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Fungicidal Activity of Some 2-Nitropropanedi-1,3-ol Derivatives

by

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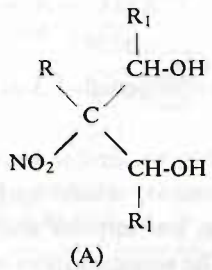
The general inactivity against fungi of 2-alkylpropanedi-1,3-ol derivatives reported by Horsfall and Dimond [1] was the main reason of the limited interest given to this groups of compounds.

It has been shown in our preliminary work [2], that by modifying the structure of the 2-nitropropanedi-1,3-ol molecule, fungicidal activity can be elicited. In further studies [3]—[4] the relationship between the chemical structure and biological activity of 2-nitropropanedi-1,3-ol derivatives, of the general formula (A), was established.



(A)

R = alkyl,, aralkyl, aryl, arylazo, NO_2, Cl, Br
R_1 = H or alkyl

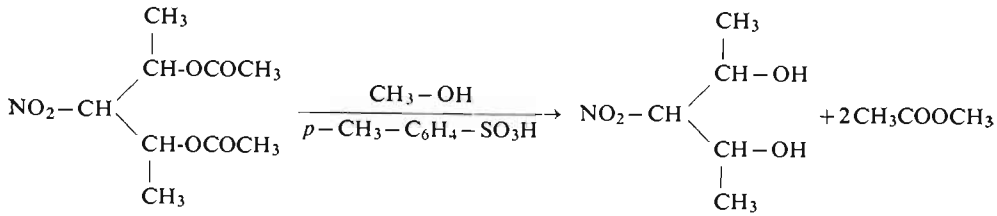
Compounds of structure (A) were prepared by the base-catalyzed aldol reaction of nitroparaffins with aldehydes, according to the following formula:

$$R\text{-}CH_2NO_2 + 2\,R_1\text{-}CHO \xrightarrow{OH} (A)$$

The reaction of nitromethane homologues with formaldehyde was carried out in the case of the alkylnitroparaffins in butanol [5] and in the case of the arylnitroparaffins series in dioxane [6]. In general, these reactions proceeded smoothly, and only the isolation of nitrodiols in crystalline form afforded some difficulty.

The condensation of formaldehyde homologues with nitromethane which led to 1,3-dialkyl-2-nitropropanedi-1,3-ols (type A compounds, where R=H and R_1= alkyl) and 1,3-dialkyl-2-halogeno-2-nitropropanedi-1,3-ols (type (A)) compounds, where R=Cl, Br and R_1=alkyl) was carried out according to the method previously

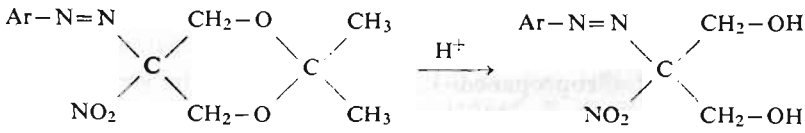
described [7], [8]. It should be pointed out that crystalline 1,3-dimethyl-2-nitropropanedi-1,3-ol could readily be obtained by hydrolysing the corresponding diacetyl derivative:



(I)

Toluenesulphonic acid used in this reaction in catalytic quantity caused the formation of methyl acetate and this was removed from the reaction medium by distillation. The above mentioned method of preparation of 1,3-dimethyl-2-nitropropanedi-1,3-ol (compound I) is more convenient than those described so far in the literature [9].

2-Arylazo-2-nitropropanedi-1,3-ol derivatives were obtained by the method based on hydrolysis of cyclic ketals (type B compounds).



(B)

(XXXIX) – Ar = 4–F–C_6H_4
(XL) – Ar = 4–Br–C_6H_4

The properties of the new derivatives of 2-nitropropanedi-1,3-ol are listed in Table I.

All the compounds were examined for their ability to inhibit growth of three phytopathogenic fungi: *Fusarium culmorum*, *Alternaria tenuis* and *Rhizoctonia solani*. In biological test the poisoned food technique was applied and agar culture medium with potato extract and dextrose was used. The concentration of compounds required to reduce mycelial growth is indicated in Table II.

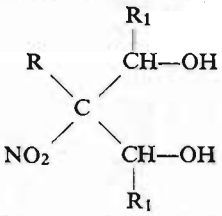
The results presented in Table II show that some 2-nitropropanedi-1,3-ol derivativess possess an appreciable fungicidal activity, this being strongly dependent on the structure of the compounds in question. On the basis of biological tests some conclusions may be drawn.

The highest activity of 1,3-dialkyl-2-nitropropanedi-1,3-ol derivatives was observed when the *n*-propyl group was attached to the carbon atom in position 1 or 3. The introduction of a bromine atom into position 2 in some 1,3-dialkyl-2-nitropropanedi-1,3-ols led to a marked increase of fungitoxicity. The most effective were compounds (VI) and (VII), therefore, it would appear that antifungal activity of compounds (V)—(VII) is due to the cationic character of the bromine atom. The lack of the fungicidal act vity in the case of the chlorine derivative (compound (IX)) seems to support this opinion. It must be pointed out, however, that the

difficulties in the preparation and the allergenic properties of the bromine derivatives (compounds V—VII) make impossible their practical application.

TABLE I

Properties and yields of 2-nitropropanedi-1,3-ol derivatives of the general formula (A)



(A) R_1=H for all compounds

Compound No.	R	Yield %	M.p. °C	Analysis N %	
				Required	Found
(X)	CH_3	84.0	147–150 a)		
(XI)	CH_3CH_2	78.0	55–57 b)		
(XII)	$CH_3(CH_2)_2$	72.0	80–82 c)		
(XIII)	$CH_3(CH_2)_3$	70.0	56–57 d)		
(XIV)	$CH_3(CH_2)_4$	75.0	58–59 e)		
(XV)	$CH_3(CH_2)_5$	83.0	69.0–70	6.8	7.1
(XVI)	$CH_3(CH_2)_6$	85.0	70.5–71.5	6.5	6.9
(XVII)	$CH_3(CH_2)_7$	81.0	62.5–63.5	6.0	6.2
(XVIII)	$CH_3(CH_2)_8$	84.0	59–60.5	5.7	6.1
(XIX)	$CH_3(CH_2)_9$	88.0	57–58	5.4	5.7
(XX)	$CH_3(CH_2)_{14}$	85.0	66–67.5	4.3	4.7
(XXI)	$CH_3(CH_2)_{16}$	93.0	70–73	3.9	4.1
(XXVII)	2-Cl-C_6H_4	70.0	121–122	6.0	6.2
(XXVIII)	3-Cl-C_6H_4	86.0	99–100	6.0	6.4
(XXX)	2,4-Cl_2-C_6H_3	88.0	116–117	5.3	5.4
(XXXI)	3,4-Cl_2-C_6H_3	89.0	88–89	5.3	5.7
(XXXIX)	4-F-C_6H_4-N=N	84.0	88–89	17.3	17.6
(XL)	4-Br-C_6H_4-N=N	85.0	111.5–112.5	13.5	13.8

a) Reported m.p. 149–150° [10]; b) As previously reported [5]; c) Reported m.p .81–82° [11]; d) Reported m.p. 48–49° [12]; e) Reported m.p. 53–55° [5].

In the series of 2-alkylnitropropanediol derivatives studied, compounds (X—XXI), the marked maximum of biological activity appeared when the normal aliphatic chain included seven or eight carbon atoms (Figure).

The activity subsisted in a series of 2-aryl-2-nitro-propanedi-1,3-ol derivatives, (compounds XXIII—XXXIV), however, in the case of the quinolyl derivative compound XLIX) the fungitoxicity was lost.

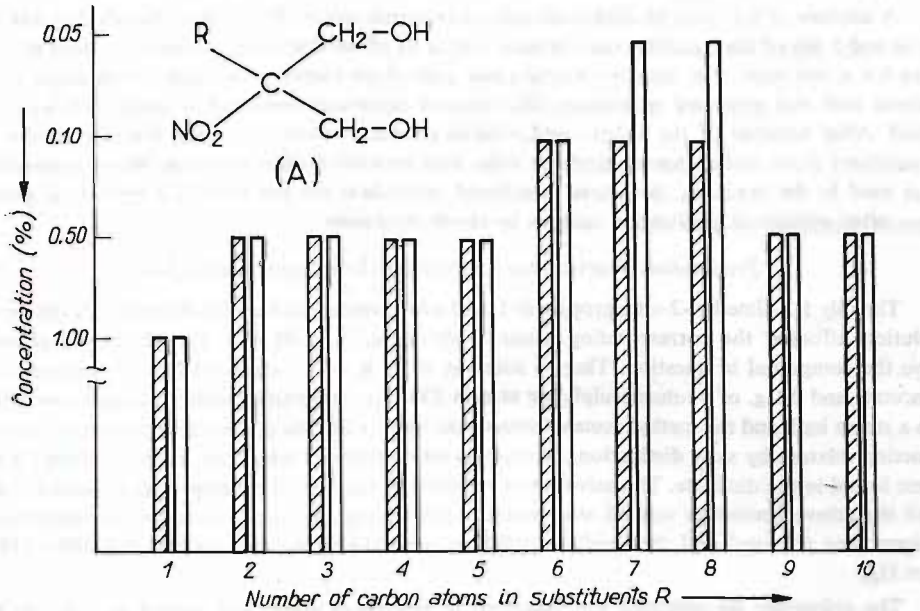
Introduction of halogen atoms into the benzene ring intensified the activity. The highest effect in this group of compounds was observed in the case of fluorine for compound (XXXII), of chlorine for compound (XXVII), and of bromine derivatives for compound (XXXIII). In the iodine derivative (compound XXXIV), however, the activity decreased.

TABLE II

Fungicidal activity of 2-nitropropanedi-1,3-ols of the general formula (A)

Compound	R	R_1	Concentration in per cent (by weight) substance to volume of agar culture medium, completely inhibiting the growth of the fungi		
			Fusarium culmorum	*Alternaria tenuis*	*Rhizoctonia solani*
(I)	H	CH_3	>0.1	>0.1	>0.1
(II)	H	CH_3CH_2	0.5	0.5	0.5
(III)	H	$CH_3CH_2CH_2$	0.05	0.05	0.05
(IV)	H	$(CH_3)_2CHCH_2$	0.05	0.5	0.5
(V)	Br	H	0.1	0.5	0.1
(VI)	Br	CH_3	0.005	0.05	0.005
(VII)	Br	$(CH_3)_2CHCH_2$	0.005	0.05	0.05
(VIII)	NO_2	H	0.1	0.1	>0.1
(IX)	Cl	H	1.0	1.0	1.0
(X)	CH_3	H	1.0	1.0	1.0
(XI)	CH_3CH_2	H	>0.5	>0.5	>0.5
(XII)	$CH_3(CH_2)_2$	H	0.5	0.5	0.5
(XIII)	$CH_3(CH_2)_3$	H	0.5	0.5	0.5
(XIV)	$CH_3(CH_2)_4$	H	0.5	0.5	0.5
(XV)	$CH_3(CH_2)_5$	H	0.1	0.1	0.1
(XVI)	$CH_3(CH_2)_6$	H	0.1	0.05	0.05
(XVII)	$CH_3(CH_2)_7$	H	0.5	0.05	0.05
(XVIII)	$CH_3(CH_2)_8$	H	>0.5	0.5	0.5
(XIX)	$CH_3(CH_2)$	H	>0.5	0.5	0.5
(XX)	$CH_3(CH_2)_4)$	H	>0.5	>0.5	>0.5
(XXI)	$CH_3(CH_2)_6$	H	>0.5	>0.5	>0.5
(XXII)	cyclohexenyl (2	H	0.5	0.5	0.5
(XXIII)	C_6H_5	H	0.01	0.25	0.05
(XXIV)	4-CH_3-C_6H_4	H	0.5	0.1	0.1
(XXV)	3-NO_2-C_6H_4	H	0.5	0.05	0.5
(XXVI)	4-NO_2-C_6H_4	H	0.25	0.01	0.25
(XXVII)	2-Cl-C_6H_4	H	0.05	0.05	0.005
(XXVIII)	3-Cl-C_6H_4	H	0.1	0.05	0.05
(XXIX)	4-Cl-C_6H_4	H	0.1	0.05	0.05
(XXX)	2,4-Cl_2-C_6H_3	H	0.05	0.05	0.0005
(XXXI)	3,4-Cl_2-C_6H_3	H	0.05	0.05	0.05
(XXXII)	4-F-C_6H_4	H	0.1	0.05	0.05
(XXXIII)	4-Br-C_6H_4	H	0.1	0.05	0.05
(XXXIV)	4-J-C_6H_4	H	0.1	0.1	0.05
(XXXV)	4-NO_2-$C_6H_4CH_2$	H	0.25	0.01	0.25
(XXXVI)	$C_6H_5N=N$	H	0.1	0.1	0.1
(XXXVII)	4-CH_3-$C_6H_4N=N$	H	0.1	0.1	0.1
(XXXVIII)	4-NO_2-$C_6H_4N=N$	H	0.25	0.25	0.1
(XXXIX)	4-F-$C_6H_4N=N$	H	0.05	0.05	0.05
(XL)	4-Cl-$C_6H_4N=N$	H	0.01	0.01	0.01
(XLI)	4-Br-$C_6H_4N=N$	H	0.05	0.05	0.05
(XLII)	4-$ClCH_2SO_2C_6H_4N=N$	H	>0.1	>0.1	>0.1
(XLIII)	$C_{10}H_7N=N$-(2)	H	1.0	0.1	1.0
(XLIV)	quinolyl-(2)	H	0.5	0.5	0.5

In a series of chlorine derivatives, the influence of one or two chlorine atoms in the aromatic ring on the fungicidal activity was examined. The highest activity was observed, when a chlorine atom was introduced in the *ortho* position. The substitution at the *meta* or *para* position of the benzene ring by a chlorine atom, reduced biological activity, particularly against *Fusarium culmorum*. Maximum fungitoxicity was achieved in the case of compound (XXX), having two chloride atoms in *ortho* and *para* positions.



Dependence between number of carbon atoms in substitutents R of compounds of the formula (A) and concentration inhibiting the growth of test moulds. Clear bar: concentration completely inhibiting the growth of *Alternaria tenuis* and *Rhizoctonia solani*; shaded bar: concentration completely inhibiting the growth of *Fusarium culmorum*

When the aromatic ring was separated by the methylene or azo group from the 2-nitropropanediol molecule, the fungitoxicity decreased (compounds XXXV—XLIII). The azo group itself gives a uniform activity against the three test moulds. In the group of halogen derivatives the highest antifungal action was shown by the chloiine derivative (XL).

The results presented here have the character of a preliminary investigation for screening of the more important compounds. A detailed study of 2-nitro-2-arylozopropanedi-1,3-ol derivatives seems to be of particular interest.

Experimental

Preparation of 2-alkyl-2-nitropropanedi-1,3-ol according to the method given in [5]

A suspension of 6 g. (0.2 mole) of paraformaldehyde in 10 ml. of *n*-butyl alcohol and 1 ml. of triethylamine was refluxed until the reaction mixture became homogeneous. After cooling to room temperature, 0.1 mole of the corresponding nitroalkane was added dropwise to the stirred

solution. The addition of the nitroparaffin was controlled to maintain the temperature below 70°. The clear solution was heated for 30 min. at 70–75° and kept at room temperature overnight. Generally 2-alkyl-2-nitropropanedi-1,3-ols were obtained as crystalline precipitates. In the case of compounds (XVIII) and (XIX), solid products were isolated as follows: the solvent was evaporated in vacuum, and the residue was treated with ether–petroleum ether solution, cooled at −40 to −60°, to give the corresponding crystalline product.

Preparation of 1,3-dialkyl-2-nitropropanedi-1,3-ol derivatives

The above compounds were prepared according to the method previously described [8].

A mixture of 0.1 mole of nitroalcohol or chloronitroalcohol, 0.1 mole of freshly distilled aldehyde and 1 ml. of triethylamine was warmed 1 hour at 35°, and allowed to stand at room temperature for a few days. The reaction mixture was poured into water, neutralized with dilute hydrochloric acid and extracted with ether. The ethereal layer was separated, washed with water and dried. After removal of the solvent and volatile products under pressure, the oily residue was crystallized from carbon tetrachloride or ether and petroleum ether solution. When acetaldehyde was used in the reaction, the above mentioned procedure did not furnish a crystalline product even after additional purification such as by chromatography.

Preparation of crystalline 1,3-dimethyl-2-nitropropanedi-1,3-ol

The oily 1,3-dimethyl-2-nitropropanedi-1,3-ol when treated with acetyl chloride in a chloroform solution afforded the corresponding diacetyl derivative, m.p. 85–87° [7] which hydrolyzed to give the compound in question. Thus, a solution of 23 g. of 1,3-dimethyl-2-nitropropanedi-1,3-ol diacetate and 0.1 g. of *p*-toluenesulphonic acid in 250 ml. of anhydrous methyl alcohol was refluxed on a steam bath and the methyl acetate formed was removed in the course of its formation from the reaction mixture by slow distillation. Hydrolysis was completed when no traces of methyl acetate were found in the distillate. The solvent was removed in vacuum, the residue was dissolved in ether and the ethereal solution washed with water. After drying over anhydrous sodium sulphate, the solvent was removed and the residue distilled to give 13 g. of the fraction with b.p. 109–110°/0.8 mm.Hg.

The colourless oil obtained was dissolved in petroleum ether, and cooled at −40° to yield 11 g. of the product with m.p. 68–69°. The m.p. of the 1.3-dimethyl-2-nitropropanedi-1,3-ol thus obtained was identical with that described before [9].

Preparation of 2-aryl-2-nitropropanedi-1,3-ols according to the method [6]

To a mixture of 0.1 mole of the corresponding arylnitromethane, 20 ml. of dioxane 20 ml. of 30 per cent formaldehyde, and 1 ml. of triethylamine was added. The temperature rose and the mixture became homogeneous. The clear solution was warmed 2–3 hr at 70–75° and allowed to stand at room temperature overnight. Then the mixture was poured into 300 ml. water, and after separation of the organic layer, the aqueous layer was extracted with ether. The combined organic liquors were washed with water and dried. After removal of the solvent under reduced pressure, the residue was allowed to stand for a few days until it solidified. The crude product was recrystallized from chloroform–carbon tetrachloride solution.

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