (1975).
- <sup>188</sup> R. N. Warrener and F. N. Cain, Tetrahedron Lett., 3231 (1966).
- <sup>189</sup> G. Jaeger, J. Wenzelburger, and R. Wegler, Ger. Offen. 2,005,118 [CA 75, 151812 (1971)].
- <sup>190</sup> D. C. England and G. C. Krespan, J. Fluorine Chem. 3, 91 (1973).



G. 2,3-DIHYDRO-6H-1,3-OXAZINES

Cyclization of a  $\beta$ -aminocrotonamide with phosgene led to the formation of a 2-oxo-6-imino derivative (60) of 2,3-dihydro-1,3-oxazine<sup>191</sup> [Eq. (45)]. A fluorinated 2-oxo derivative of 2,3-dihydro-



2H-1,3-oxazine was obtained along with the 3,4-dihydro derivative as previously described<sup>190</sup> [Eq. (44)]. When methyl isocyanate (R = Me) was used for cyclization, only the 2,3-dihydro derivative resulted, along with the azetidinone [Eq. (44)]. Halogenated 2,6-dioxo derivatives were obtained by reacting trimethylsilylazide with halogenated maleic anhydride.<sup>192</sup>

# H. 4H-1,3-OXAZINES

4H-1,3-Oxazines were at the time of the previous review the only known 1,3-oxazine derivatives with two cyclic double bonds, but recently 2H-1,3- and 6H-1,3-oxazines have been described and will be referred to in separate paragraphs. A new group of 1,3-oxazine derivatives is the azapyrylium salts with three double bonds, and they too will be described in a separate section of the present review.

<sup>161</sup> H. L. Klopping and H. M. Loux, U.S. Patent 3,352,662 [CA 68, 114,610 (1968)].
 <sup>182</sup> J. D. Warren, J. H. MacMillan, and S. S. Washburne, J. Org. Chem. 40, 743 (1975).

#### 1. Cyclization

Schmidt<sup>4</sup> classified the synthetic routes to 1,3-oxazines with two double bonds as methods  $\mathbf{a}$ ,  $\mathbf{b}$ , and  $\mathbf{c}$  of Fig. 3. Prior to Schmidt, only



FIG. 3. Diagram of ring closure to form 4H-1,3-oxazines.

method **a** had been described in the literature.<sup>1</sup> Methods **b** and **c** both consist of the addition of 1,4-polar systems to acetylenic compounds and nitriles, according to Eqs. (46) and (47),<sup>4</sup> respectively, yielding 4H-1,3-oxazinium salts.



a. The best known method of forming 4H-1,3-oxazines is acylation of  $\beta$ -aminoketones followed by cyclization with phosphorus pentachloride,<sup>1</sup> phosphoric or oxalic acid.<sup>4</sup>

**b.** In the original method acetylenic compounds were used to react with amides,<sup>4</sup> but in a modification<sup>193</sup> the amide was replaced by a Schiff's base and an acyl chloride in the presence of  $SnCl_4$  [Eq. (48)], resulting in a 92% yield of the stannichloride (61).



<sup>193</sup> R. R. Schmidt, Angew. Chem. 77, 218 (1965); Angew. Chem., Int. Ed. Engl. 4, 241 (1965).

Oxo derivatives of 4H-1,3-oxazine can readily be obtained from acetylenic compounds and acyl isocyanates, e.g., to obtain  $62^{169}$  in 85% yield. This is a [2 + 4] cycloaddition [Eq. (49)]. A number of 4H-1,3-oxazin-4-ones have been prepared by this method.<sup>169,194-197</sup>



Acyl isocyanates can also react with ketene to give derivatives of 4H-1,3-oxazine (63)<sup>172</sup> [Eq. (50)].



c. The method consists in reacting nitriles with  $\beta$ -chloroketones<sup>198,199</sup> [Eq. (51)]. Nitriles can also react with mono-substituted malonyl



chlorides to yield 6-chloro-4-oxo derivatives of  $64.^{184}$  Similar derivatives of 4H-1,3-oxazine can also be obtained from mono-substituted malonic

- <sup>194</sup> R. R. Schmidt, Chem. Ber. 98, 3892 (1965).
- <sup>195</sup> H. J. Gais and K. Hafner, Tetrahedron Lett., 5101 (1970).
- <sup>196</sup> B. A. Arbuzov, N. N. Zobova, F. B. Balabanova, and A. V. Fuzhenkova, Dokl. Vses. Konf. Khim. Atsetilena 1, 500 (1972) [Ref. Zh. Khim. 3 Zh 355 (1973)].
- <sup>167</sup> B. A. Arbuzov, N. N. Zobova, F. B. Balabanova, A. V. Fuzhenkova, and V. D. Pankratova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1580 (1973).
- <sup>188</sup> M. Lora-Tamayo, R. Madroñero, G. G. Muñoz, and H. Leipprand, *Chem. Ber.* 97, 2234, 2244 (1964).
- <sup>199</sup> M. Lora-Tamayo, D. Gracian, and V. Gomez-Parra, *Tetrahedron, Suppl.* 8, Part I, 305 (1967).

acids and aromatic amides in the presence of phosphorus chlorides, thionyl chloride, or acetic anhydride.<sup>200</sup>

Ignatova *et al.*<sup>201</sup> described an interesting cyclization that differs from methods **a**, **b**, and **c**. The addition of methyl iodide to ketothiourea derivatives yields iodides of S-methylisothioureas that cyclize to 4H-1,3-oxazines of general structure **65**.



#### 2. Addition with Proton Elimination

4H-1,3-Oxazine derivatives can be formed from 1,3-oxazinium salts substituted in positions 4, 5, and 6 by aromatic residues by addition of active CH compounds in position 6 of the oxazinium salt.<sup>4</sup> The product can be subjected to further transformations [as described in Section III,F,2,c; Eq. (82)].

#### I. 2H-1, 3-OXAZINES

The 2*H*-1,3-oxazine ring was first described by King and Durst<sup>202</sup> who revised earlier work of Kohler and Blatt<sup>203</sup> and established that the "anhydro compounds" formed by the action of alkalis on isoxazolium salts are 2*H*-1,3-oxazines (**66**) [Eq. (52)]. The same ring system is obtained from an  $\alpha$ -cyano- $\alpha$ -bromo ester with triisopropyl phosphite through an



- <sup>200</sup> E. Ziegler and H. Meindl, Monatsh. 95, 1318 (1964).
- <sup>201</sup> L. A. Ignatova, A. E. Gekhman, M. A. Spektor, P. L. Ovechin, and B. V. Unkovskii, *Zh. Geterotsikl. Soedin.*, 764 (1974).
- <sup>202</sup> J. P. King and T. Durst, Can. J. Chem. 40, 882 (1962).
- <sup>203</sup> E. P. Kohler and A. H. Blatt, J. Am. Chem. Soc. 50, 1217 (1928).

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intermediate N-phosphorylated ketenimine, which readily cyclizes to the 1,3-oxazine.<sup>204</sup>

# J. 6H-1,3-OXAZINES

The first representative of this group, a  $\beta$ -acylamino- $\alpha$ , $\beta$ -unsaturated ester, yielded 67 through pyrolysis in diphenyl ether<sup>205-207</sup> [Eq. (53)]. A modification of this method used a Schiff's base instead of the *N*-acyl derivative of a  $\beta$ -amino- $\alpha$ , $\beta$ -unsaturated acid.<sup>208</sup> Similarly, enamino esters react with benzoyl chloride to yield 6*H*-1,3-oxazines.<sup>209</sup>



Meier,<sup>210</sup> and Krantz and Hoppe<sup>211</sup> obtained 6H-1,3-oxazin-6-one (68) by pyrolysis (650°C) of 3-ethoxycarbonylaminoprop-2-enal.<sup>211</sup> It shows interesting properties, described in Section III,E.



According to Sasaki *et al.*,<sup>212</sup> diphenylcyclopropenone reacts with *N*-iminopyridinium ylids on refluxing in benzene to produce 2,4,5trisubstituted-6*H*-1,3-oxazine-6-one (**69**) [Eq. (54)]. Matsukubo and Kato<sup>213</sup> described the reaction of diphenylcyclopropenone and benzonitrile oxide through a hypothetical spiro intermediate to give **69** (R = Ph) in 40% yield [Eq. (55)].

- <sup>204</sup> E. Gore, M. F. Chasle, and A. Foucaud, *Tetrahedron* 28, 5055 (1972).
- <sup>205</sup> F. Eiden and B. S. Nagar, Naturwissenschaften 50, 403 (1963).
- <sup>206</sup> E. Buschmann and W. Steglich, Angew. Chem. 86, 414 (1974).
- <sup>207</sup> W. Steglich, E. Buschmann, and O. Hollitzer, Angew. Chem. 86, 594 (1974).
- <sup>208</sup> N. D. Bondarchuk, V. V. Mamot, L. A. Lazuhina, G. V. Petetskaya, and V. P. Kukhar, Zh. Org. Khim., 10, 735 (1974).
- <sup>209</sup> H. B. Kagan and Y-H. Suon, Bull. Soc. Chim. Fr., 1819 (1966).
- <sup>210</sup> G. Meier, Angew. Chem., Int. Ed. Engl. 13, 425 (1974).
- <sup>211</sup> A. Krantz and B. Hoppe, J. Am. Chem. Soc. 97, 6590 (1975).
- <sup>212</sup> T. Sasaki, K. Kanematsu, and A. Kakehi, J. Org. Chem. 36, 2451 (1971).
- <sup>213</sup> H. Matsukubo and H. Kato, J. Chem. Soc. Chem. Commun., 412 (1974).

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Lown and Matsumoto<sup>214</sup> reacted diphenylcyclopropenethione with N-iminopyridinium ylids and obtained 2,4,5-trisubstituted-6H-1,3-oxazine-6-thione (70) [Eq. (56)].



Another interesting formation of 6H-1,3-oxazin-6-one derivatives by the oxidation of pyrrole derivatives was described by Sprio<sup>215</sup> [Eq. (57)] (see also Yee *et al.*<sup>216</sup>).



Ziegler and Steiner<sup>217</sup> described a general method for 6-amino-4oxo-6H-1,3-oxazines (71) from amides and cyanoacetic acid [Eq. (58)].

- <sup>214</sup> J. W. Lown and K. Matsumoto, Can. J. Chem. 50 584 (1972).
- <sup>215</sup> V. Sprio, Gazz. Chim. Ital. 85, 569 (1956).
- <sup>216</sup> T. T. Yee, W. E. McEwen, and A. P. Wolf, Tetrahedron Lett., 3115 (1965).
- <sup>217</sup> E. Ziegler and E. Steiner, Monatsh. Chem. 96, 212 (1965).



6H-1,3-Oxazines can be obtained by treating 1,3-oxazinium salts with hydrogen sulfide in basic medium<sup>4</sup> (Section III,F,2,d).

# K. 1,3-OXAZINIUM (3-AZAPYRYLIUM) SALTS

These cations (72) were first obtained by Wohl in 1901<sup>1,218</sup> from 4H-1,3-oxazine and trityl perchlorate in acetonitrile [Eq. (59)]. Later



Schmidt *et al.*<sup>219</sup> cyclized  $\beta$ -acylaminocarbonyl compounds with perchloric acid to obtain 73 [Eq. (60)], in ca. 60% yield. The ring is opened in alkali.



Schmidt<sup>4</sup> also described two possible 1,4-polar cycloadditions (Fig. 4,  $\mathbf{a}$  and  $\mathbf{b}$ ) leading to 1,3-oxazinium salts [Eq. (61)] similar to



FIG. 4. Diagram of 1,4-polar cycloaddition to form 1,3-oxazinium salts.

<sup>218</sup> A. Wohl, Chem. Ber. 34, 1914 (1901).

<sup>219</sup> R. R. Schmidt, D. Schwille, and S. Sommer, Ann. Chem. 723, 111 (1969).



those in Eqs. (46) and (47). In method **a**,  $\beta$ -chlorovinylarylketones react with arylcarbonitriles in the presence of SnCl<sub>4</sub> to yield the 2,6-diaryl-1,3-oxazinium salts.<sup>220</sup> In **b**, *N*-acylimidochlorides react with arylacetylenes in the presence of SnCl<sub>4</sub> to give 2,4,6-triaryl-1,3-oxazinium salts (74; R = aryl).<sup>220</sup>

# **III.** Chemical Properties

#### A. TETRAHYDRO-1,3-OXAZINES

As indicated previously,<sup>1</sup> ring opening occurs readily with tetrahydro-1,3-oxazines. This property was recently reviewed,<sup>37</sup> and the review includes a description of the formation of 3-amino-2-nitropropanol and of 2-amino-1-nitro compounds, hydrolysis and degradation products, respectively, of the tetrahydro-1,3-oxazines.

Meyers *et al.*<sup>221,222</sup> showed that tetrahydro-1,3-oxazines exist in tautomeric ring-chain forms [Eq. (62)]. When a 5,6-dihydro-1,3-oxazine is reduced to a tetrahydro-1,3-oxazine, some 3-aminoalcohol can also be formed through the reduction of the open-chain imino form [cf. Eq. (62)]. To avoid this the reduction should be carried out with sodium borohydride at  $-40^{\circ}$ C.



- <sup>220</sup> R. R. Schmidt, Chem. Ber. 98, 334 (1965).
- <sup>221</sup> A. I. Meyers and A. Nabeya, J. Chem. Soc., Chem. Commun., 1163 (1967).
- <sup>222</sup> A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, J. Org. Chem. 38 36 (1972).

# Sec. III.A.1]

### 1. Synthesis of Aldehydes

The ring opening of tetrahydro-1,3-oxazines to aldehydes has recently found wide application through the work of Meyers.<sup>2.3</sup> 2-Alkylidenetetrahydro-1,3-oxazines, prepared from the readily available 5,6dihydro-4*H*-1,3-oxazines, possess strong nucleophilic properties and can react with alkyl halides and carbonyl compounds. The derivatives so obtained can be reduced to tetrahydro-1,3-oxazines, and through ring opening the latter can furnish acyclic, alicyclic, and  $\alpha,\beta$ -unsaturated aldehydes and their C-1 deuterated derivatives.<sup>221-223,226</sup>

The first step consists of the formation of lithio salts by treatment of 5,6-dihydrooxazines with phenyl-, *n*-butyl-, or *t*-butyllithium in tetrahydrofuran at  $-78^{\circ}$ .<sup>1,3,22,223</sup> The lithio salts can readily be alkylated by alkyl halides to 75, and the product can be reduced with aqueous sodium borohydride (or borodeuteride) at pH 7 in tetrahydrofuranethanol-water at  $-35^{\circ}$  to  $-45^{\circ}$ C to tetrahydro-1,3-oxazines (76) in quantitative yield. The latter <sup>224-228,236</sup> on hydrolysis with aqueous oxalic acid give aldehydes (77) [Eq. (63)].



- <sup>223</sup> A. I. Meyers, A. Nabeya, H. W. Adickes, and I. R. Politzer, J. Am. Chem. Soc. 91, 763 (1969).
- A. I. Meyers, G. R. Malone, and H. W. Adickes, Tetrahedron Lett., 3715 (1970).
- <sup>225</sup> A. I. Meyers, A. Nabeya, H. W. Adickes, J. M. Fitzpatrick, G. R. Malone, and I. R. Pollitzer, J. Am. Chem. Soc. 91, 764 (1969).
- <sup>226</sup> A. I. Meyers, H. W. Adickes, I. R. Politzer, and W. N. Beverung, J. Am. Chem. Soc.
  91, 765 (1969).
- <sup>227</sup> H. W. Adickes, I. R. Politzer, and A. I. Meyers, J. Am. Chem. Soc. 91, 2155 (1969).
- A. I. Meyers and A. C. Kovelesky, Tetrahedron Lett., 1783 (1969).
- <sup>229</sup> A. I. Meyers and N. Nazarenko, J. Am. Chem. Soc. 94, 3243 (1972).
- A. I. Meyers and H. W. Adickes, Tetrahedron Lett., 5151 (1969).
- <sup>231</sup> G. R. Malone and A. I. Meyers, J. Org. Chem. 39, 713 (1974).
- <sup>232</sup> A. I. Meyers and A. C. Kovelesky, Tetrahedron Lett., 4809 (1969).

The lithio salt can react with various electrophiles, as in the reaction of 78 with ketones to yield 79, which after reduction and hydrolysis furnish unsaturated aldehydes  $(80)^{225}$  [Eq. (64)].



Further development of the reaction leads to cycloalkanecarboxaldehydes.<sup>222,226</sup> The carbanion (75) can react with  $\alpha,\omega$ -dibromoalkanes, with further base, to obtain the product 81 after reduction and hydrolysis [Eq. (65)]. From 1 mole of the dibromoalkanes and 2 moles of



lithium salt (75) followed by borohydride and acid hydrolysis, dialdehydes (82) were formed.<sup>224</sup>



 $\gamma$ -Hydroxyaldehydes (83) can be obtained similarly from 5,6-dihydro-4H-1,3-oxazines and epoxides<sup>227</sup> [Eq. (66)].

<sup>233</sup> A. I. Meyers and A. C. Kovelesky, J. Am. Chem. Soc. 91, 5887 (1969).

- <sup>234</sup> A. I. Meyers and E. M. Smith, *Tetrahedron Lett*, 4355 (1970).
- <sup>235</sup> A. I. Meyers, E. M. Smith, and A. F. Jurjevich, J. Am. Chem. Soc. 93, 2314 (1971).
- <sup>236</sup> A. I. Meyers and E. M. Smith, J. Am. Chem. Soc. 92, 1084 (1970).



The scope of the synthesis was extended by using a 2-vinyloxazine, which led to the formation of propionaldehyde derivatives.<sup>227</sup> Another modification of the aldehyde synthesis started with quaternary salts that were treated with sodium hydride, alkylated, then reduced with sodium borohydride to tetrahydro-1,3-oxazines.<sup>229</sup>

Another conversion of 5,6-dihydro-4*H*-1,3-oxazine derivatives into tetrahydro-1,3-oxazines treats the former with butyllithium in ether or tetrahydrofuran at  $-78^{\circ}$ C.<sup>230</sup> This method was applied to some 5,6-dihydro compounds that resisted borohydride such as  $\beta$ -keto derivatives (substituted in position 2) of 5,6-dihydrooxazines.<sup>231</sup>

# 2. Synthesis of Ketones

Ketones are produced from tetrahydrooxazines with branched substituents in position 2,<sup>232-235</sup> as summarized in Eq. (67).<sup>234</sup> Ketenimine



intermediate (84) leads to substituted ketones by addition of organometallics.

Another synthesis of tetrahydro-1,3-oxazines with two substituents in

position  $2^{236-240}$  is based on the increased electrophilicity of the C=N bond on quaternization. Addition of organometallics such as organolithium compounds and Grignard reagents to these occurs at room temperature [Eq. (68)].



Preparative details for passing from dihydro- to tetrahydro-1,3oxazines followed by ring opening have been given.<sup>241,242</sup> The methods have been used to synthesize systems related to natural products<sup>243</sup> including those with a pyrrole ring.<sup>244-246</sup>

# B. 5,6-DIHYDRO-4H-1,3-OXAZINES

#### 1. Hydrolysis

5,6-Dihydro-1,3-oxazines can be hydrolyzed and ring opened as described previously.<sup>1</sup> The reaction was used to obtain benzoylhydroxy-lysine and pseudoephedrine derivatives.<sup>4</sup>

a. Synthesis of Aldehydes, Ketones, and Isocyanates. Meyers et al.<sup>247</sup> prepared aldehydes and ketones without using tetrahydro-1,3-oxazines.

- <sup>237</sup> A. I. Meyers and E. M. Smith, J. Org. Chem. 37, 4289 (1972).
- <sup>238</sup> A. I. Meyers and N. Nazarenko, J. Org. Chem. 38, 175 (1973).
- <sup>239</sup> A. I. Meyers, E. M. Smith, and M. S. Ao, J. Org. Chem. 38, 2199 (1973).
- <sup>240</sup> G. R. Malone and A. I. Meyers, J. Org. Chem. 39, 623 (1974).
- <sup>241</sup> J. M. Fitzpatrick, G. R. Malone, I. R. Politzer, H. W. Adickes, and A. I. Meyers, Org. Prep. Proc. 1, 193 (1969).
- <sup>242</sup> A. C. Kovelesky and A. I. Meyers, Org. Prep. Proc. 1, 213 (1969).
- 243 A. I. Meyers and E. W. Collington, Tetrahedron 27, 5979 (1971).
- <sup>244</sup> A. I. Meyers, T. A. Narwid, and E. W. Collington, J. Heterocycl. Chem. 8, 875 (1971).
- <sup>245</sup> A. I. Meyers and R. L. Nolen, E. W. Collington, T. A. Narwid, and R. C. Strickland, J. Org. Chem. 38, 1974 (1973).
- <sup>246</sup> T. A. Narwid and A. I. Meyers, J. Org. Chem. 39, 2572 (1974).
- <sup>247</sup> A. I. Meyers, A. C. Kovelesky, and A. F. Jurjevich, J. Org. Chem. 38, 2136 (1973).

The reactions [Eq. (69)] yield an aldehyde (88) by direct hydrolysis or a ketone (89) through the formation of a ketenimine.



Isocyanates (90) were formed by pyrolysis of 2-bromo-5,6-dihydro-1,3-oxazine<sup>228</sup> [Eq. (70)].



b. Synthesis of Acids. Hydrolysis of 5,6-dihydro-4H-1,3-oxazines (91) can also yield carboxylic acids (92) according to Eq. (71).



The 5,6-dihydrooxazine system is inert toward Grignard reagents<sup>236,248</sup> unless quaternized. Consequently, the dihydro system represents a protecting group for reactions involving Grignard reagents. This property allows the synthesis of both aliphatic and aromatic acyl carboxylic acids (93) from appropriately substituted dihydro-1,3-oxazines<sup>248</sup> [Eq. (72)].

<sup>&</sup>lt;sup>248</sup> A. I. Meyers, I. R. Politzer, B. K. Bandlish, and G. R. Malone, J. Am. Chem. Soc. 91, 5886 (1969).



2-Chloromethyl-5,6-dihydro-1,3-oxazines react with aryl Grignard reagents, giving ultimately an arylacetic acid.<sup>249</sup> Quaternary salts of 5,6-dihydro compounds also furnish carboxylic acids.<sup>240</sup>

# 2. Thermolysis

Thermolysis of 5,6-dihydro-1,3-oxazines, e.g. (36), gave N-allylamides (RCONHCH<sub>2</sub>CH=CH<sub>2</sub>) in good yield.<sup>152,156</sup>

#### 3. Addition

Although the C—N double bond is not very active, some additions have been recorded; for instance, the addition of epoxides.<sup>15,59,227</sup>

Michael addition of substituted electrophilic olefins to the activated 2-substituent yields pyrrolooxazines on cyclization.<sup>244–246</sup>

5,6-Dihydro-1,3-oxazines are usually reduced by borohydrides<sup>2,3</sup>; reasons for some failures have been discussed.<sup>229</sup> Catalytic hydrogenation led to ring opening.<sup>58</sup>

#### 4. Tautomerism

As pointed out previously (Section II,B,1,e), 2-amino-5,6-dihydro-4H-1,3-oxazines are tautomeric with 2-imino-tetrahydro-1,3-oxazines<sup>125</sup> [Eq. (23)].

## 5. Polymerization

The interesting ability of 5,6-dihydro-4H-1,3-oxazine to take part in a new type of copolymerization, without catalyst, involves the combination of a cationic and an anionic monomer.<sup>250</sup> The formation of the

<sup>&</sup>lt;sup>249</sup> G. R. Malone and A. I. Meyers, J. Org. Chem. 39, 618 (1974).

<sup>&</sup>lt;sup>250</sup> T. Saegusa, Y. Nagura, and S. Kabayashi, *Macromolecules* 6, 495 (1973); T. Saegusa, *Int. Symp. Polymerization of Heterocycles* (Ring-Opening), *IUPAC*, 1st, 1975, Abstr., p. 21.

monomeric unit (94) through an intermediate cation is shown in Eq. (73).



C. 3,4-DIHYDRO-2H-1,3-OXAZINES

4-Oxo-2-thiono-3,4-dihydro-1,3-oxazine rearranges<sup>188</sup> into the 2,4-dioxo-1,3-thiazine (95) [Eq. (74)].



# D. 4H-1,3-OXAZINES

4H-1,3-Oxazines react with trityl perchlorate to yield, for example, the 2,4,6-triphenyl derivative (96) which is readily hydrolyzed to a



(96)

 $\beta$ -acylaminocarbonyl compound [Eq. (60)].<sup>219-220</sup> 4H-1,3-Oxazine also reacts with *p*-benzoquinone yielding 97.<sup>208</sup> Kato *et al.*<sup>251</sup> described the addition of an enamine to give a pyridine derivative (98).



<sup>261</sup> T. Kato, Y. Yamamoto, and M. Kondo, *Heterocycles* 3, 293 (1975) [CA 83, 97165 (1975)].

## E. 6H-1,3-OXAZINES

6H-1,3-Oxazin-6-one afford novel synthetic possibilities. Ring opening of their 5-methoxycarbonyl derivatives by alcoholic potassium hydroxide yielded aminomethylene derivatives of malonic ester.<sup>252</sup> Ammonia in ethanol converted 2,4,5-triphenyl-6H-1,3-oxazin-6-one into the corresponding pyrimidone.<sup>253</sup> 6H-1,3-Oxazin-6-ones react exothermically with diethylpropynylamine to yield pyridine derivatives (**99**) [Eq. (75)].<sup>254</sup> Similarly the reaction with enamines yields pyridines.



6H-1,3-Oxazin-6-one (68) is readily hydrolyzed to an open-chain product. It is isomerized by UV irradiation to the bicycle with fused four-membered rings (100), which on heating reverted to 68.<sup>210,211</sup> Prolonged irradiation decomposed the substance into hydrogen cyanide, carbon dioxide, and acetylene.<sup>211</sup>



# F. 1,3-OXAZINIUM (3-AZAPYRYLIUM) SALTS

The properties of 1,3-oxazinium salts are similar to those of pyrylium salts.<sup>4,194,219,255-259</sup> 1,3-Oxazinium salts are intermediates for the synthesis of derivatives of pyrazole, isoxazole, pyridine, pyrimidine, quinoline, isoquinoline, chromene, benzopyrylium salts, butadiene, etc.<sup>4</sup>

- <sup>253</sup> V. Sprio, Ric. Sci., Parte 2, Sez. B [2] 4, 585 (1964) [Chem. Zentr. 8, 1144 (1967)].
- <sup>254</sup> W. Steglich, E. Buschmann, and O. Hollitzer, Angew. Chem. 86, 596 (1974).
- <sup>255</sup> K. Dimroth, Angew. Chem. 72, 331 (1960).
- <sup>256</sup> W. Schroth, Z. Chem. 4, 281 (1964).
- <sup>257</sup> R. R. Schmidt, Tetrahedron Lett., 4357 (1965).
- <sup>258</sup> R. R. Schmidt and D. Schwille, Chem. Ber. 102, 269 (1969).
- <sup>259</sup> R. R. Schmidt, D. Schwille, and H. Wolf, Chem. Ber. 103, 2760 (1970).

<sup>&</sup>lt;sup>252</sup> G. Lo Vecchio and M. Gattuso, Atti Soc. Peloritana Sci. Fis. Mat. Nat. 14, 439 (1968) [CA 74, 3538 (1971)].

#### Sec. III.F.1]

# 1. Ring Opening and Closure

a. Reactions with Water and Nucleophiles Containing Nitrogen.<sup>4</sup> Through nucleophilic attack by water at position 6 the ring of **101** can be opened and the intermediate attacked by a nitrogen nucleophile, such as ammonia, urea, or their derivatives. Ring closure to pyrimidine derivatives **102** and **103** follows<sup>4</sup> [Eqs. (76) and (77)].



Hydrazine and hydroxylamine give pyrazoles (104) and isoxazoles, respectively, as shown in Eq. (78).



Enamines (e.g., morpholinocyclohexene) react with an oxazinium ion yielding two products—a butadiene analog (105) and a tetrahydroquinoline (106),<sup>4,134</sup> as shown in Eq. (79).

# 2. Reactions with Nucleophilic Carbon Compounds

a. *Reactions with Phenols.*<sup>4</sup> Nucleophilic attack of phenoxide at position 6 of the 1,3-oxazinium ion yields a benzopyrylium salt (109)



through intermediates 107 and 108 [Eq. (80)]. Intermediates 107 and 108 may be isolated depending on the phenol used.<sup>225</sup>



Sec. III.F.2]

b. *Reactions with Grignard Reagents.*<sup>4</sup> Pyridines, e.g., **110**, are formed by nucleophilic attack of a benzyl Grignard reagent [Eq. (81)].



c. Reactions with C-H Acidic Compounds. Monosubstituted malononitriles with oxazinium salts in an anhydrous basic medium yield *cis*and *trans*-butadienes (111), which on heating cyclize to pyridines  $(112)^{4.194,219}$  [Eq. (82)].



d. Reactions with Nucleophilic Sulfur Compounds. The hydrogen sulfide anion with an oxazinium salt yields eventually the 1,3-thiazinium perchlorate  $(113)^4$  [Eq. (83)].



e. Proton Elimination. Aryl-substituted 1,3-oxazinium salts are electrophilic and their electron deficiency can be compensated by elimination of a proton from an  $\alpha$ -C—H bond. With bases the 4H-1,3-oxazine (114) can be formed<sup>4</sup> [Eq. (84)]. The oxazinium salt is regenerated with acids.



f. Oxazinyl Anion. Recently, Schmidt<sup>260</sup> studied the formation of the oxazinyl anion through the action of strong bases on 4H-1,3-oxazines [Eq. (85)]. The latter loses a proton to yield the anion (115), which, in turn, is in equilibrium with oxazabicyclo[3,1,0]hexenyl anions (116a, b, and c). The oxazinyl anion with an antiaromatic octet of  $\pi$ -electrons is highly reactive.

## **IV.** Conformation

Investigations of the conformational analysis of 5-alkyl-5-nitrotetrahydro-1,3-oxazines by dipole moments<sup>1</sup> have been extended to derivatives with various substituents in positions 3 and  $5.^{261,262}$  They

<sup>261</sup> T. Urbański, Zh. Vses. Khim. Ova. 7, 396 (1962).

<sup>&</sup>lt;sup>260</sup> R. R. Schmidt, Angew. Chem. 87, 603 (1975).

<sup>&</sup>lt;sup>262</sup> T. Urbański, D. Gürne, R. Koliński, H. Piotrowska, A. Jończyk, B. Serafin, M. Szretter-Szmid, and M. Witanowski, *Tetrahedron* 20, Suppl. 1, 195 (1964).



confirmed the previous finding of the chair form with axial 5-nitro and equatorial 5-alkyl and 3-cyclohexyl groups. A *t*-butyl was equatorial, but all primary alkyl groups occupy the axial position (117).<sup>262</sup> A possible explanation for the preference of both 5-NO<sub>2</sub> and 3-alkyl to be axial was given<sup>37,263</sup> in terms of a 1,3-attractive interaction, the nitro group being the electron acceptor, and the alkyls or aralkyls the electron donors.



When hydrogen was in position 5, an equilibrium between axial  $NO_2$ -axial *N*-methyl and equatorial  $NO_2$ -equatorial *N*-methyl was suggested on the basis of dipole moment measurement [Eq. (86)].



(118)

<sup>263</sup> T. Urbański, J. Sci. Ind. Res. 33, 124 (1974).

These findings have been confirmed by NMR analysis.<sup>264–266</sup> Allingham and Crabb *et al.*<sup>267</sup> agreed with these conclusions on the basis of NMR examination, but they did not rule out a certain amount of form **119** existing in equilibrium with **117** due to nitrogen inversion.



Eliel *et al.*<sup>268</sup> seem to confirm the observation that the nitro group in this type of heterocyclic system is preferred in the axial position. Katritzky *et al.*<sup>269–271</sup> have found on the basis of dipole moment measurements that tetrahydro-1,3-oxazines without a 5-nitro group have *N*-alkyl in the preferred equatorial position, although the axial N-CH<sub>3</sub> and  $-C_2H_5$  are important minor contributors (42 and 32%, respectively).

Since the advent of NMR as a tool for conformational analysis, a number of papers have been dedicated to conformation of tetrahydro-1,3-oxazine in addition to those mentioned above. Nevertheless, conclusions based on coupling constant measurements are valid only for closely related compounds.<sup>269</sup>

Inversion at the nitrogen atom, mentioned already,<sup>267</sup> was also discussed by Italian,<sup>16</sup> French,<sup>17</sup> and Soviet authors<sup>272</sup> on the basis of NMR examination of derivatives of tetrahydro-1,3-oxazine. In another series of papers,<sup>32,33,273</sup> Soviet authors concluded from NMR, dipole

- <sup>264</sup> D. Gürne, L. Stefaniak, T. Urbański, and M. Witanowski, *Tetrahedron* 20, Suppl. 1, 211 (1964).
- <sup>265</sup> R. C. Cookson and T. A. Crabb, Tetrahedron 24, 2385 (1968).
- <sup>266</sup> P. J. Chivers and T. A. Crabb, Tetrahedron 26, 3389 (1970).
- <sup>267</sup> Y. Allingham, R. C. Cookson, T. A. Crabb, and S. Very, *Tetrahedron* 24, 4625 (1968).
- <sup>268</sup> M. K. Kaloustian, N. Dennis, S. Mager, S. A. Evans, F. Alcudia, and E. L. Eliel, J. Am. Chem. Soc. 98, 956 (1976).
- <sup>269</sup> P. J. Halls, A. R. Katritzky, M. Snarey, and D. L. Trepanier, J. Chem. Soc. B, 132; (1971).
- <sup>270</sup> R. A. Y. Jones, A. R. Katritzky, A. C. Richards, S. Saba, A. J. Sparrow, and D. L. Trepanier, J. Chem. Soc., Chem. Commun., 673 (1972).
- <sup>271</sup> I. G. Ferguson, A. R. Katritzky, and D. M. Read, J. Chem. Soc., Chem. Commun., 255 (1975).
- <sup>272</sup> Yu. E. Kazantsev, I. P. Boiko, Yu. F. Malina, O. I. Zhuk, Yu. Yu. Samitov, and B. V. Unkovskii, *Zh. Org. Khim.* 9, 2597 (1973).
- <sup>273</sup> Yu. Yu. Samitov, O. I. Zhuk, B. V. Unkovskii, I. P. Boiko, and Yu. F. Malina, *Zh. Org. Khim.* 9, 201 (1973).

moments, and magnetic susceptibilities that three types of conformation of tetrahydro-1,3-oxazine exist—chair, boat, and twist boat. Tetrasubstituted derivatives present a particular interest: 3,5-dimethyl-6,6diphenyl (120) and 3,4,4,6-tetramethyl-6-phenyl have a preferred boat conformation.



Solvent effects can also play an important part in determining the preferred conformation.

Infrared spectra and dipole moments led to the conclusion that the N-H in tetrahydro-1,3-oxazines is predominantly axial.<sup>270</sup>

Examination of CH–NH coupling constants at low temperature indicated that the N–H axial conformation is the dominant or sole conformation and that an N-methyl substituent is in part axial.<sup>25</sup> The latter finding was in agreement with that from dipole moment measurements.<sup>26</sup> At different temperatures ( $30^{\circ}-75^{\circ}C$ ),<sup>17,18</sup> NMR gave the thermodynamic functions for the activation energy to ring inversion:  $\Delta G^{\ddagger} =$ 10.8 kcal/mole,  $\Delta H^{\ddagger} = 10.4$  kcal/mole,  $\Delta S^{\ddagger} = -0.5$  cal/mole/deg. Lowtemperature NMR spectra of N-methyl and N,C-polymethyl derivatives of tetrahydro-1,3-oxazine permitted Katritzky *et al.*<sup>271</sup> to calculate conformational equilibria and N-methyl inversion barriers. They found the free energy of activation for inversion  $\Delta G^{\ddagger} = 6.8-7.6$  kcal/mole. Direct integration of the two N-methyl peaks gave  $\Delta G^{\circ}_{298} = 0.16$  kcal/mole, a figure close to that found earlier<sup>26</sup> from dipole moment measurements.

As noted in Section II,A,3, diastereoisomeric quaternary salts of 5-nitrotetrahydro-1,3-oxazines are formed through different conformations of substituents in position 3 [Eqs. (4) and (5)].<sup>61</sup>

The conformations of the 2-oxo-tetrahydro-1,3-oxazines obtained from phosgene and the isomeric 3-amino-2,3-diphenylpropanols were used by Fodor *et al.* as an ingenious criterion for the configurational determination of the aminopropanols.<sup>13,14</sup> The erythro form yielded an oxazinone that showed optical activity 4–8 times stronger than that from the threo form.

Kurtev and co-workers<sup>274</sup> examined the conformation of *trans*-4,5diphenyltetrahydro-1,3-oxazin-2-one (121) by NMR. They concluded

<sup>&</sup>lt;sup>274</sup> A. S. Orahovats, S. M. Mishev, I. G. Pozharliev, and B. J. Kurtev, *Dokl. Bolg. Akad. Nauk* 26, 1625 (1973) [*Ref. Zh., Khim.* 14 Zh, 48 (1974)].

that both diequatorial (a) and diaxial (b) forms are in equilibrium [Eq. (87)]. A more bulky R favors the diaxial conformation, and when R is isopropyl practically only **b** exists.



# **V.** Possible Practical Applications

#### A. BIOLOGICAL ACTIVITY

#### 1. Antibiotics

Oxazinomycin  $(1)^5$  is a 1,3-oxazine antibiotic. There are five other antileukemic antibiotic macrolides of known tetrahydro-1,3-oxazine-2one structures. Maytansine, Maytanprine, and Maytanbutine were found by Kupchan *et al.*<sup>275,276</sup> in *Maytenus ovatus* and *Maytenus buchananii*, and in *Maytenus serrata* by Meyers *et al.*,<sup>277</sup> and Calubrinol



- <sup>275</sup> S. M. Kupchan, Y. Komoda, W. A. Court, G. J. Thomas, R. M. Smith, A. Karim, C. J. Gilmore, R. C. Haltivanger, and R. F. Bryan, J. Am. Chem. Soc. 94, 1354 (1972).
- <sup>276</sup> S. M. Kupchan, Y. Komoda, G. J. Thomas, and H. P. J. Hintz, J. Chem. Soc., Chem. Commun., 1065 (1972).
- <sup>277</sup> A. I. Meyers, C. C. Shaw, D. Horne, L. M. Trefonas, and R. J. Majeste, *Tetrahedron Lett.*, 1745 (1975).

and Calubrinol acetate, isolated by Wani *et al.*<sup>278</sup> from *Calubrina texennsis*. *Maytenus* macrolides are represented by formula **122**; R is Me, Et, and *i*-Pr in Maytansine, Maytanprine, and Maytanbutine, respectively. Calubrinol differs from Maytansine only by the presence of an additional hydroxy group and this is acetylated in Calubrinol acetate.

Recently Kupchan *et al.*<sup>279</sup> isolated two Maytansinoids: Maytanacine and Maytansinol. They differ from the previously described Maytansinoids by different substituents at C-3, both being without an amino acid residue at that position. Semisynthetic Maytansinoids have also been prepared by esterification of the 3-OH group of Maytansinol.

Corey and Bock<sup>280</sup> designed a synthetic route to Maytansine, and obtained a fragment of the molecule containing the 1,3-oxazine ring.

Rice<sup>281</sup> isolated Leucogenenol, a metabolite of *Penicillium gilmanii*, and attributed to it the *spiro-2H-1,3-oxazine structure* (123). It is also found in bovine and human liver.<sup>282</sup>



(123)

# 2. Antitumor Activity

5-Nitrotetrahydro-1,3-oxazine derivatives show cytotoxic activity in vitro,  $^{283,284}$  and antitumor properties against subcutaneous tumors in mice.  $^{64,285}$  Compound 124 reduced tumors by 70%. The preparation of these compounds is covered by patents.  $^{41-45}$ 

- <sup>278</sup> M. C. Wani, H. L. Taylor, and M. E. Wall, J. Chem. Soc., Chem. Commun., 390 (1973).
- <sup>279</sup> S. M. Kupchan, A. R. Branfman, R. Alan, A. T. Sueden, A. K. Verma, R. G. Dailey, Y. Komoda, and Y. Nagao, J. Am. Chem. Soc. 97, 5294 (1975).
- <sup>280</sup> E. J. Corey and M. G. Bock, Tetrahedron Lett., 2643 (1975).
- <sup>281</sup> F. A. H. Rice, J. Chem. Soc. C, 2599 (1971).
- <sup>282</sup> F. A. H. Rice and B. Shaikh, Biochem. J. 116, 709 (1970).
- <sup>283</sup> S. Slopek, H. Mordarska, M. Mordarski, T. Urbański, and D. Gürne, Bull. Acad. Pol. Sci., Ser. Sci. Chim. Geol. Geogr. 6, 361 (1958).
- <sup>284</sup> Z. Eckstein, P. Gluziński, E. Grochowski, M. Mordarski, and T. Urbański, Bull. Acad. Pol. Sci., Ser. Sci. Chim. 10, 331 (1962).
- <sup>285</sup> J. B. Chylińska, E. Grochowski, M. Mordarski, and T. Urbański, Acta Unio Int. Cancrum 20, 118 (1964) [CA 61, 8784 (1964)].

63



1,3-Oxazines without a nitro group have also been suggested as antitumor compounds.<sup>56</sup> Maytansinoids possess antileukemic and antitumor activity<sup>275-279,286</sup> with the exception of Maytansinol.<sup>279</sup>

# 3. Various Activities

The only 1,3-oxazine so far with clinical application seems to be 5,5-diethyltetrahydro-1,3-oxazine-2,4-dione (125), known under trade names of Dioxone, Dietadion, and Diethadion. Its preparation was



described in patents.<sup>109,287</sup> It is effective against barbiturate poisoning,<sup>287-289</sup> as an analeptic and convulsant, stronger than Cardiazole,<sup>79,290-296</sup> and in other ways.<sup>30,297</sup> Action was found on the central

- <sup>286</sup> S. Renullard, L. I. Rebhun, G. A. Havic, and S. M. Kupchan, *Science* 189, 1002 (1975) [*CA* 83, 188257 (1975)].
- <sup>287</sup> Aspro-Nicholas Ltd., French Patent 1,575,005 [CA 72, 111110 (1970)].
- <sup>288</sup> P. F. Mannaioni, Clin. Ter. 21, 14 (1961) [Chem . Zentr., 5756 (1962)].
- <sup>289</sup> F. B. Nicolis, C. Scocella, A. Ghisellini, G. Cenacchi, and G. Alberti, *Chemotherapia* (Basel) 4, 485 (1962) [*Chem. Zentr.*, 20506 (1963)].
- 290 G. Scocella and A. Ghisellini, Clin. Ter. 21, 19 (1961) [Chem. Zentr., 5756 (1962)].
- <sup>291</sup> G. Genacchi and G. Alberti, Clin. Ter. 21, 44 (1961) [Chem. Zentr., 5756 (1962)].
- <sup>292</sup> G. Maffii, V. M. Dezulian, and B. Silvestrini, J. Pharm. Pharmacol. 13, 244 (1961) [Chem. Zentr., 5756 (1962)].
- <sup>293</sup> G. Maffii, G. Bianchi, P. Schiatti, and B. Silvestrini, Brit. J. Pharmacol. Chemother. 16, 231 (1961) [Chem. Zentr., 14773 (1963)].
- <sup>294</sup> G. Maffii and B. Silvestrini, Farmaco, Ed. Sci. 16, 39 (1961).
- <sup>296</sup> E. Fadiga, G. Maffii, and B. Silvestrini, Boll. Soc. Ital. Biol. Sper. 39, 188 (1963).
- 296 E. Fadiga, T. Gessi, and G. Maffii, Boll. Soc. Ital. Biol. Sper. 39, 191 (1963).
- <sup>297</sup> E. Fadiga, T. Gessi, and G. Maffii, Arch. Sci. biol. 18, 149 (1964) [Chem. Zentr. 42, 1523 (1966)].

nervous system,<sup>138,298,299</sup> on blood pressure,<sup>18,73,132,175,219</sup> and as an antiinflammatory agent.<sup>16,132</sup>

Many patents describe the preparation of 1,3-oxazine derivatives as antibacterials and antifungals.<sup>21,22,27,69,81,87,89,90,129,300,301</sup> Strong antiprotozoal activity of 5-bromo-5-nitrotetrahydro-1,3-oxazines, e.g., **126**, was also registered.<sup>302,303</sup> N-Nitroso derivatives were found to be



molluscicides.<sup>65-67</sup> Some oxazines are insecticides<sup>304</sup> or herbicides.<sup>189,191</sup> A few patents refer to the preparation of 1,3-oxazines with less defined medical use.<sup>305,306</sup>

# **B.** OTHER PRACTICAL APPLICATIONS

1,3-Oxazines with an olefinic substituent were suggested as polymerizable monomers.<sup>307-309</sup> 1,3-Oxazines were claimed as plasticizers for cellulose acetate,<sup>309</sup> tanning agents,<sup>19</sup> and corrosion inhibitors.<sup>310</sup> *N*-Oxides of 1,3-oxazines were reported to be antioxidants and polymerization inhibitors.<sup>34</sup>

- <sup>298</sup> D. M. Teller, C. J. Guinosso, S. C. Bell, and G. H. Duglas, U.S. Patent 3,817,994 [CA 81, 105531 (1974)].
- <sup>209</sup> F. Hoffmann-La Roche A.G., British Patent 1,047,110 (1966) [Chem. Zentr. 44, 1559 (1968)].
- <sup>300</sup> Norwich Pharmacal Co., British Patent 944,594 [Chem. Zentr. 36, 1783 (1966)].
- <sup>301</sup> S. Ozaki, Japanese Patent 72 36742 [CA 77, 164,717 (1972)].
- <sup>302</sup> B. Orłowska, M. Mordarski, D. Gürne, and T. Urbański, Arch. Immunol. Ther. Exp. 15, 404 (1967).
- <sup>303</sup> B. Orłowska, M. Mordarski, D. Gürne, and T. Urbański, Arch. Immunol. Ther. Exp 15, 728 (1967).
- <sup>304</sup> R. L. McConnell and H. W. Coover (Eastman Kodak Co.) U.S. Patent 2,992,219 [Chem. Zentr. 15, 2025 (1964)].
- <sup>305</sup> C. Fauran, C. Douzon, G. Huguet, G. Raynaud, and Y. Bailly (Delalande S.A), Ger. Offen. 2,221,408 [CA 78, 58,435 (1973)].
- <sup>306</sup> M. Nakanishi, K. Arimura, and H. Aoi (Yotsitomi Seyaku), Japanese Patent 74 31993 [Ref. Zh. Khim. 80129P (1975)].
- <sup>307</sup> L. S. Luskin and P. La Roche de Bonneville (Rohm & Haas Co.), Ger. Offen. 1,067,437 [Chem. Zentr., 19785 (1963)].
- <sup>308</sup> W. F. Tousignant, W. E. Walles, and T. Houtman (Dow Chemical Co.), U.S. Patent 3,030,339 [Chem. Zentr. 49, 2943 (1966)].
- <sup>309</sup> S. H. Metzger (Mobay Chemical Co.), U.S. Patent 3,479,351 [CA 72, 21699 (1970)].
- <sup>310</sup> Chemische Werke Huels A.G., French Patent 1,585,475 [CA 74, 42365 (1971)].