ROCZNIKI CHEMII
ANN. SOC. CHIM. POLONORUM
47, 1233 (1973)

# HYDROGENATION OF 5-NITRO-1,2,3,4-TETRAHYDROPYRIMIDINES *

by Hanna PIOTROWSKA, Wojciech SAS, and Tadeusz URBAŃSKI

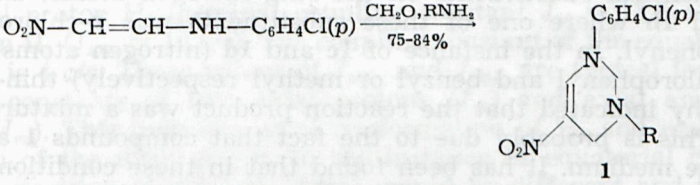
*Institute of Organic Chemistry and Technology, Polytechnical University, 00661 Warszawa*

Redukcja 1,3-dwualkilo- lub 1,3-dwuarylo-5-nitro-1,2,3,4-tetrahydropirymidyn prowadzi do powstania odpowiednich pochodnych 5-nitroheksahydropirymidyny (**3**). Widma NMR związków **3** świadczą o ekwatorialnym położeniu grupy nitrowej.

Восстановление 1,3-диалкил- или 1,3-диарил-5-нитро-1,2,3,4-тетрагидропиримидинов ведет к образованию соответствующих 5-нитрогексагидропиримидинов (**3**). Спектры ЯМР соединений **3** свидетельствуют об экваториальном положении нитро группы.

Reduction of 1,3-dialkyl- or 1,3-diaryl-5-nitro-1,2,3,4-tetrahydropyrimidines yielded the corresponding derivatives of 5-nitrohexahydropyrimidine (**3**). NMR spectra of compounds **3** indicate the equatorial position of the nitro group.

As has been shown by Dąbrowska-Urbańska, Katritzky, and Urbański [1] 1-N-(*p*-chlorophenyl)amino-2-nitroethylene [2] can readily react with formaldehyde and primary amines to yield derivatives of 5-nitro-1,2,3,4-tetrahydropyrimidine (**1**):



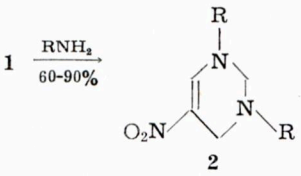

**1**

**1a** : R = $C_6H_4Cl(p)$
**1b** : R = $C_6H_5$
**1c** : R = $CH_2C_6H_5$
**1d** : R = $CH_3$

Compounds **1** easily undergo transamination when treated with an excess of the amine R-$NH_2$ to give symmetrically substituted 5-nitro-1,2,3,4-tetrahydropyrimidines (**2**):

---

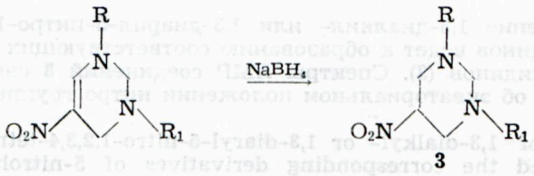
* Part CX on Chemistry of Nitroparaffins. Part CIX: Piotrowska H., Urbański T., Kmiotek I., *Roczniki Chem.*, **47**, 409 (1973).



**2a** : R = $C_6H_5$
**2b** : R = $CH_2C_6H_5$
**2c** : R = $CH_3$

The aim of this work was to investigate the reduction products of tetrahydropyrimidines **1** and **2**. We used as starting materials compounds **1a**—**1d** and **2a**—**2c**. Two of them (**1b** and **2a**) have not been described in the literature. Their structure was confirmed on the basis of elemental analysis and NMR spectra which possessed similar pattern as those described already for other of 5-nitro-1,2,3,4-tetrahydropyrimidine derivatives [1].

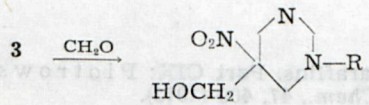
We subjected compounds **1** and **2** to reduction with the aid of sodium borohydride. This reagent is known to convert nitroolefins into corresponding nitroparaffins [3]. The reaction was carried out in ethanol at room temperature. In these conditions the double bond in compounds **1a**, **1b**, **2a**—**2c** was hydrogenated and the corresponding 1,3-disubstituted 5-nitrohexahydropyrimidines **3a**—**3c** were formed in good yields:



**3a** : R = $R_1$ = $C_6H_4Cl(p)$
**3b** : R = $C_6H_4Cl(p)$, $R_1$ = $C_6H_5$
**3c** : R = $R_1$ = $C_6H_5$
**3d** : R = $R_1$ = $CH_2C_6H_5$
**3e** : R = $R_1$ = $CH_3$

Satisfactory results were obtained from all tetrahydropyrimidines containing identical substituents on the ring nitrogen atoms, and from the compound **1b** where one of these substituents was *p*-chlorophenyl and another phenyl. In the instance of **1c** and **1d** (nitrogen atoms substituted with *p*-chlorophenyl and benzyl or methyl respectively) thin-layer chromatography indicated that the reaction product was a mixture of several species. This is probably due to the fact that compounds **1** are unstable in alkaline medium. It has been found that in these conditions they may undergo a type of "semi-disproportionation" in which transaminations occur with the amines formed by fission of the original tetrahydropyrimidine [1].

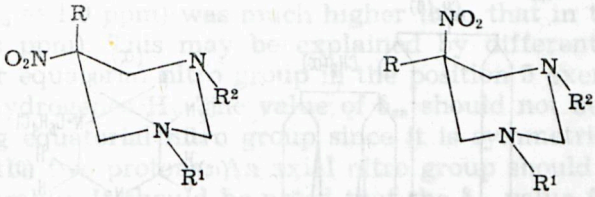
We also subjected compounds **1** and **2** to catalytic hydrogenation in the presence of platinum catalyst. Only two of them (**2b** and **2c**) gave the corresponding 5-nitrohexahydropyrimidines **3d** and **3c**. In other instances a complicated mixture of products was formed.



**4a** : R = $CH_2C_6H_5$
**4b** : R = $CH_3$

Compound **3d** has previously been prepared by splitting off formaldehyde from 1,3-dibenzyl-5-hydroxymethyl-5-nitrohexahydropyrimidine [4]. Samples obtained by both methods possessed identical properties. Compound **3e** was unstable and difficult to purify for analytical purposes. It was therefore converted into its 5-hydroxymethyl derivative **4b** by a treatment with formaldehyde in alkaline medium. Similarly **3d** was converted into **4a** [5].

The attempt to determine the stereochemistry of 5-nitrohexahydropyrimidine derivatives was previously done [4] by dipole moment measurements. The comparison of the experimental values with the dipole moments calculated for different conformations of 1,3-dialkyl-5-nitrohexahydropyrimidines suggested the chair form with the nitro group in an axial and equatorial position when in position 5 an alkyl and hydrogen was present respectively:




A. R = H
$R^1 = R^2$ = alkyl or aryl

B. R = alkyl
$R^1 = R^2$ = alkyl

Conformation of 5-nitrohexahydropyrimidine derivatives
Konformacja pochodnych 5-nitroheksahydropirymidyny

Now we measured the NMR spectra of compounds **3**. We also prepared deuterated compounds **3** (5-d-**3**). For the derivatives of 5-nitrohexahydropyrimidine the signals of protons in the positions 4 and 6 ($H_\alpha$) are instructive for the determination of the stereochemistry of compounds **3**, because their position depends on the conformation of the nitro group. Fig. 1 shows the spectrum of compound **3a** and its deuterated analogue 5-d-**3a**. In the spectrum of **3a** each of the axial protons $H_\alpha$ is coupled with the equatorial proton $H_\alpha$ (geminal coupling constant $J_{ae} = 13.5$ c/s) and with the proton $H_5$ ($J_{aH_5} = 10$ c/s). The coupling constant of the equatorial $H_\alpha$ and $H_5$ ($J_{eH_5}$) is 4 c/s. These values of $J_{aH_5}$ and $J_{eH_5}$ are typical for the vicinal coupling constants of two axial protons ($J_{aa}$) and axial and equatorial protons ($J_{ea}$). This indicates axial conformation of $H_5$ and equatorial conformation of the nitro group. In the instance of equatorial conformation of $H_5$ the position of axial $H_\alpha$ signal would be different and the coupling constant $J_{aH_5}$ would be lower [6].

The spectrum of the deuterated compound 5-d-**3a** reveals two AB systems: one of the four protons $H_\alpha$, and second of two protons $H_\beta$.

Similar results were obtained for the compounds **3b** and **3c**. In the instance of compounds **3d** and **3e** the spectra were difficult to analyze because of superimposition of the signals. However in this case the signal of $H_5$ may supply some information about the conformation of these compounds. In the spectra of all compounds **3** the signal of the proton $H_5$ is a multiplet which disappeared after deuteration. It is easily distinguishable in the spectra of **3d** and **3e**. It has the form of an almost regular septet ($H_1$ possesses a similar shape in the NMR spectrum of nitrocyclo-

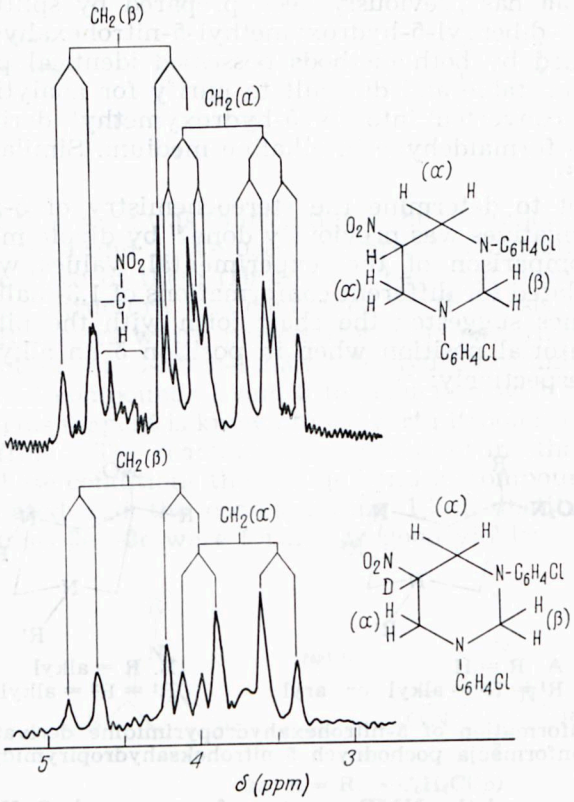



Fig. 1. NMR spectra of 1,3-di(*p*-chlorphenyl)-5-nitrohexahydropyrimidine (**3a**) and its 5-deuterated analogue

Rys. 1. Widma NMR 1,3-dwu-(*p*-chlorofenylo)-5-nitroheksahydropirymidyny (**3a**) i jej 5-deuterowanego analogu

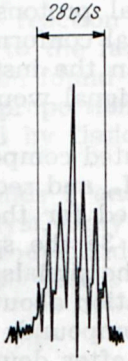



Fig. 2. Signal of proton $H_5$ of compounds **3d** and **3e**

Rys. 2. Sygnał protonu $H_5$ w związkach **3d** i **3e**

hexane [7]) at $\delta = 4.52$ ppm for **3d** and $\delta = 4.60$ ppm for **3e** (Fig. 2). Its width is 28 c/s. This value corresponds well to the values of $J_{aH_5}$ and $J_{eH_5}$ found for compounds **3a**, **3b** and **3c**.

For axial $H_5$ these coupling constants should also be similar in **3d** and **3e**, and the width of $H_5$ signal would be equal to the sum of $2J_{aa} + 2J_{ea}$ i.e. to 28 c/s. In the instance of equatorial conformation of $H_5$ its signal would be a deformed quintet of the width not exceeding 20 c/s ($2J_{ea} + 2J_{ee}$). These results suggest that the conformation of compounds **3d** and **3e** is the same as that of compounds **3a**—**3c**.

It was interesting to compare the NMR spectra of compounds **3** with 1,3,5-trialkyl-5-nitrohexahydropyrimidines containing an alkyl substituent in the position 5. For the latter the dipole moment measurements indicated the axial conformation of the nitro group [4]). This was done for 1,3-dibenzyl-5-nitrohexahydropyrimidine (**3d**) and its 5-methyl derivative (**5**). In the spectrum of **5** the relative chemical shift within the axial-equatorial pair of protons $H_\alpha$ ($\delta_{ea} = 1.0$ ppm) was much higher than that in the spectrum of **3d** ($\delta_{ea} = 0.46$ ppm). This may be explained by different deshielding effect of axial or equatorial nitro group in the position 5 exerted on axial and equatorial hydrogenes $H_\alpha$. The value of $\delta_{ea}$ should not be affected by the neighbouring equatorial nitro group since it is symmetrically located with respect to the two protons. An axial nitro group should increase the $\delta_{ea}$ value considerably. It should be noted that the $\delta_{ea}$ value found for the compound **5** is similar to that observed for 1,3-di-(2-nitrobutyl)-5-ethyl-5-nitrohexahydropyrimidine ($\delta_{ea} \approx 1$ ppm) [8]).

## EXPERIMENTAL

Compounds **1a**, **1c**, **1d**, **2b** and **2c** were prepared according to the method described by Dąbrowska-Urbańska, Katritzky, and Urbański [1]). Compound **5** was prepared according to Senkus [5]).

NMR spectra were taken on Jeol JNM-C 60H spectrometer.

### 1-*p*-Chlorophenyl-3-phenyl-5-nitro-1,2,3,4-tetrahydropyrimidine (1b)

19.8 g (0.1 mole) of 1-N-(*p*-chlorophenyl)amino-2-nitroethylene [2]), 200 cm³ of ethanol, 30 cm³ of 30% formalin and 18.6 g (0.2 mole) of aniline were alkalized with triethylamine to pH = 8 and stirred at room temperature for 10 hrs. The precipitated crystals of **1b** were filtered off and crystallized from benzene. The yield of **1b** was 29.6 g (75%), m.p. 181.5—183.5°C.

Analysis:

For $C_{16}H_{14}O_2N_3Cl$ — Calcd.: 13.3% N;
found: 13.5% N.

NMR spectrum $\delta$ ($CDCl_3$): 4.55 (s, 2H) — $H_4$, $H_4$,; 4.98 (s, 2H) — $H_2$, $H_2$,; 6.8—7.2 (m, 9H) — $C_6H_5$ and $C_6H_4Cl$, 8.25 (s, 1H) — vinyl proton.

### 1,3-Diphenyl-5-nitro-1,2,3,4-tetrahydropyrimidine (2a)

9.5 g (0.03 mole) of **1b**, 7.5 g (0.08 mole) of aniline and 60 cm³ of ethanol were refluxed to dissolve the crystals of **1b**. The solution was then left overnight at room temperature. The precipitated crude **2a** was crystallized from the methanol—benzene mixture. The yield 5.1 g (60%). M.p. 145.5—147.5°C.

Analysis:
For $C_{16}H_{15}O_2N_3$ — Calcd.: 15.0% N;
found: 15.1% N.

NMR spectrum δ ($CDCl_3$): 4.52 (s, 2H) — $H_4$, $H_{4'}$; 5.00 (s, 2H) — $H_2$, $H_{2'}$; 6.80—7.20 (m, 10H) — $C_6H_5$; 8.28 (s, 1H) — vinyl proton.

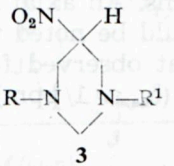
### Reduction of compounds 1 and 2 with sodium borohydride

0.005 mole of the compound **1** or **2** was suspended in 40 cm³ of ethanol and 0.6 g (0.016 mole) of $NaBH_4$ was added with stirring. The mixture was stirred for 3 hrs and then 3 cm³ of acetic acid added. The solvent was removed in vacuo, the residue treated with water, neutralized with sodium bicarbonate and extracted with chloroform. The chloroform solution was washed with water, dried over anh. $MgSO_4$ and solvent evaporated. The residual oils were then crystallized: **3a** from 96% ethanol, **3b**, **3c** and **3d** from ethanol — ether mixture. Compound **3e** was unstable and its 5-hydroxymethyl derivative was analyzed. The yield of products are collected in Table 1, their properties in Table 2.

Table 1 — Tablica 1

Yield of hydrogenation of compounds **1** and **2**

Wydajność uwodornienia związków **1** i **2**



**3**

| Compound No Nr związku | R | $R^1$ | Yield — Wydajność, % | |
|---|---|---|---|---|
| | | | $NaBH_4$ | $H_2$/Pt |
| **3a** | $C_6H_4Cl$ | $C_6H_4Cl$ | 75—80 | — |
| **3b** | $C_6H_4Cl$ | $C_6H_5$ | 60—65 | — |
| **3c** | $C_6H_5$ | $C_6H_5$ | 60—65 | — |
| **3d** | $C_6H_5CH_2$ | $C_6H_5CH_2$ | 70—75 | 70—75 |
| **3e** | $CH_3$ | $CH_3$ | 60—65 | 70—75 |

### Catalytic hydrogenation of compounds 2b and 2c

0.005 mole of **2b** or **2c** and 70 mg of Adams catalyst were suspended in 80 cm³ of ethyl acetate and hydrogenated under normal pressure until 0.005 mole of hydrogen was consumed (2—3 hrs). The catalyst was filtered off, the solvent evaporated in vacuo. The residue was dissolved in carbon tetrachloride and the unchanged **2b** or **2c** filtered off. The solvent was evaporated and the product purified as described above. The yields are given in Table 1.

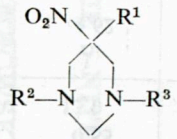
### Reaction of compounds 3d and 3e with formaldehyde

0.2 g of **3d** or 0.1 g of **3e**, 0.5 cm³ of 30% formalin, a small amount of potassium carbonate and 5 cm³ of ethanol were refluxed for 3 hrs and left overnight. The solvent was evaporated, compound **4a** was crystallized from benzene, m.p. 136.5—138.5°C (lit.[5]: 121°C) compound **4b** — from ethanol, m.p. 133—135°C (lit.[9]: 124°C). The yields were 60—70%.

Table 2 — Tablica 2

Properties of compounds **3**, **4** and **5**

Własności związków **3**, **4** i **5**



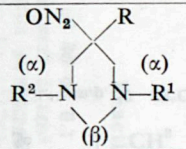
| Compound Nr związku | $R^1$ | $R^2$ | $R^3$ | M.p. T.t. °C | Empirical formula Wzór sumaryczny | Analysis — Analiza, % | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Calcd. — obliczono | | | Found — otrzymano | | |
| | | | | | | C | H | N | C | H | N |
| **3a** | H | $C_6H_4Cl$ | $C_6H_4Cl$ | 111.5—112.5 | $C_{16}H_{15}N_3O_2Cl_2$ | 54.5 | 4.3 | 11.9 | 54.7 | 4.4 | 12.0 |
| **3b** | H | $C_6H_4Cl$ | $C_6H_5$ | 78—80 | $C_{16}H_{16}N_3O_2Cl$ | 60.4 | 5.1 | 13.2 | 60.6 | 5.2 | 13.3 |
| **3c** | H | $C_6H_5$ | $C_6H_5$ | 65—67 | $C_{16}H_{17}N_3O_2$ | 67.8 | 6.1 | 14.8 | 67.9 | 6.3 | 14.7 |
| **3d**[a] | H | $C_6H_5CH_2$ | $C_6H_5CH_2$ | 63—64.5 | — | — | — | — | — | — | — |
| **4a**[b] | $CH_2OH$ | $CH_3$ | $CH_3$ | 136.5—138.5 | $C_7H_{15}N_3O_3$ | 44.4 | 8.0 | 22.2 | 44.6 | 8.2 | 22.4 |
| **5**[c] | $CH_3$ | $C_6H_5CH_2$ | $C_6H_5CH_2$ | 115.5—116.5 | $C_{19}H_{23}N_3O_2$ | — | — | 12.9 | — | — | 13.1 |

[a] Lit.[4]: m.p. 57—58°C. [b] Lit.[5]: m.p.121°C. [c] Lit.[5]: m.p. 113.5°C.

Table 3 — Tablica 3

NMR spectra of 5-nitrohexahydropyrimidine derivatives

Widma NMR pochodnych 5-nitroheksahydropirymidyny




| | R | Ha | Ha | Ha | Da | Da | $CH_3$a | $CH_2OH$b | $CH_2OH$b |
|---|---|---|---|---|---|---|---|---|---|
| | $R^1$ | $C_6H_4Cl$ | $C_6H_4Cl$ | $C_6H_5$ | $C_6H_5CH_2$ | $CH_3$ | $C_6H_5CH_2$ | $C_6H_5CH_2$ | $CH_3$ |
| | $R^2$ | $C_6H_4Cl$ | $C_6H_5$ | $C_6H_5$ | $C_6H_5CH_2$ | $CH_3$ | $C_6H_5CH_2$ | $C_6H_5CH_2$ | $CH_3$ |
| α-$CH_2$ | a | 3.57 | 3.57 | 3.51 | 2.80 | 2.71 | 2.40 | 2.87 | 2.83 |
| | e | 4.02 | 4.15 | 4.17 | 3.26 | 3.24 | 3.40 | 3.15 | 3.08 |
| | ea | 0.55 | 0.58 | 0.66 | 0.46 | 0.53 | 1.00 | 0.28 | 0.25 |
| | $J_{ea}$ | 13.5 | 13.5 | 12.0 | 12.0 | 12.0 | 13.5 | 13.5 | 12.0 |
| | $J_{aH_5}$ | 10.0 | 10.0 | 10.0 | | | | | |
| | $J_{eH_5}$ | 4.0 | 4.0 | 5.0 | | | | | |
| β-$CH_2$ | a | 4.17 | 4.17 | 4.14 | 3.02 | 2.86 | 2.90 | 3.12 | |
| | e | 4.83 | 4.93 | 4.99 | 3.39 | 3.29 | 3.27 | 3.25 | |
| | ea | 0.66 | 0.76 | 0.85 | 0.37 | 0.43 | 0.37 | 0.13 | 3.03 |
| | $J_{ea}$ | 12.0 | 13.0 | 13.0 | 10.5 | 10.5 | 10.5 | 10.0 | |
| R | | 4.60 | 4.68 | 4.62 | | | 1.45 | $CH_2$ 4.00 OH 2.4 | $CH_2$ 6.08 OH 3.6 |
| $R^1$ and $R^2$ | | 6.81—7.34 (m) | 6.86—7.32 (m) | 6.80—7.32 (m) | $CH_2$ 3.54 $C_6H_5$ 7.08 | 2.33 | $CH_2$ 3.45 $C_6H_5$ 7.08 | $CH_2$ 3.55 $C_6H_5$ 7.08 | 2.33 |

[1240]

aIn $CCl_4$. bIn $CDCl_3$.

**Deuteration of compounds 3a, 3d, 3e**

0.1 g of the corresponding compound **3**, 10 $cm^3$ of dry tetrahydrofuran, 3 $cm^3$ of deuterium oxide and a small amount of potassium carbonate were left at room temperature for 36 hrs. Tetrahydrofuran was evaporated in vacuo, and the residue extracted with benzene. The benzene solution was dried over anh. $MgSO_4$, benzene evaporated. The residual oil crystallized after some time. The NMR spectra of the deuterated products did not show any presence of the $H_5$ proton.

*Received November 30th, 1972.*

REFERENCES

1. Dąbrowska-Urbańska H., Katritzky A. R., Urbański T., *Tetrahedron*, **25**, 1617 (1969).
2. Meister W., *Ber.*, **40**, 3435 (1907).
3. Hassner A., Heathcock C., *J. Org. Chem.*, **29**, 1350 (1964).
4. Piotrowska H., Urbański T., *J. Chem. Soc.*, **1962**, 1942.
5. Senkus M., *J. Am. Chem. Soc.*, **68**, 1611 (1946).
6. Gürne D., Stefaniak L., Urbański T., Witanowski M., *Tetrahedron*, **20**, Suppl. 1, 211 (1964).
7. Hofman W., Stefaniak L., Urbański T., Witanowski M., *J. Am. Chem. Soc.*, **86**, 554 (1964).
8. Kamieński B., Koliński R., Urbański T., Witanowski M., *Tetrahedron Letters*, **16**, 1281 (1969).
9. Malinowski S., Urbański T., *Roczniki Chem.*, **25**, 183 (1951).

## UWODORNIENIE 5-NITRO-1,2,3,4-TETRAHYDROPIRYMIDYN

H. PIOTROWSKA, W. SAS i T. URBAŃSKI

*Instytut Chemii i Technologii Organicznej Politechniki, 00661 Warszawa*

Serię pochodnych 5-nitro-1,2,3,4-tetrahydropirymidyny zawierających w położeniach 1,3 dwa podstawniki *p*-chlorofenylowe (**1a**), fenylowe (**2a**), benzylowe (**2b**), metylowe (**2c**) lub w położeniu 1 resztę *p*-chlorofenylową a w położeniu 3 fenyl (**1b**), benzyl (**1c**) lub metyl (**1d**) poddano redukcji $NaBH_4$ i redukcji katalitycznej w obecności katalizatora platynowego. W przypadku redukcji wodorkiem wszystkie związki zawierające jednakowe podstawniki przy atomach azotu pierścienia (**1a**, **2a**—**c**) oraz związek **1b** zostały przeprowadzone z dobrymi wydajnościami w odpowiednie pochodne 5-nitro-heksahydropirymidyny (**3**). Katalityczna redukcja związków **2b** i **2c** dała analogiczne produkty. W pozostałych przypadkach powstawały złożone mieszaniny związków. Wydajności poszczególnych reakcji zebrano w tablicy 1, a własności otrzymanych produktów — w tablicy 2.

Zbadano widma NMR związków **3** oraz ich pochodnych deuterowanych w pozycji 5 (5-d-**3**). Wyniki pomiarów zebrano w tablicy 3.

W widmach związków **3a**—**c** (rys. 1) wartości stałych sprzężenia aksjalnych i ekwatorialnych protonów w położeniach 4 i 6 ($H_n$) z protonem $H_5$ są typowe dla wicynalnych stałych sprzężenia dwóch protonów aksjalnych lub protonu ekwatorialnego i aksjalnego. W widmach związków **3d** i **3e** wyraźnie widoczny sygnał protonu $H_5$ jest prawie regularnym septetem (rys. 2) o szerokości 28 c/s, która odpowiada stałym sprzężenia protonów $H_n$ i $H_5$ znalezionym dla związków **3a**—**c**. Wyniki te pozwalają przypisać grupie nitrowej w związkach **3** położenie ekwatorialne (wzory, str. 1235).