REACTION OF 3,5-DICYANO-2,4,4,6-TETRAMETHYL--1,4-DIHYDROPYRIDINE WITH NITRIC ACID

Antonín KURFÜRST and Josef KUTHAN

Department of Organic Chemistry,
Institute of Chemical Technology, 166 28 Prague 6

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Reaction of the title compound *I* with nitric acid in acetic acid afforded a mixture of products which on column chromatography afforded 5-cyano-4,4,6-trimethyl-2-nitromethylene-3-oxo--1,2,3,4-tetrahydropyridine (*II*), (*Z*)-5-(1-acetoxy-2-nitrovinyl)-3,5-dicyano-4,4-dimethyl-2-pyrazoline (*III*) and 3-acetoxy-3-cyano-4,4,6-trimethyl-5-oxo-2,3,4,5-tetrahydropyridazine (*IV*). Reaction of *I* with nitrating mixture in chloroform gave only the compound *II*. The probable mechanism of formation of compounds *II*, *III* and *IV*, together with their ^{1}H NMR, ^{13}C NMR, IR and mass spectra, is discussed.

Reaction of 1-substituted 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridines with nitric acid in acetic acid or acetic anhydride affords[1,2] products substituted at the methyl groups in position 2 or 6. Similarly, polysubstituted 3,5-dicyano-1,4-dihydropyridines react[3,4] with bromine to give 2,6-bis(bromomethyl) or 2,6-bis(dibromomethyl) derivatives. It was of interest whether the reaction, published[1,2] for 1-substituted 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridines and nitric acid, could be of a more general character and take place also with the 1-unsubstituted derivative *I*.

Reaction of the 1,4-dihydropyridine derivative *I* with fuming nitric acid in acetic acid afforded a mixture of products from which four principal components were isolated by chromatography on a silica gel column.

The first fraction gave a red compound of composition $C_{10}H_{11}N_3O_3$ in 5% yield. Its ^{1}H NMR spectrum showed two equivalent and one non-equivalent methyl groups, one olefinic hydrogen and one NH group. IR spectrum displayed vibrations due to C—H, N—H and C=C bonds and CN, CO and NO_2 groups. On the basis of these data we suggested that the compound was 5-cyano-4,4,6-trimethyl-2-nitromethylene-3-oxo-1,2,3,4-tetrahydropyridine (*II*). This structure was confirmed by our X-ray diffraction study[5]. Also the ^{13}C NMR spectrum agreed with this structure (Scheme 1). Probable fragmentation of the compound *II* on electron impact at 70 eV is shown in Scheme 2. The molecular ion (*m/z* 221) is aromatized by loss of methyl radical under formation of the ion at *m/z* 206. This fragmentation is confirmed

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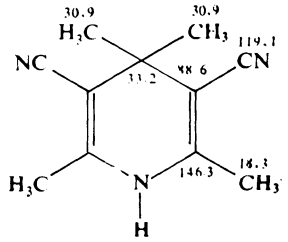
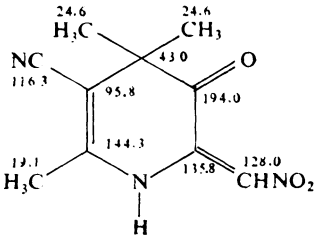
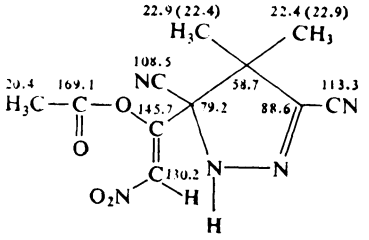
also by the presence of the metastable ion, (m/z 192·0). The fission of the NO radical from the ion at m/z 206 is in accord[6] with the presence of a nitro group in the molecule of compound *II*. The base peak (m/z 28) arises by a more profound fragmentation of the ions at m/z 176 and m/z 148.



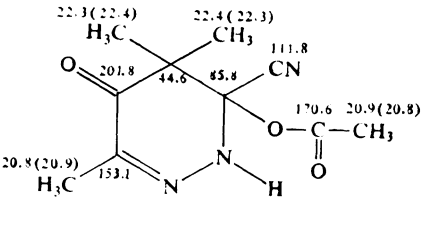
I



II



III



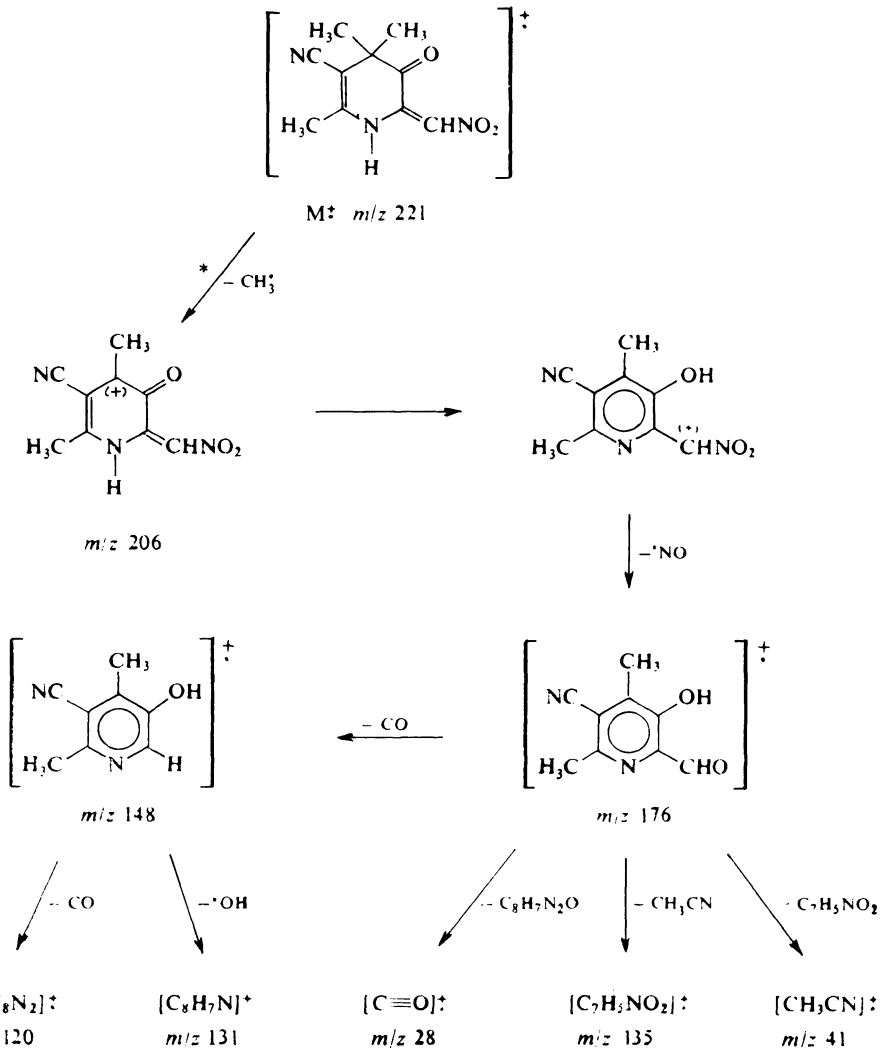
IV

SCHEME 1

Assignment of signals in the ^{13}C NMR spectra of compounds *I*—*IV* in hexadeuteriodimethyl sulfoxide. Chemical shifts are given in ppm (δ-scale). Values in parentheses denote signals which cannot be assigned unequivocally.

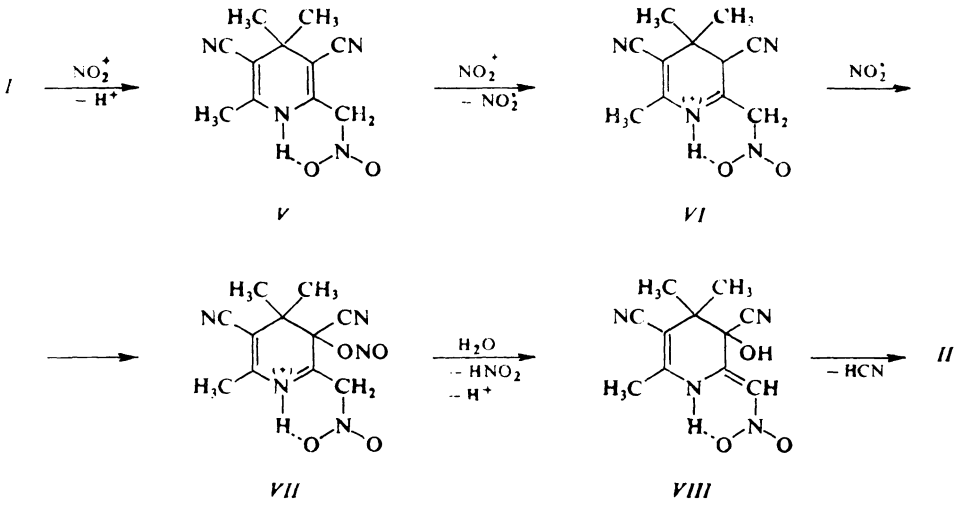
We assume that the 1,4-dihydropyridine derivative *I* (Scheme 3) is converted primarily into the 2-nitromethyl derivative *V* by a mechanism analogous to that found for formation of 3,5-dicyano-1,4,4,6-tetramethyl-2-nitromethyl-1,4-dihydropyridine[1,2]. The intermediate *V* is attacked by nitronium cation to give the radical cation *VI* to which the NO_2 radical is added. The arising nitrite *VII* is hydrolyzed to the cyanohydrin *VIII* which loses hydrogen cyanide affording the compound *II* (similar eliminations have been observed[7]).

Second fraction afforded yellow crystalline compound (7·5%) of the composition $C_{11}H_{11}N_5O_4$. Its ^1H NMR spectrum showed the presence of three non-equivalent methyl groups, an olefinic proton and an NH group; the IR spectrum exhibited bands due to NH, C=O, C=N and NO_2 groups. In addition, Raman spectroscopy



SCHEME 2

revealed the presence of a nitrile group. Of several alternative structures, X-ray diffraction[5] proved the structure *III*, *i.e.* (*Z*)-5-(1-acetoxy-2-nitrovinyl)-3,5-dicyano--4,4-dimethyl-2-pyrazoline. Also the ^{13}C NMR spectrum was in accord with this structure. Scheme 4 suggests fragmentation paths of the compound *III* following an electron impact at 70 eV. The molecular ion (*m*/*z* 277) is cleaved in several ways. Loss of acetonitrile leads to the aromatic ion at *m*/*z* 236. The elimination of NO_2 radical shows the presence of a nitro group and the ions at *m*/*z* 235 and *m*/*z* 43

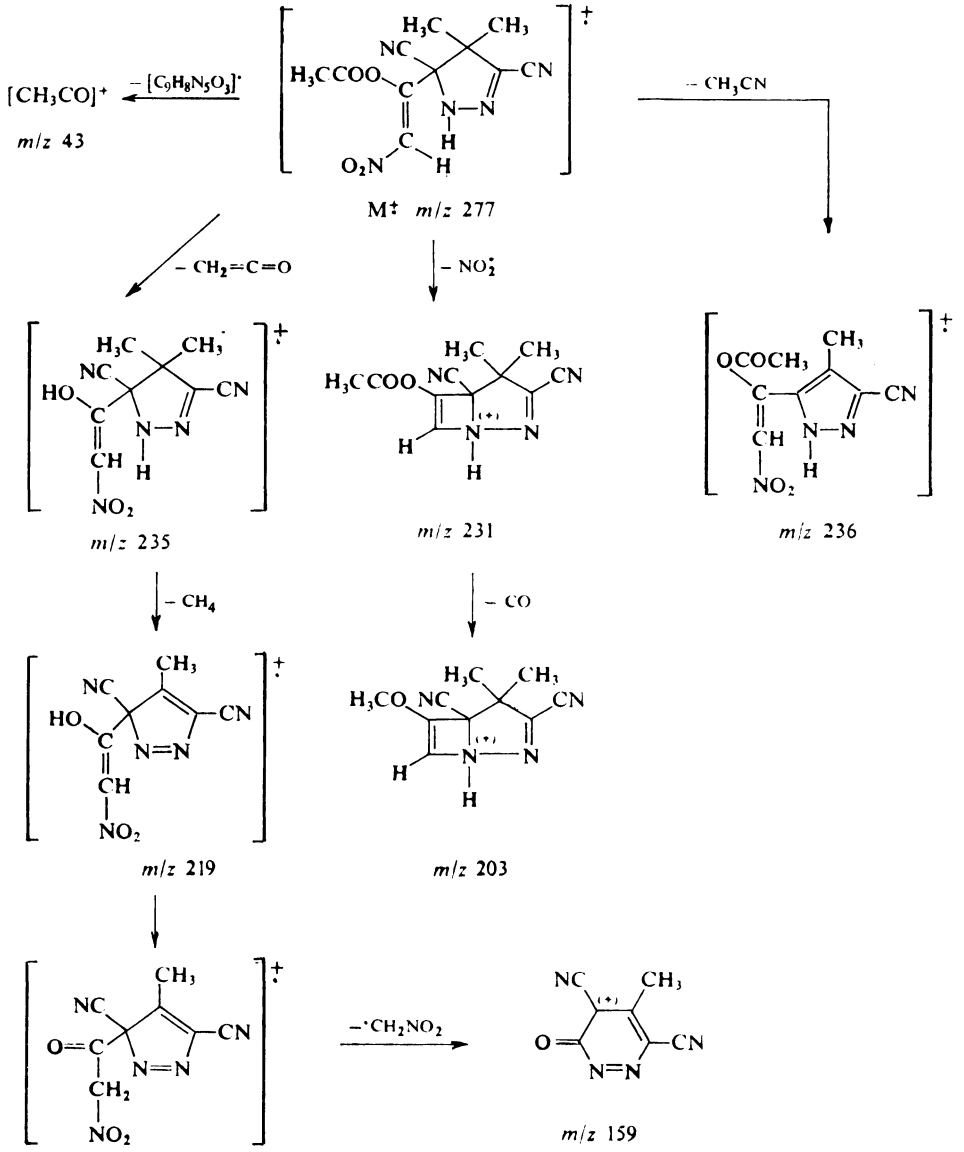


SCHEME 3

indicate a CH_3COO— group in the molecule of *III*. Concerning the mechanism of formation of *III*, we consider the 2-nitromethyl derivative *V* to be the primary product[1,2].

The third fraction (16%) of the chromatography consisted of the starting 1,4-dihydropyridine *I*.

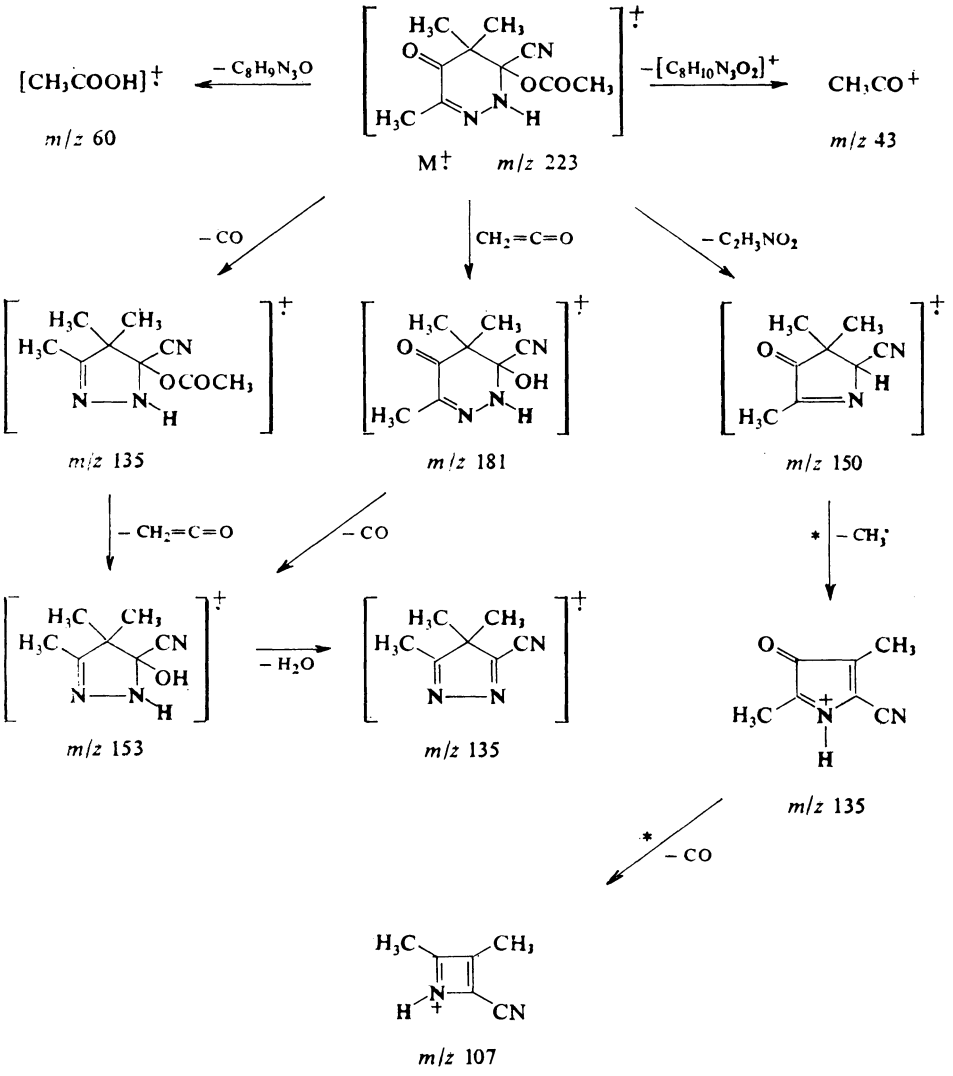
The last fraction gave a yellowish compound of composition $C_{10}H_{13}N_3O_3$ in 21% yield. Its ^{1}H NMR spectrum exhibited signals of four non-equivalent methyl groups and an NH group, the IR spectrum displayed bands due to vibrations of N—H, C—H, C=N, C≡N bonds and two carbonyl groups. The ^{13}C NMR spectrum confirmed the presence of one keto and one ester group, a nitrile group and four non-equivalent methyls and agrees with the assumed structure 3-acetoxy-3-cyano-4,4,6-trimethyl-5-oxo-2,3,4,5-tetrahydropyridazine (*IV*). Probable fragmentation of the compound *IV* on electron impact at 70 eV is shown in Scheme 5. The molecular ion (*m/z* 223) of low intensity gives rise to very intensive ions at *m/z* 60 and *m/z* 43, confirming the presence of an acetoxy group in *IV*. The ion at *m/z* 150 is formed from the rearranged molecular ion and is aromatized by loss of methyl radical to give the ion at *m/z* 135 (base peak in the spectrum) which represents probably two different species: one arises by the mentioned fragmentation from the ion at *m/z* 150 (as confirmed by the presence of the metastable ion at *m/z* 121·5) and loses carbon monoxide to give the ion at *m/z* 107, the second is probably formed by a side fragmentation path from the ions at *m/z* 195 and *m/z* 181 *via* the ion at *m/z* 153. For the formation of the compound *IV* we assume an analogous mechanism as for the compounds *II* and *III*.



SCHEME 4

From the structure of compounds *II*, *III* and *IV* it is evident that the formation of *III* and *IV* requires the presence of acetic acid (or acetic anhydride) in the reaction mixture. This was confirmed by carrying out the reaction of *I* with nitrating mixture in chloroform. As expected, in this case neither *III* nor *IV* were detected by thin-

-layer or high performance liquid chromatography and the compound *II* was obtained by column chromatography as the sole product. The above-mentioned results show that, contrary to 1-substituted 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridines[1,2], compound *I* does not give with nitric acid 2- and/or 6-nitromethyl derivatives (although such products can act as intermediates), affording instead a mixture of much more complicated products *II*, *III* and *IV*.



SCHEME 5

EXPERIMENTAL

Melting points were determined on a Boetius block and are uncorrected. IR spectra were measured in chloroform on a Perkin–Elmer 325 spectrometer. ^{1}H NMR spectra were taken in deuteriochloroform on a Varian XL 100 (100 MHz) instrument, ^{13}C NMR spectra in hexadeuteriodimethyl sulfoxide on a Tesla BS 567 spectrometer, both with tetramethylsilane as internal standard, $\delta = 0$ ppm. The ^{13}C NMR spectra were interpreted on the basis of data published[8] for some functional groups, using the APT technique and comparing the spectra of compounds *I*–*IV*. Mass spectra were measured on an LKB 9000 spectrometer (direct inlet, 70 eV). The starting 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine was prepared by a modified Hantzsch synthesis[9] from 3-aminocrotononitrile and acetone; m.p. 243–244°C (stated[10] 238°C).

Reaction of Compound *I* with Nitric Acid in Acetic Acid

Fuming nitric acid ($d = 1{\cdot}5$ g cm^{-3}; 10 ml; 0·24 mol) was added dropwise at +5°C during 1 h to a stirred and cooled mixture of 1,4-dihydropyridine *I* (10 g; 0·053 mol) and glacial acetic acid (100 ml) the temperature being kept below +10°C. After stirring at this temperature for an additional 1 h, the mixture was poured into ice-cold water (300 ml). The formed suspension was extracted with chloroform (5 × 50 ml), the combined organic layers were washed with water (2 × 100 ml) and dried over magnesium sulfate. Removal of the solvent afforded 8·4 g of product which partially crystallized. A part (5·2 g) was chromatographed on a column of silica gel (530 g; Silpearl). Elution with chloroform gave four principal fractions:

1) Red crystals of 5-cyano-4,4,6-trimethyl-2-nitromethylene-3-oxo-1,2,3,4-tetrahydropyridine (*II*), m.p. 145–147°C (267 mg, 5%). ^{1}H NMR spectrum (C^2HCl_3), δ (ppm); 1·54 (s, $(CH_3)_2$); 2·38 (s, CH_3); 7·21 (s, —CH=); 10·24 (s, NH). IR spectrum ($CHCl_3$), ν_{max} (cm^{-1}): 3 290 m, 3 140 w (N—H); 3 020 m, 2 970 m, 2 950 w, 2 850 w (C—H); 2 210 s (C≡N); 1 723 s (C=O); 1 650 s, 1 614 s (C=C); 1 567 s, 1 316 s (NO_2). For $C_{10}H_{11}N_3O_3$ (221·2) calculated: 54·30% C, 5·00% H, 19·00% N; found: 54·27% C, 5·06% H, 19·08% N.

2) Yellow crystals of (*Z*)-5-(1-acetoxy-2-nitrovinyl)-3,5-dicyano-4,4-dimethyl-2-pyrazoline (*III*), m.p. 184–186°C (380 mg, 7·5%). ^{1}H NMR spectrum (C^2HCl_3), δ (ppm): 1·44 (s, CH_3); 1·94 (s, CH_3); 1·62 (s, (NH); 2·36 (s, CH_3COO); 6·95 (s, —CH=). IR spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 3 250 w, 3 140 w (N—H); 3 020 w, 2 980 w (C—H); 1 741 m (C=O); 1 620 m (C=N); 1 550 w, 1 321 m (NO_2). Raman spectrum ($CHCl_3$), $\tilde{\nu}_{max}$ (cm^{-1}): 2 260 s (C≡N); 1 730 s (C=O); 1 626 m (C=N); 1 556 s, 1 328 m (NO_2). For $C_{11}H_{11}N_5O_4$ (277·2) calculated: 47·66% C, 4·00% H, 25·26% N; found: 47·59% C, 4·04% H, 25·32% N.

3) The starting compound *I*, m.p. 242–244°C (stated[10] 238°C); yield 843 mg (16%).

4) Yellowish crystals of 3-acetoxy-3-cyano-4,4,6-trimethyl-5-oxo-2,3,4,5-tetrahydropyridazine (*IV*), m.p. 128–130°C, (1·067 g; 20·5%). ^{1}H NMR spectrum ((C^2HCl_3), δ (ppm): 1·44 (s, CH_3); 1·66 (s, CH_3); 1·69 (s, CH_3); 1·96 (s, CH_3COO); 6·92 (s, NH). IR spectrum (C^2HCl_3), $\tilde{\nu}_{max}$ (cm^{-1}): 3 435 s, 3 360 m (N—H); 3 010 m, 2 940 m, 2 875 w (C—H); 2 205 w (C≡N); 1 745 s, 1 685 s (C=O); 1 573 m (C=N). For $C_{10}H_{13}N_3O_3$ (22·1·15) calculated: 53·79% C, 5·87% H, 18·83% N; found: 54·02% C, 6·01% H, 19·03% N.

Reaction of Compound *I* with Nitrating Mixture in Chloroform

A mixture of nitric acid (2 ml) and conc. sulfuric acid (2·4 ml) was added dropwise at 0°C during 30 min to a stirred mixture of compound *I* (2 g; 0·01 mol) and chloroform (20 ml) the temperature being kept under +5°C. After further 30 min, the mixture was poured into ice-cold water

(100 ml), the organic layer separated and the aqueous one extracted with chloroform (3 × 50 ml). The combined organic layers were washed with water (3 × 50 ml), dried over anhydrous magnesium sulfate and taken down, affording 1·65 g of the crude product. A part (0·5 g) of it was chromatographed on a column of silica gel (Silpearl; 50 g) in chloroform, yielding 0·26 g (52%) of compound *II*, m.p. 145—146°C.

Mass spectra of compounds *II*—*IV*; *m/z* (rel. intensity, %):

II: 221 (11); 206 (44); 176 (5); 148 (12); 135 (6); 132 (14); 131 (11); 120 (6); 119 (9); 86 (11); 84 (17); 81 (9); 79 (11); 77 (14); 69 (11); 66 (17); 65 (11); 57 (14); 55 (16); 43 (13); 42 (19); 41 (28); 32 (30); 30 (17); 29 (8); 28 (100); 27 (16); 26 (19).

III: 277 (2); 236 (8); 235 (9); 231 (13); 219 (8); 203 (16); 159 (7); 142 (10); 96 (6); 70 (7); 66 (8); 54 (5); 53 (11); 52 (7); 44 (26); 43 (100); 42 (18); 41 (23); 40 (9); 39 (14); 30 (12); 28 (9); 27 (11).

IV: 223 (0·1); 195 (2); 182 (2); 181 (5); 153 (3); 151 (5); 150 (43); 136 (13); 135 (100); 113 (10); 107 (12); 105 (4); 102 (4); 95 (2); 94 (9); 92 (5); 82 (13); 80 (8); 70 (5); 67 (3); 66 (16); 65 (6); 64 (5); 60 (23); 53 (8); 52 (5); 51 (5); 44 (4); 43 (48); 42 (36); 41 (16); 39 (17); 30 (2); 29 (6); 28 (11); 27 (2).

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