CHEMICAL TRANSFORMATIONS OF NITROMETHYL GROUP IN 3,5-DICYANO-1,4,4,6-TETRAMETHYL-2-NITROMETHYL--1,4-DIHYDROPYRIDINE*

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Chemical transformations have been studied of nitromethyl group in 3,5-dicyano-1,4,4,6-tetramethyl-2-nitromethyl-1,4-dihydropyridine (*I*) brought about by action of acetic acid and/or acetic anhydride, diazomethane, and phosphorus trichloride and giving also the products *VIII* and *IX* of intramolecular reaction with the neighbouring cyano group. Spectral characteristics of the synthetized compounds and their splitting by electron impact in mass spectrometer are given, and mechanism of the individual transformations is discussed.

Polysubstituted 3,5-dicyano-1,4-dihydropyridines contain an electron-donor conjugated system[1] resembling aromatic system by its effect in some cases. As a nitromethyl group connected with aromatic skeleton[2] can be transformed into other functional groups, *i.e.*, carboxylic[3], aldehydic[4-8], aldoxime[9-14], and nitrile[15-17], we were interested in the problem how this group would behave when connected with the dihydropyridine nucleus. For transformation of nitromethyl group into carboxylic group the Nef reaction is often used[3] which consists in hydrolysis of the respective nitronic acid; application of this approach is limited[18] by length of life of the latter. We found the nitronic acid *II* formed by transformation of nitro compound *I* under the conditions[2] of the Nef reaction to be very unstable, and we always isolated from the reaction mixture only the starting nitro compound *I* instead of the expected carboxylic acid *III*. After this failure of the preparation of carboxylic acid *III* we tried to prepare its nitrile *IV*. Transformation of nitromethyl group into nitrile group can be carried out by several ways[15-17]. The method[15] using reaction of primary nitro compounds with hexamethylphosphortriamide in 1,2-dichloroethane was applied to compound *I* without success, the starting nitro compound *I* only being isolated from the final reaction mixture. Another method[16] using reaction of phosphorus trichloride with primary nitro compounds in pyridine was applied to give 58% yellow compound $C_{12}H_{12}N_4$ which was assigned structure *IV* on the basis of spectral data. ^{1}H NMR spectrum of this compound exhibits three signals

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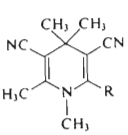
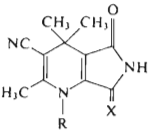


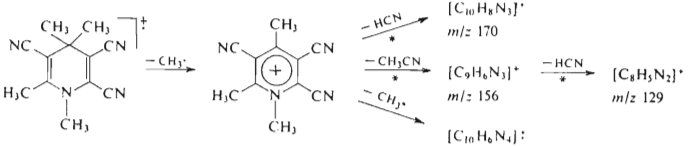


I, R = CH_2NO_2
II, R = CH=N(O)OH
III, R = COOH
IV, R = CN

V, R = CH_3
VI, R = CH=N(O)OCH_3
VII, R = $CONHCOCH_3$

VIII, X = O, R = CH_3
IX, X = NOH, R = CH_3
X, X = NOH, R = $CH_2C_6H_5$

of four methyl groups, and its IR spectrum contains, besides the vibrational modes usually found in dihydropyridine derivatives, bands of valence vibrations of two types of nitrile groups. Comparison with IR spectrum of compound *V* reveals that compound *IV* differs by the presence of a further nitrile group. Scheme 1 represents domi-



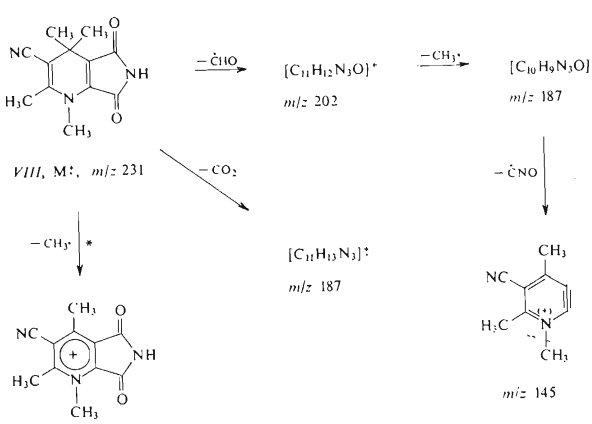
IV, M^+, *m/z* 212 *m/z* 197

SCHEME 1

nant fragmentation of compound *IV* by electron impact of 70 eV energy in mass spectrometer. The most intensive ion *m/z* 197 is formed by splitting off of methyl radical from molecular ion, which is a typical splitting of 4,4-disubstituted 1,4-dihydropyridine derivatives[19]. Further significant ions are formed from the main ion *m/z* 197 by splitting off hydrogen cyanide (*m/z* 170), methyl cyanide (*m/z* 156) or methyl radical (*m/z* 182). Formation of the ions *m/z* 170 and *m/z* 156 by the suggested way was confirmed by finding metastable ions at *m/z* 147·2 and 124·1, and similarly was confirmed formation of ion *m/z* 129 from ion *m/z* 156 by splitting off of hydrogen cyanide ($m^* = 107{\cdot}0m/z$).

Primary nitro compounds can be transformed into aldoximes by several methods[9–14]. One of them makes use the decomposition[18] of esters of nitronic acids which can be prepared[14] by reaction of primary nitro compound with diazomethane. We applied this procedure[14] to nitro compound *I* and isolated chromatographically

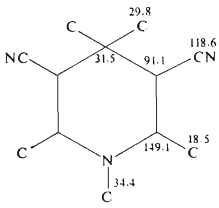
two products from the reaction mixture. One of them was a red substance $C_{12}H_{13}.N_3O_2$ (yield 22%). On the basis of spectral data this compound was assigned the structure of 5-cyano-1,4,4,6-tetramethyl-1,4-dihydropyridine-2,3-dicarboximide (*VIII*) ^{1}H NMR spectrum shows the presence of two equivalent and two non-equivalent methyl groups and one N—H group. In IR spectrum we found characteristical absorption bands of C—H bonds, dihydropyridine skeleton, nitrile group, and two carbonyl groups. The suggested structure *VIII* also agrees with analysis of the mass spectrum (Scheme 2). The most intensive ion *m/z* 216 is formed by aromatization



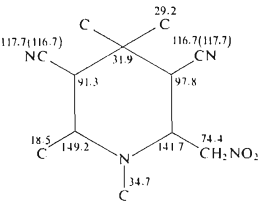
SCHEME 2

of molecular ion by splitting off of methyl radical. This typical splitting of 4,4-disubstituted 1,4-dihydropyridine derivatives[19] is also confirmed by the presence of metastable ion at 202·2. Further fragments are formed by the splitting typical of dicarboxylic acid imides[20,21]. Another confirmation of the suggested structure was provided by analysis of the ^{13}C NMR spectrum of compound *VIII* confronted with analogous spectra of compounds *I* and *V*. Assignment of the ^{13}C NMR signals to individual carbon atoms in molecules of compounds *I*, *V*, *VIII* (carried out on the basis of published data[22]) is given in Fig. 1. The spectrum of compound *VIII* contains four signals of four primary carbon atoms and eight signals of eight quaternary carbon atoms. Obviously the lowest chemical shifts (about 18 ppm) are those due to signals of methyl

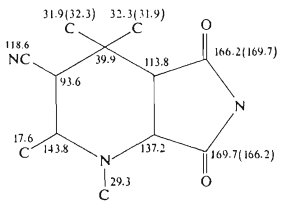
groups at 2 or 6 positions of all the three compounds (*I*, *V*, *VIII*). The 4,4-geminal methyl groups have chemical shift in the region 29–32 ppm and exhibit a single signal in compounds *I* and *V* and two slightly resolved signals in compound *VIII*. The methyl group at nitrogen atom in compounds *I* and *V* gives a signal in the region about 34·5 ppm in contrast to compound *VIII* whose corresponding signal has a smaller chemical shift (29·3 ppm) due to changed anisotropy of the 2 substituent. The signal at 74·4 ppm of the nitro compound *I* belongs unambiguously to methylene carbon atom at 2 position. Quaternary carbon atom at 4 position (forming single bonds only) has the chemical shift in the region 30–40 ppm in all the three compounds (*I*, *V*, *VIII*). Signals of nitrile groups are found[22] in the region 113–119 ppm in accordance with the assignment in Fig. 1. Also carbonyl carbon atoms of compound *VIII* show the expected[22] value of chemical shift at 166–170 ppm and are mutually interchangeable. The signals of 2- and 6-carbon atoms of 1,4-dihydropyridine nucleus exhibit a higher chemical shift than those of 3- and 5-carbon atoms, which agrees with electron distribution at double bonds.



I



V

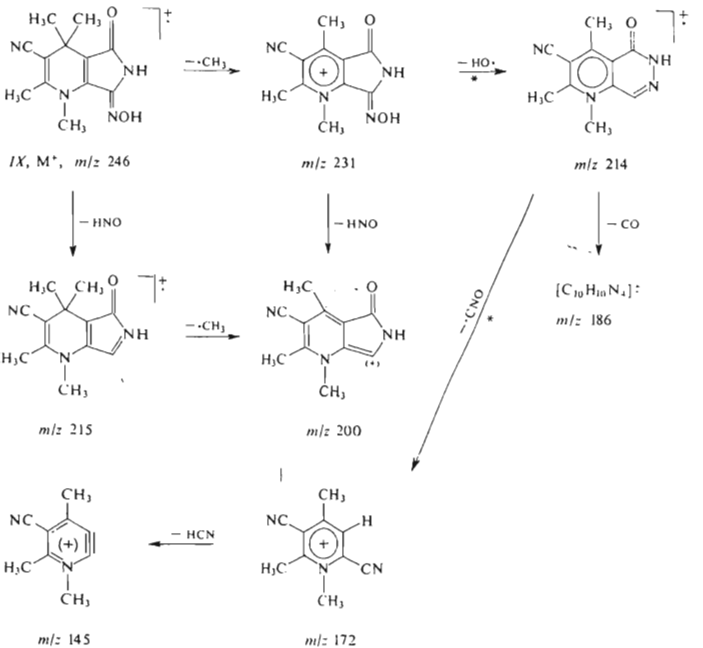


VIII

FIG. 1

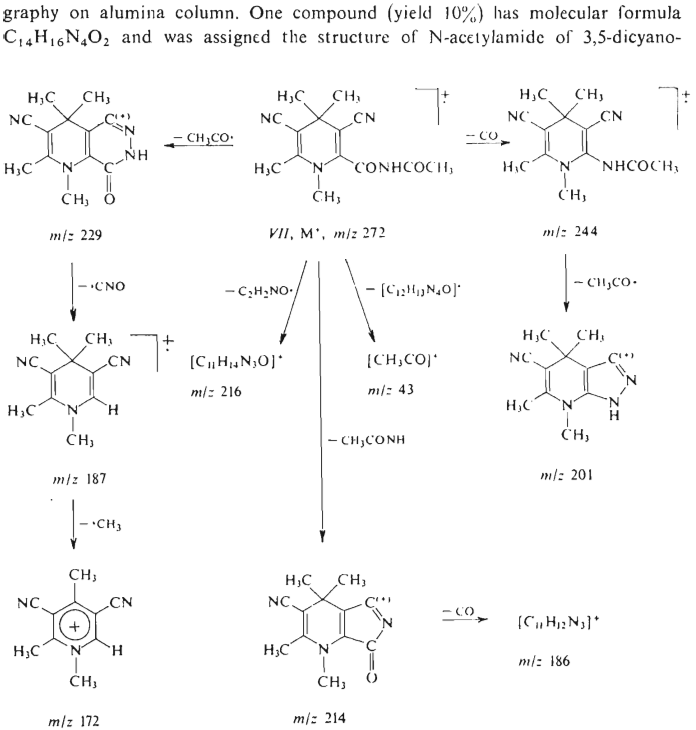
^{13}C NMR chemical shifts (ppm) in spectra of compounds *I*, *V*, *VIII* in hexadeuteriodimethyl sulphoxide (the values of chemical shifts given in brackets have mutually interchangeable assignments)

The other product was a yellow compound $C_{12}H_{14}N_4O_2$ (yield 38%). Comparison of ^{1}H NMR and IR spectra reveals structural similarity of this product to the oximino derivative *X* isolated[23] after nitration of 1-benzyl-3,5-dicyano-2,4,4,6-tetramethyl--1,4-dihydropyridine. The structure of monooxime of 5-cyano-1,4,4,6-tetramethyl--1,4-dihydropyridine-2,4-dicarboximide (*IX*) suggested for this product corresponds to the spectral characteristics and was confirmed by analysis of the mass spectrum. Scheme 3 shows the dominant fragmentation of compound *IX* by electron impact of 70 eV energy. The most intensive is the ion *m/z* 231 formed by typical[19] aromatization of molecular ion. Other characteristical fragmenations are: splitting off of nitrous acid from ions *m/z* 246 and *m/z* 231, splitting off of hydroxyl radical from ion *m/z* 231, and splitting off of CNO radical from ion *m/z* 214; for the last two splitting meta-



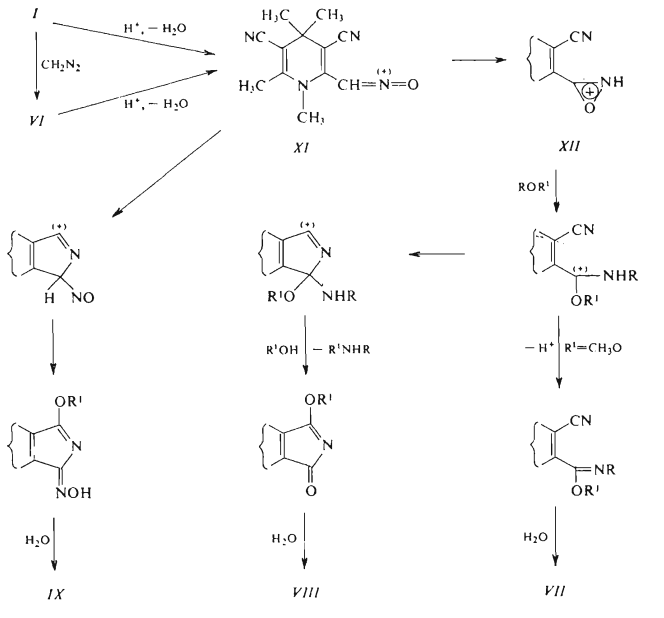
SCHEME 3

stable ions were found at 198·3 and 138·2. As the nitro compound *I* is synthetized by nitration of dihydropyridine *V* in acetic acid or acetanhydride medium, we studied also transformations of the nitro compound *I* during heating in the presence of these substances. From the reaction mixture after heating the nitro compound *I* in glacial acetic acid two products were isolated chromatographically: 68% imide *VIII* and 18% imidoxime *IX*. Heating of *I* with 80% acetic acid produces imidoxime *IX* (80%), whereas the heating in a mixture of acetic acid and acetanhydride with exclusion of atmospheric moisture gave only the imide *VIII* (85%). The reaction carried out in neat acetanhydride gave a mixture separable into two compounds by chromatography on alumina column. One compound (yield 10%) has molecular formula $C_{14}H_{16}N_4O_2$ and was assigned the structure of N-acetylamide of 3,5-dicyano-



SCHEME 4

-1,4,4,6-tetramethyl-1,4-dihydropyridine-2-carboxylic acid (*VII*) on the basis of spectral data. Its ^{1}H NMR spectrum shows the presence of two equivalent and three non-equivalent methyl groups and one N—H group. In IR spectrum of compound *VII* bands of stretching vibrations of N—H, C—H, and C≡N bonds, of two carbonyl groups and dihydropyridine skeleton were found. Scheme 4 interprets dominant fragmentation of compound *VII* by the electron impact. Intensive fragments *m/z* 229 and *m/z* 43 show the presence of acetyl group in molecule *VII*. Also other fragments *m/z* 244, 214, 216, 201, and 186 indicate the presence of N-acetylcarboxamide group in molecule of the compound *VII*. The most intensive fragment *m/z* 187 is formed probably from the ion *m/z* 229 by splitting off of CNO· group, and it is aromatized by splitting off of methyl radical to give the ion *m/z* 172. The other



R = CH_3O, R^1 = H or R

SCHEME 5

compound with molecular formula $C_{12}H_{13}N_3O_2$ isolated in the yield 33% was identified as the imide *VIII*.

Scheme 5 suggests a mechanism of formation of the compounds *VII*, *VIII*, and *IX* by the above-described reactions. The first step of the reaction of *I* with diazomethane is formation[14] of methyl ester of nitronic acid *VI*; its presence in the reaction mixture was proved by means of ^{1}H NMR spectrum. The consideration of the mentioned mechanism uses the available findings about similar transformations of primary nitro compounds (see ref.[24] and the references cited therein). Isomeric cation *XI* and *XII* are suggested to be the key reactive intermediates, the former can be a precursor of imidoxime *IX*, and the latter can lead to two further isolated products *VII* and *VIII*. An alternative source of imide *VIII* could be also cyclization of the carboxylic acid *III* formed by the mechanism postulated in ref.[24].

EXPERIMENTAL

The melting points were measured with a Boetius apparatus; the temperature data are not corrected. The IR spectra were measured in chloroform (the compound *IX* by the KBr technique) using a Perkin–Elmer 325 spectrophotometer. The ^{1}H NMR spectra were measured in deuteriochloroform (compound *IX* in hexadeuteriodimethyl sulphoxide) using a Varian XL 100 apparatus (100 MHz), the ^{13}C NMR spectra were measured in hexadeuteriodimethyl sulphoxide using a Tesla BS 567 apparatus (100 MHz) with tetramethylsilane as internal standard ($\delta = 0$ ppm) in both the cases. The mass spectra were measured with an LKB 9000 spectrometer (direct inlet, 70 eV). 3,5-Dicyano-1,4,4,6-tetramethyl-2-nitromethyl-1,4-dihydropyridine (*I*) was prepared by nitration[23] of 3,5-dicyano-1,2,4,4,6-pentamethyl-1,4-dihydropyridine (*V*) in acetanhydride, and it melted at 150–152°C (ref.[23] m.p. 149–152°C).

Reaction of Nitro Compound *I* with Phosphorus Trichloride

Mixture of 1 g (4 mmol) nitro compound *I* and 0·4 g (4 mmol) phosphorus trichloride in 10 ml pyridine was heated at 70°C (reflux condenser, drying tube with calcium chloride) 1·5 h. The mixture was added to 70 ml diluted hydrochloric acid (1 : 1) and extracted with 3 × 50 ml chloroform. The combined extracts were washed with water (3 × 50 ml), dried with anhydrous magnesium sulphate, and evaporated to give 0·5 g (58%) compound *IV*, m.p. 107°C (ethanol). For $C_{12}H_{12}N_4$ (212·2) calculated: 67·92% C, 5·66% H, 26·42% N; found: 67·92% C, 5·82% H, 26·26% N. ^{1}H NMR spectrum (C^2HCl_3), δ (ppm): 1·46 (s, $(CH_3)_2$), 2·24 (s, CH_3), 3·36 (s, N—CH_3). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 015 w, 2 980 m, 2 930 w (C—H); 2 237 w, 2 219 s (C≡N); 1 641 s, 1 577 s (dihydropyridine skeleton); 1 381 s, 1 399 s (C—H).

Reaction of Nitro Compound *I* with Diazomethane

The solution of diazomethane in ether prepared from 4·1 g (40 mmol) N-nitrosomethylurea was added with stirring to a suspension of 2 g (8 mmol) nitro compound *I* in 150 ml ether. After dissolution of *I* (about 10 h) the solution was allowed to evaporate. The obtained yellow solid (2·3 g) turned red when recrystallized from ethanol. The mixture (1·2 g) was submitted to column chromatography (Silpearl) with chloroform as eluent to give 0·263 g (22%) compound *VIII*, m.p. 229–231°C (tetrachloromethane). For $C_{12}H_{13}N_3O_2$ (231·2) calculated: 62·34% C, 5·63% H 18·18% N; found: 62·42% C, 5·83% H, 18·22% N. ^{1}H NMR spectrum (C^2HCl_3), δ (ppm)

1·56 (s, $(CH_3)_2$), 2·24 (s, CH_3), 3·51 (s, N—CH_3), 7·74 (s, NH). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 445 m (N—H); 3 030 i, 3 010 i, 2 975 m, 2 940 i (C—H); 2 210 m (C≡N); 1 776 s, 1 730 s (C=O); 1 668 s, 1 580 m (dihydropyridine skeleton); 1 413 m, 1 356 s, 1 323 s (C—H). Further elution with chloroform gave 452 mg compound *IX*, m.p. 266—268°C (38%). For $C_{12}H_{14}N_4O_2$ (246·2) calculated: 58·54% C, 5·69% H, 22·76% N; found: 58·53% C, 5·97% H, 22·63% N. ^{1}H NMR spectrum (hexadeuteriodimethyl sulphoxide), δ (ppm): 1·49 (s, $(CH_3)_2$), 2·16 (s, CH_3), 3·43 (s, N—CH_3). IR spectrum (KBr), $\tilde{\nu}_{max}$ (cm^{-1}): 3 310 s, 3 281 i (N—H, O—H); 2 995 s, 2 978 s, 2 930 s (C—H); 2 203 s (C≡N); 1 725 s (C=O); 1 708 i (C=N); 1 649 s, 1 582 s (dihydropyridine skeleton), 1 415 s, 1 334 s, 1 278 s (C—H). This reaction was repeated with 0·2 g nitro compound *I*. After dissolution of *I*, ether was distilled off in vacuum at 20°C. The obtained solid residue was dissolved in deuteriochloroform, and its ^{1}H NMR spectrum was measured which confirmed the presence of methyl ester of nitronic acid *VI* besides its decomposition products *VIII* and *IX*. ^{1}H NMR spectrum (C^2HCl_3), δ (ppm): 1·40 (s, $(CH_3)_2$), 2·27 (s, CH_3), 3·17 (s, N—CH_3), 3·83 (s, O—CH_3), 6·46 (s, N=C—H).

Thermal Decomposition of Nitro Compound *I* in Glacial Acetic Acid

Mixture of 1 g (4 mmol) nitro compound *I* and 10 ml glacial acetic acid was refluxed 10 h (until disappearance of *I*; TLC, Silufol). The mixture was diluted with 50 ml water and extracted with 3 × 30 ml chloroform. The combined extracts were washed with water, dried with anhydrous magnesium sulphate, and evaporated to give 0·87 g oil which, on chromatography (alumina column), gave 0·59 g (68%) compound *VIII*, m.p. 229—231°C, and 0·16 g (18%) compound *IX*, m.p. 266—268°C.

In 80% acetic acid: Mixture of 1 g (4 mmol) nitro compound *I* and 20 ml 80% acetic acid was refluxed 8 h (until disappearance of *I*; TLC, Silufol). Compound *IX* precipitated on cooling (0·6 g), and further portion (0·2 g) was obtained by dilution of the mixture with 100 ml water and filtration of the separated crystals. Total yield 0·8 g (80%) compound *IX*, m.p. 267—268°C (ethanol).

In mixture of acetic acid and acetanhydride: Mixture of 1 g (4 mmol) nitro compound *I*, 10 ml glacial acetic acid and 10 ml acetanhydride was refluxed with exclusion of atmospheric moisture 8 h (until disappearance of *I*; TLC, Silufol). Compound *VIII* (0·6 g red crystals) precipitated on cooling, and a further portion (0·2 g) was obtained by dilution of the mixture with 100 ml water. Total yield 0·8 g (85%) compound *VIII*, m.p. 229—231°C (tetrachloromethane).

Attempt at Transformation of Compound *IX* into Imide *VIII*

50 mg compound *V* was heated with 5 ml acetic acid or 5 ml 96% ethanol under reflux 10 h. TLC showed no detectable amounts of imide *VIII*, in both the cases the reaction mixture only contained the starting monooxime *IX*.

Reaction of Nitro Compound *I* with Acetanhydride

0·5 g (2 mmol) nitro compound *I* in 20 ml acetanhydride was refluxed 12 h and poured into 100 ml cold water. After extraction with 3 × 30 ml chloroform, the combined extracts were washed with 2 × 30 ml saturated sodium hydrogencarbonate solution, with 50 ml water, and dried with anhydrous magnesium sulphate. Removal of the solvent by distillation gave 0·45 g red sirupy product which was submitted to chromatography on alumina column. Elution with 2% ethanol solution in chloroform gave 0·045 g (10%) compound *VII*, m.p. 197—199°C. For $C_{14}H_{16}N_4O_2$ (272·2) calculated: 61·76% C, 5·88% H, 20·59% N; found: 61·82% C, 5·85% H,

20·61% N. ^{1}H NMR spectrum (C^2HCl_3), δ (ppm): 1·38 (s, $(CH_3)_2$), 2·16 (s, CH_3), 2·25 (s, CH_3), 3·10 (s, N—CH_3), 8·70 (s, N—H). IR spectrum (KBr), $\tilde{\nu}_{max}$ (cm^{-1}): 3 405 w (N—H); 3 000 w, 2 290 w (C—H); 2 200 s (C≡N); 1 718 m, 1 700 i (C=O); 1 650 s, 1 582 m (dihydropyridine skeleton), 1 390 m, 1 386 s, 1 372 s, 1 370 s (C—H). Further elution with 2% ethanol solution in chloroform gave 150 mg (33%) compound *VIII*, m.p. 229—231°C.

Attempt at the Nef Reaction of Compound *I*

Solution of 0·3 g (1·2 mmol) nitro compound *I* in 2·7 ml 2M-NaOH was added drop by drop with cooling to 3·6 ml 3·5M-H_2SO_4. After 15 min the mixture was worked up to give 0·25 g of the starting nitro compound *I*.

Attempt at Reaction of Nitro Compound *I* with Hexamethylphosphortriamide

Solution of 0·5 g (2 mmol) nitro compound *I* in 10 ml 1,2-dichloroethane was stirred and treated with 0·85 g (5 mmol) dry hexamethylphosphortriamide. The mixture was refluxed under nitrogen 6 h and worked up to give 0·5 g *I*.

Mass Spectra of Compounds *IV*, *VII*, *VIII*, and *IX*, *m/z* (relative intensity, %)

IV: 212 (6), 198 (16), 197 (100), 182 (4), 181 (2), 170 (2), 156 (5), 155 (2), 154 (3), 129 (7), 128 (3), 127 (2), 102 (6), 77 (3), 76 (4), 67 (3), 66 (2), 65 (2), 64 (5), 63 (2), 57 (3), 56 (4), 55 (3), 52 (3), 51 (3), 43 (4), 42 (4), 41 (4), 39 (5), 29 (4), 28 (4); m*: 147·2, 124·1, 107·0.

VII: 272 (0·5), 244 (15) 230 (10), 229 (58), 216 (5), 214 (5), 201 (5), 188 (40), 187 (100), 186 (10), 172 (18), 158 (8), 149 (5), 144 (9), 137 (8), 97 (6), 83 (7), 81 (7), 71 (7), 69 (11), 57 (12), 56 (22), 55 (11), 43 (61), 42 (10), 41 (11), 39 (7), 29 (7), 28 (17), 27 (7).

VIII: 231 (5), 217 (15), 215 (100), 202 (2), 187 (5), 145 (14), 130 (2), 104 (2), 102 (2), 94 (2), 91 (3), 80 (2), 77 (4), 66 (2), 65 (3), 64 (2), 57 (3), 56 (4), 53 (2), 52 (2), 51 (3), 43 (3), 42 (4), 41 (3), 39 (5), 28 (2), 27 (3); m*: 202·0.

IX: 246 (8), 232 (7), 231 (100), 216 (6), 215 (24), 214 (8), 186 (18), 172 (15), 171 (6), 158 (5), 157 (5), 145 (17), 129 (5), 102 (5), 78 (6), 58 (5), 56 (10), 43 (7), 42 (8), 41 (5), 39 (7), 36 (5), 28 (6), 27 (5); m*: 198·3, 161·7, 138·2.

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