BULLETIN DE L'ACADÉMIE
POLONAISE DES SCIENCES
Série des sciences chimiques
Volume XXV, No. 9, 1977

ORGANIC CHEMISTRY

Preparation and Stereochemistry of 2-Methyl and 2-Phenyl Derivatives of 1,3-Diphenyl-5-methyl-5-nitrohexahydropyrimidine

by

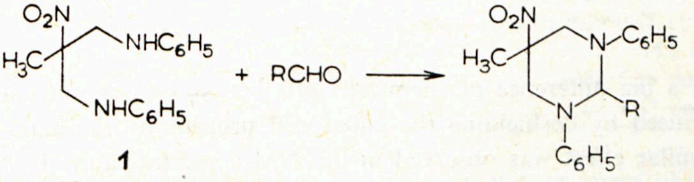
Hanna PIOTROWSKA, Wojciech SAS, Tadeusz URBAŃSKI

Presented by T. URBAŃSKI on May 4, 1977

Summary. Reaction of diamine **1** with acetaldehyde and benzaldehyde gave 2-methyl (**2**) and 2-phenyl (**3**) derivatives of 1,3-diphenyl-5-methyl-5-nitrohexahydropyrimidine. The cyclization yielded only one isomer (*trans*-**2**) of compound **2** and both possible isomers of compound **3**. Isomer *trans*-**2** was found to undergo spontaneous (catalyzed by acids) isomerization to *cis*-**2**. The composition of the equilibrium mixture depends on the polarity of the solvent used.

Continuing our research on 5-nitrohexahydropyrimidines we prepared now 1,3-diphenyl-5-methyl-5-nitrohexahydropyrimidine derivatives containing methyl (**2**) or phenyl (**3**) group in position 2.

Compounds **2** and **3** were obtained in reaction of N,N'-diphenyl-2-methyl-2-nitro-1,3-diaminopropane (**1**) [1] with acetaldehyde and benzaldehyde, respectively.



1

2 $R = CH_3$

3 $R = C_6H_5$

Scheme 1

In the case of compound **2** only one isomer was formed, whose structure was established on the basis of ^1H NMR spectrum (Fig. 1*a*). The absence of long-range coupling of H-2 protons with the equatorial protons in positions 4 and 6 (H-4e and H-6e) indicates that the 2-methyl group occupies the equatorial position. The coupling of this type is observed in NMR spectra of such hexahydropyrimidine derivatives which in position 2 contain an equatorial proton ([2], Fig. 1).

The configuration of carbon C-5 was established from the difference of chemical shifts (Δ_{ea}) of the equatorial (H-4e, H-6e) and axial (H-4a, H-6a) protons. The observed value of $\Delta_{ea} = 1.15$ ppm (Fig. 1*a*) corresponds to the axial position of the

---

Note. Part CXXIV in the series: Chemistry of Nitroparaffins.

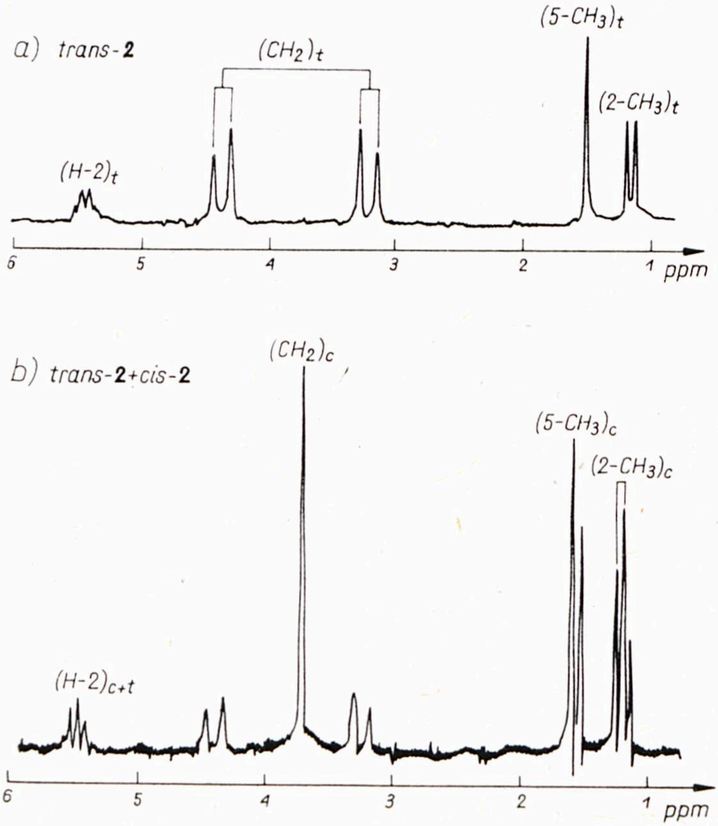
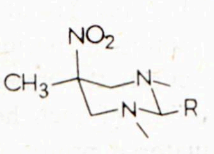


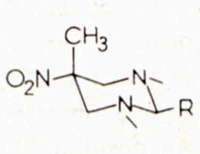
Fig. 1. ^{1}H NMR spectrum of *trans*-2 in CCl$_4$ (*a*), and of *trans*-**2** after 72 h (a mixture of *trans*-**2** and *cis*-**2**

(*b*) *c*—*cis* isomer, *t*—*trans* isomer

nitro group. Such a big difference of chemical shifts between equatorial and axial protons can be caused by deshielding the equatorial protons by the axial vicinal nitro group. A similar effect was observed in the NMR spectra of *cis*-1-t-butyl-4-nitrocyclohexane [3], and derivatives of 1,3-dioxane containing the axial nitro group in position 5 and equatorial alkyls in positions 2 and 5 [4]. On the basis of these results the structure of the isomer of **2** obtained by direct cyclization is that of *trans*-**2**.



trans



cis

However, we have found that compound *trans*-**2** underwent isomerization in solution, and after some time its NMR spectrum exhibited the presence of new signals characteristic of another isomer of compound **2**, i.e. *cis*-**2** (Fig. 1*b*).

The Δ_{ea} value of this isomer is equal to zero, and does not depend on the solvent used. This indicates the *cis* configuration of methyl groups in positions 2 and 5. The existing data report that in derivatives of cyclohexane [5] and 1,3-dioxane [6] the methyl group in axial position deshields the neighbouring axial proton and shields the equatorial protons thus diminishing the Δ_{ea} value. Also the presence of the equatorial nitro group influences the Δ_{ea} value. In the instance of isomeric 1,3-dibenzyl-2-phenyl-5-nitrohexahydropyrimidines [7] in the isomer with the equatorial nitro group it was noted that the H-4e and H-6e protons give signals at a higher field value than in the isomer with the axial nitro group, while the position of protons H-4a and H-6a almost does not change. In the NMR spectra of isomeric 2-alkyl-5-methyl-5-nitro-1,3-dioxanes the Δ_{ea} value for isomers with the axial nitro group is much higher than for isomers with the equatorial nitro group [4].

The preferred conformations and NMR data for *cis*- and *trans*-**2** are collected in Table I.

TABLE I

	trans	*cis*
	2, $R=CH_3$	
4-,6-CH_2	$\delta_{ea}=3.91$ ppm (AB) $\Delta_{ea}=1.15$ ppm $J_{ea}=-14.0$ cps	$\delta_{ea}=3.81$ ppm $\Delta_{ea}=0.00$ pm —
H-2	$\delta=5.58$ ppm $J=6.2$ cps	$\delta=5.58$ ppm $J=6.2$ cps
2-CH_3	$\delta=1.18$ ppm	$\delta=1.12$ ppm
5-CH_3	$\delta=1.54$ ppm	$\delta=1.62$ ppm
	3, $R=C_6H_5$	
4-,6-CH_2	$\delta_{ea}=4.08$ ppm $\Delta_{ea}=1.34$.ppm $J_{ea}=-15.3$ cps	$\delta_{ea}=3.98$ ppm $\Delta_{ea}=0.22$ ppm $J_{ea}=-14.8$ cps
H-2	$\delta=6.56$ ppm	$\delta=6.56$ ppm
5-CH_3	$\delta=1.34$ ppm	$\delta=1.62$ ppm

Compound **3** was obtained as a mixture of two geometrical isomers. This was found on the basis of NMR spectra. The assignment of spectrum signals to the individual protons of both isomers was done similarly as in the case of compound **2**. The preferred conformations and NMR data for *cis*- and *trans*-**3** are also collected in Table I.

As mentioned before, compound *trans*-**2** isomerizes spontaneously in solution into *cis*-**2**. This process is rather slow, and the thermodynamic equilibrium is reached after some 70 h. However, the addition of catalytic amounts of acetic acid accelerates the isomerization, and the equilibrium is reached after several minutes.

This property of compound **2** enabled us to investigate the influence of solvents on the composition of the equilibrium mixture. The results are collected in Table II. They indicate that the increase of solvent polarity increases the concentration of isomer *trans*-**2** containing the nitro group in axial position, i.e. the isomer of a higher dipole moment. These data confirm our former findings concerning the solvent dependence of the conformational equilibrium of 5-nitrohexahydropyrimidines [8]. They also explain the formation of only one isomer of **2** (*trans*-**2**) in the cyclization reaction. The reaction product was crystallized from ethanol which is a polar solvent able to form hydrogen bonds and which stabilizes the isomer with the axial nitro group [7].

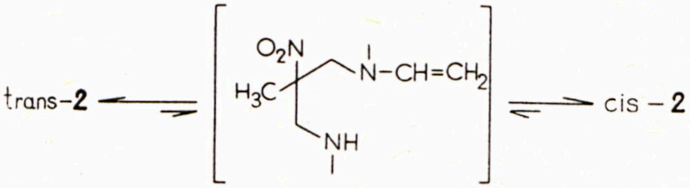
TABLE II

Equilibrium concentrations of *trans*-2 in various solvents

Solvent	Dielectric constant of the solvent	Mole % of *trans*-2
CCl_2 [a])	2.24	46
$CDCl_3$	4.80	63
C_6H_6	2.28	63
$C_6H_6+CH_3COOH$ [b])	—	67
C_6H_5CN	25.2	89
CH_3CN	37.5	96

[a]) Saturated solution, 0.1 mmole in 1 ml of CCl_4

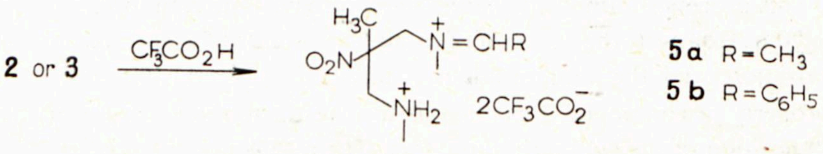
[b]) Molar ratio of *trans*-**2**:CH_3COOH = 1:3.2



4

Scheme 2

The isomerization of *trans*-**2** into *cis*-**2** proceeds most probably through the linear form **4** which contains an enamine group (Scheme 2). We could not detect the formation of compound **4** by spectral methods. However, the fact that the isomerization is catalyzed by acids, and that compound **3** does not undergo spontaneous isomerization (compound of the type **4** cannot be formed) supports the proposed reaction course.



5

Scheme 3

We have also examined the NMR spectra of **2** and **3** in trifluoroacetic acid. In these conditions both compounds have the linear structure **5** (Scheme 3). Only the spectrum of **3** could be properly interpreted (Fig. 2) because compound **2** decomposed too rapidly. As can be seen in Fig. 2, the signals of protons 4-CH_2 and 6-CH_2 are at the same field value. This is probably caused by the reaction shown in Scheme 4. The result of it is a quick exchange (in NMR time scale) of magnetic surroundings of protons at carbons C-4 and C-6.

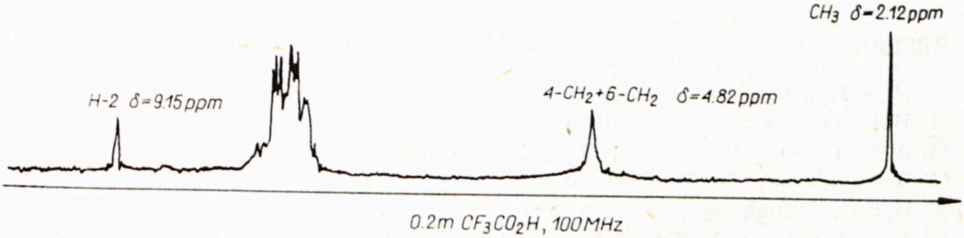
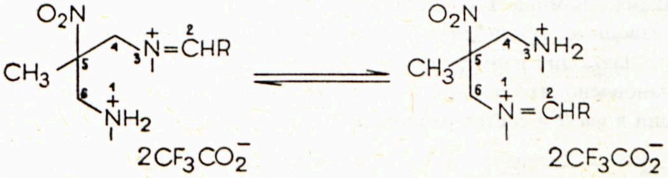


Fig. 2. ^1H NMR spectrum of **3** in CF_3COOH



Scheme 4

Experimental

The NMR spectra were measured on a Jeol JNM-MH-100 spectrometer at 31±1 °C using TMS as internal standard.

The preparation of compound **1** was described previously [1].

*Compound trans-***2**. 1.42 g of compound **1**, 0.5 ml of acetaldehyde, 1.5 ml of acetic acid, 25 ml of benzene and 3 g of anhydrous magnesium sulfate were heated at 100 °C in a sealed tube for 1.5 h. The reaction mixture was left overnight at room temperature, solid potassium carbonate was added, the inorganic precipitate filtered off, and benzene removed *in vacuo*. The oily residue was crystallized twice from ethanol. The yield was 40%, m.p. 125–127 °C.

Analysis for $C_{18}H_{21}O_2N_3$: calc: 69.4%C; 6.8% H; 13.5% N; found: 69.6% C; 6.8% H; 13.8% N.

Compound **3**. 2.84 g of compound **1**, 3 g of freshly distilled benzaldehyde, catalytic amount of *p*-toluenesulfonic acid, and 70 ml of toluene were refluxed in nitrogen atmosphere for 14 h, water being removed azeotropically. The reaction mixture was cooled, a small amount of potassium carbonate added, and the inorganic precipitate filtered off. Toluene was evaporated *in vacuo*, and the residue treated with methanol. The crystalline precipitate was filtered off, washed with methanol, and crystallized from *n*-propanol. The yield was 80%, m.p. 175–179 °C. The NMR spectrum indicates that the product contains 40% of *cis*-**3** and 60% of *trans*-**3**.

Analysis for $C_{23}H_{23}O_2N_3$: calc.: 73.9% C; 6.2% H; 11.2% N; found: 74.1% C; 6.3% H; 11.4% N.

Equilibration of trans-**2**. 0.062 g (0.2 mmole) of compound *trans*-**2** was dissolved in 1 ml of the appropriate solvent. TMS was added, the NMR spectrum recorded, the sample left for 3 days, and the spectrum recorded again.

INSTITUTE OF ORGANIC CHEMISTRY AND TECHNOLOGY, TECHNICAL UNIVERSITY, KOSZYKOWA 75, 00-661 WARSAW
(INSTYTUT CHEMII I TECHNOLOGII ORGANICZNEJ, POLITECHNIKA WARSZAWSKA)

REFERENCES

[1] H. G. Johnson, J. Am. Chem. Soc., **68**, 14 (1964).
[2] H. Piotrowska, W. Sas, T. Urbański, Roczniki Chem., **47**, 1233 (1973).
[3] A. C. Huitric, W. F. Trager, J. Org. Chem., **27**, 1926 (1962).
[4] B. Kędzierski, Ph. D. Thesis, Warsaw, 1973.
[5] H. Both, Tetrahedron, **22**, 615 (1966).
[6] A. V. Bogatskii, Y. Y. Samitov, Z. D. Bogatskii, Zh. Org. Khim., **5**, 2230 (1969).
[7] H. Piotrowska, W. Sas, T. Urbański, Bull. Acad. Polon. Sci., Sér. Sci. Chim., **25**, 519 (1977).
[8] — , — , — , Roczniki Chem., **51**, 1541 (1977).

Г. Пиотровска, В. Сас, Т. Урбаньски, **Получение и стереохимия 2-метил- и 2-фенилпроизводных 1,3-дифенил-5-метил-5-нитрогексагидропиридина**

Содержание. Реакция диамина **1** с ацетальдегидом и бензалсдегидом дала 2-метил (**2**) и 2-фенил (3) производные 1,3-дифенил-5-метил-5-нитрогексагидропиримидина. При циклизации получено только один изомер (*транс*-**2**) соединения 2 и оба возможные изомеры соединенения 3. Установлено, что *транс*-**2** подвергается спонтанической, катализованной кислотами изомеризации в *цис*-**2** и состав равновесной смеси зависит от полярности растворителя.