LXXXVIII.—*The Influence of Nitro-groups on the Reactivity of Substituents in the Benzene Nucleus. Part IX. 2 : 3- and 2 : 5-Dinitro-4-methoxytoluenes.*

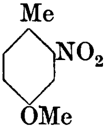
By HERBERT ERIC DADSWELL and JAMES KENNER.

IN an earlier paper (Kenner, Tod, and Witham, J., 1925, **127**, 2343), the behaviour of 4-chloro-2 : 3- and -2 : 5-dinitrotoluenes towards ammonia and sodium methoxide was examined, with the object of comparing the influences of the methyl group and the chlorine atom on the reactivities of the nitro-groups.

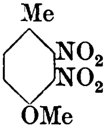
A similar comparison of the methyl and methoxyl groups has now been made by a study of 2 : 3- (II) and 2 : 5- (III) dinitro-4-methoxytoluenes.

It was stated by Kaufler and Wenzel (*Ber.*, 1901, **34**, 2238) that the former of these compounds is the main product of the nitration of 2-nitro-4-methoxytoluene (I), but a repetition of their work, whilst confirming the formation of this compound, showed that they had not obtained it in a pure condition, and that the 2 : 5-isomeride also can be isolated from the products of the reaction. The separation is, however, tedious and wasteful, and the ethers are more accessible from 2 : 3- and 2 : 5-*dinitro*-p-*cresols*. These are produced approximately in the proportion of 2 : 1 when 2-nitro-*p*-cresol is nitrated, and are comparatively easily separated. These results are of interest as illustrating the general tendency, emphasised by Jones and Robinson (J., 1917, **111**, 907; compare Rây and Robinson, J., 1925, **127**, 1608), for the entering group in such cases to take up the 3-position, ortho- to the nitro-group. As in the cases of the dimethyl ether of 2-nitroquinol and of 2-nitroaceto-*p*-toluidide (Page and Heasman, J., 1923, **123**, 3240; Scott and Robinson, J., 1922, **121**, 844), however, this does not occur to the entire exclusion of substitution in the 5-position. Conversely, we have found that the conditions prescribed by Scott and Robinson (*loc. cit.*) for the preparation of 2 : 5-dinitroaceto-*p*-toluidide also lead to the production of some of the 2 : 3-isomeride.

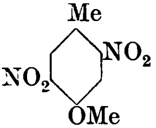
(I.)



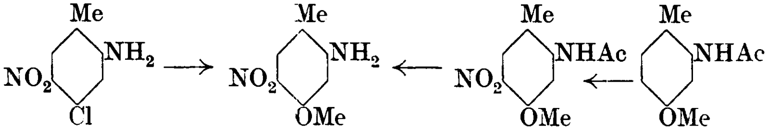
(II.)



(III.)



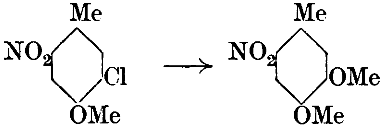
A study of the action of methyl-alcoholic ammonia on 2 : 5-dinitro-4-methoxytoluene led to no result useful for the present purpose, for most of the material was recovered unchanged after treatment at 140°, and at 150° it was converted into a mixture consisting partly of black insoluble material, from which neither of the expected toluidines could be obtained. Of these, 5-*nitro*-4-*methoxy*-o-*toluidine* (IV) was obtained by the action of sodium methoxide on 4-chloro-5-nitro-*o*-toluidine (Kenner, Tod, and Witham, *loc. cit.*), and its acetyl derivative was the sole product isolated from the nitration of 4-methoxyaceto-*o*-toluidide :



(IV.)

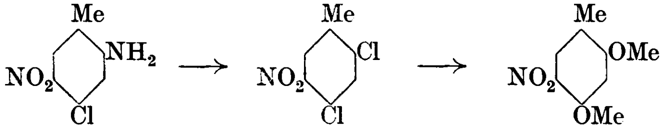
Similarly, 4-methoxyaceto-*m*-toluidide was converted by each of the methods of nitration employed solely into 6-nitro-4-methoxyaceto-*m*-toluidide (compare Limpach, *Ber.*, 1899, **22**, 790). These results are in interesting contrast to the behaviour of the corresponding chloro-compounds, from each of which both the possible isomerides are obtained (Kenner, Tod, and Witham, *loc. cit.*).

Of the possible products of the action of sodium methoxide on the above dinitro-compound, 6-nitrohomoveratrole (V) was already known (Cousin, *Ann. Chim. Phys.*, 1898, **13**, 480; Kostanecki and Paul, *Ber.*, 1902, **35**, 2608; Gilbody and W. H. Perkin, J., 1902, **81**, 1040), and has now been prepared from 3-*chloro*-6-*nitro*-4-*methoxytoluene* (de Vries, *Rec. trav. chim.*, 1909, **28**, 401) through the agency of sodium methoxide :



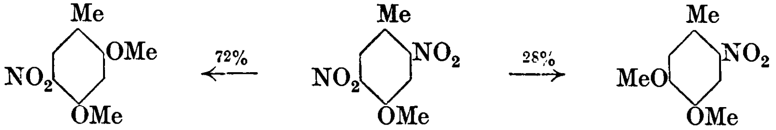
(V.)

In the same way, 5-*nitro*-2 : 4-*dimethoxytoluene* (VI) resulted from 2 : 4-*dichloro*-5-*nitrotoluene*, derived from 4-chloro-5-nitro-*o*-toluidine (Kenner, Tod, and Witham, *loc. cit.*) :

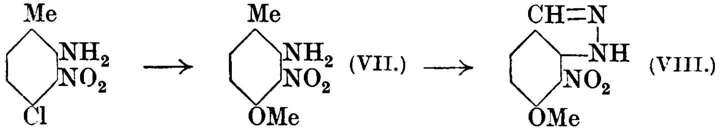


(VI.)

The 2:4-dimethoxy-derivative (VI) was also isolated from the mixture of methoxy-derivatives obtained by the action of sodium methoxide on 2 : 5-dinitro-4-methoxytoluene. This indication that displacement of the 2- predominates over that of the 5-nitro-group in this reaction was confirmed by thermal analysis, which showed that the two products are formed in the ratio 72 : 28.

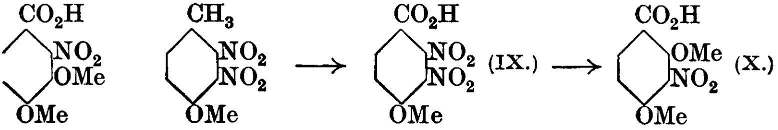


Preliminary to the study of the action of ammonia on 2 : 3-dinitro-4-methoxytoluene, 3-*nitro*-4-*methoxy*-o-*toluidine* (VII) was prepared from 4-chloro-3-nitro-*o*-toluidine by treatment with sodium methoxide, and shown to be convertible in excellent yield into 7-nitro-6-methoxyindazole (VIII) :



(VII.) (VIII.)

Application of this reaction to the oily mixture of bases obtained from the dinitro-compound indicated that it consisted to the extent of 30% of the *o*-toluidine. In general confirmation of this result, it was possible to isolate from the mixture a base, different from the *o*-toluidine but isomeric with it, which was therefore 2-*nitro*-4-*methoxy*-m-*toluidine*. Attempts were made by a variety of methods to prepare this base from 4-methoxy-*m*-toluidine, but without success. Both it and its isomeride could obviously be converted into the corresponding nitrodimethoxytoluenes—a point of importance in view of the interest recently evinced in the preparation of 2-nitrohomoveratrole (Merck, D.R.-P. 415315; Oberlin, *Arch. Pharm.*, 1925, **263**, 641; Gulland and Robinson, J., 1926, 1976). This was, however, deemed to be unnecessary for the present investigation, since the mixture of dimethoxynitrotoluenes arising from the action of sodium methoxide on 2 : 3-dinitro-4-methoxytoluene was an oil which offered no prospect of being separable into its components by fractional distillation. But its composition followed from its oxidation to a mixture of nitrodimethoxybenzoic acids, in which 2-nitroveratric acid (Pschorr and Sumuleanu, *Ber.*, 1899, **32**, 3409) predominated. The isomeric 3-*nitro*-2 : 4-*dimethoxybenzoic acid* (X) resulted from the action of sodium methoxide on 2 : 3-*dinitro*-4-*methoxybenzoic acid* (IX), which in turn was prepared from 2 : 3-dinitro-4-methoxytoluene.



(IX.) (X.)

It thus appears that both ammonia and sodium methoxide displace the 3- rather than the 2-nitro-group of 2 : 3-dinitro-4-methoxytoluene, but that the 2-position of the 2 : 5-isomeride is the more liable to attack. No discrepancy of this kind was observed between the chlorodinitrotoluenes, and it will therefore be of interest to examine the behaviour of 4 : 5-dinitro-2-methoxytoluene.

EXPERIMENTAL.

Nitration of 2-*Nitro*-4-*methoxytoluene*.—The quality of the fuming nitric acid available rendered it necessary slightly to modify the conditions used by Kaufler and Wenzel (*loc. cit.*).

Sulphuric acid (60 c.c.) was gradually added to a solution of 2-nitro-4-methoxytoluene (10 g.) in glacial acetic acid (100 c.c.) and nitric acid (*d* 1·49; 40 c.c.) below 5°. The product (12 g.), after prolonged and careful fractional crystallisation from methyl alcohol, yielded 4 g. of material, m. p. 132—133° (Found : N,* 13·2%) as compared with 126—128° recorded by Kaufler and Wenzel for 2 : 3-dinitro-4-methoxytoluene. The identity of the product was proved by its reduction to the diamine, m. p. 75—76° (Kaufler and Wenzel give 72—73°), which was further characterised by condensation with benzil. 8-*Methoxy*-2 : 3-*diphenyl*-5-*methylquinoxaline* separates from acetic acid in fine, grey needles, m. p. 196—197° (Found : N, 9·15. $C_{22}H_{18}N_2$ requires N, 9·0%).

2 : 5-Dinitro-4-methoxytoluene (0·5 g.) was isolated from the mother-liquors of the above crystallisation and crystallised from benzene–light petroleum in yellow needles, m. p. 123—124° (Found : N, 13·4. Calc. : N, 13·2%). The compound had been previously prepared by G. M. Robinson (J., 1916, **109**, 1089), who found it to melt at 126°. Its orientation was proved by its reduction to a diamine, m. p. 164°, and direct comparison of this with authentic 3 : 6-diamino-4-methoxytoluene from 6-nitro-4-methoxy-*m*-toluidine (Limpach, *Ber.*, 1889, **22**, 791). Further, when a suspension of this base (5·75 g.) in crushed ice (187 g.) was oxidised by shaking it for 20 hours with the paste prepared from potassium persulphate (25 g.) and sulphuric acid (50 g.), the crude nitroso-compound obtained (4·2 g.) furnished 2 : 5-dinitro-4-methoxytoluene (2 g.), m. p. 123—124°, on oxidation at 40—50° with nitric acid (*d* 1·48; 15 c.c.).

Nitration of 2-*Nitro*-p-*cresol*.—When a mixture of glacial acetic acid (20 c.c.) and nitric acid (*d* 1·49; 16 c.c.) was added to a solution of 2-nitro-*p*-cresol (40 g.) in glacial acetic acid (160 c.c.) at 18—25°, crystalline material (18 g., m. p. 154—156°) gradually separated. The material (25 g.) precipitated on dilution of the liquor yielded

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* Determinations marked with an asterisk were carried out by Pregl's micro-Dumas procedure.

another product (8 g., m. p. 112—113°) by crystallisation from alcohol, 13 g. of material being recovered from the solution. By crystallisation from glacial acetic acid, this furnished 6 g., m. p. 156—157°.

The less fusible product was 2:3-*dinitro*-p-*cresol*, which crystallised from glacial acetic acid in light yellow plates, m. p. 157—158° (Found: N, 14·1. $C_7H_6O_5N_2$ requires N, 14·1%), and was converted, by treatment in alkaline solution at 40—50° with methyl sulphate, into 2 : 3-dinitro-4-methoxytoluene, m. p. 132—133°. The lower-melting product, light brown needles, m. p. 112—113°, was 2 : 5-*dinitro*-p-*cresol* (Found : N, 14·2. $C_7H_6O_5N_2$ requires N, 14·1%), since it furnished 2 : 5-dinitro-4-methoxytoluene, m. p. 123—124°, on alkylation with methyl sulphate.

The possibility of utilising 2 : 5-dinitro-*p*-toluidine as a source of the cresol was also examined, but abandoned when it was found that the material prepared according to the directions of Scott and Robinson (*loc. cit.*) was a mixture. From 4 g. of the crude base, 1 g. of almost pure 2 : 5-dinitro-*p*-toluidine, m. p. 186—187°, was obtained by crystallisation first from alcohol and then from benzene. By crystallising the material recovered from the mother-liquors twice from methyl alcohol, 2 : 3-dinitro-*p*-toluidine (0·75 g.), m. p. 122—123°, was obtained; it was identified by comparison with an authentic specimen. The remaining material was a mixture of the isomerides.

5-*Nitro*-4-*methoxy*-o-*toluidine* was obtained in quantitative yield when 4-chloro-5-nitro-*o*-toluidine (2·7 g.) was heated for 6 hours at 130° with a solution of sodium (0·3 g.) in methyl alcohol (12 c.c.). It separated from methyl alcohol in light purple prisms, m. p. 158—159°, which darkened rapidly on exposure (Found: N, 15·6. $C_8H_{10}O_3N_2$ requires N, 15·4%). It was converted by reduction into the *p*-diamine, m. p. 163°, already mentioned, and furnished an *acetyl* derivative which separated from alcohol in needles, m. p. 154—155° (Found: N, 12·8. $C_{10}H_{12}O_4N_2$ requires N, 12·5%). This compound was also produced apparently as sole product when a solution of 4-methoxyaceto-*o*-toluidide (10 g.) in glacial acetic acid (15 c.c.) and sulphuric acid (20 c.c.) was treated at 15—20° with nitric acid (*d* 1·49; 3 c.c.). It was conveniently hydrolysed in 1 hour by boiling it with 50% sulphuric acid. Attempts to obtain an indazole derivative from the base (compare 3-nitro-4-methoxy-*o*-toluidine, later) were unsuccessful.

6-Nitro-4-methoxyaceto-*m*-toluidide was prepared by Limpach (*loc. cit.*) from 4-methoxyaceto-*m*-toluidide. The nitration was repeated under various conditions which, in the case of acetanilide, are known to favour ortho-nitration : (1) a suspension of the acetotoluidide (21·6 g.) in acetic anhydride (20 c.c.) was treated at 10—20° with a mixture of nitric acid (*d* 1·48; 10 g.), urea (0·2 g.), and acetic anhydride (6 g.); (2) nitric acid (*d* 1·48; 3 c.c.) was added to a solution of the acetotoluidide (11 g.) in glacial acetic acid (15 c.c.) and sulphuric acid (20 c.c.) at 10—15°; (3) a solution of 4-methoxy-*m*-toluidine (5·5 g.) in acetic anhydride (6 c.c.) was added at 40—50° to a mixture of cupric nitrate (5 g.) and acetic anhydride (15 c.c.) (compare Menke, *Rec. trav. chim.*, 1925, **44**, 141). In every case a large proportion of the pure acetyl derivative was at once obtained, whilst hydrolysis of material recovered from the crystallisation liquors furnished the corresponding amine, with no evidence of its isomeride.

4-*Methoxy*-m-*oxalotoluidide*, from 4-methoxy-*m*-toluidine and ethyl oxalate, was precipitated from methyl-alcoholic solution by addition of chloroform in needles, m. p. 218° (Found: N, 8·7. $C_{18}H_{20}O_4N_2$ requires N, 8·5%). Attempts to use this for the preparation of 2-nitro-4-methoxy-*m*-toluidine (compare Hadfield and Kenner, P., 1914, 253) were also unsuccessful.

2 : 4-*Dichloro*-5-*nitrotoluene*, prepared from 4-chloro-5-nitro-*o*-toluidine by the usual procedure, crystallised from alcohol in needles, m. p. 49—50° (Found: N, 6·7. $C_7H_5O_2NCl_2$ requires N, 6·8%).

5-*Nitro*-2 : 4-*dimethoxytoluene* was produced when 2 : 4-dichloro-5-nitrotoluene (4 g.) was heated for 6 hours at 115—120° with a solution of sodium (0·8 g.) in methyl alcohol (32 c.c.). It separated from light petroleum in yellow needles, m. p. 117—118° (Found: N, 7·4. $C_9H_{11}O_4N$ requires N, 7·1%).

3-*Chloro*-6-*nitro*-4-*methoxytoluene*, from 6-nitro-4-methoxy-*m*-toluidine, crystallised from alcohol in needles, m. p. 94—95° (Found: N,* 7·1. $C_8H_8O_3NCl$ requires N, 6·95%). It was converted in 6 hours by methyl-alcoholic sodium methoxide at 115—120° into 6-nitro-3 : 4-dimethoxytoluene, m. p. 119—120° (Found: N, 7·2%). De Vries (*loc. cit.*) gives 94° as the melting point.

Action of Sodium Methoxide on 2 : 5-*Dinitro*-4-*methoxytoluene*.—When the dinitro-compound (1·5 g.) was heated with a boiling solution of sodium (0·15 g.) in methyl alcohol (6 c.c.), neutrality was attained after 5 hours. The product, after four crystallisations from light petroleum (b. p. 80—110°), yielded 5-nitro-2 : 4-dimethoxytoluene (0·2 g.), m. p. 116—117°, which did not depress the melting point of an authentic specimen. In order to ascertain the actual proportion of this and its isomeride formed in the reaction, the product from another similar operation was isolated and dried in the usual manner. It solidified at 90·6°, and after the addition of 0·28 g. to 1·2 g. of the material, the solidifying point was 96°. A series of determinations of the temperatures of solidification of mixtures of the two isomerides yielded the following results (*a* is the percentage of 6-nitro-3 : 4-dimethoxytoluene) :

a.	100	91·8	83·2	76·3	66·5	60·7	55·7	54·3	51·5	51·2
s.p.	115·5°	110·6°	105·5°	100·2°	90·7°	83·0°	78·6°	77·7°	77·6°	78·2°
a.	50·0	48·3	47·8	47·3	44·9	41·6	38·8	31·4	25·3	19·3
s.p.	78·8°	78·0°	77·6°	77·2°	79·2°	81·7°	82·8°	87·6°	93·2°	98·6°
a.	10·2	0								
s.p.	105·2°	113°								

From these it appears that the two isomerides combine in molecular proportion, and that the above-mentioned mixture contained 72% of 5-nitro-2 : 4-dimethoxytoluene.

3-*Nitro*-4-*methoxy*-o-*toluidine* was prepared by heating 4-chloro-3-nitro-*o*-toluidine (4·1 g.) for 6 hours at 125—130° with a solution of sodium (0·46 g.) in methyl alcohol (18·2 c.c.). The mixture was then neutral and yielded a product, which crystallised from dilute methyl alcohol in yellow needles, m. p. 61—62°. This was free from halogen and depressed the melting point of the original chloro-compound (Found : N,* 15·3. $C_8H_{10}O_3N_2$ requires N, 15·4%). Its *acetyl* derivative crystallised from benzene in needles, m. p. 176—176·5° (Found : N,* 12·6. $C_{10}H_{12}O_4N_2$ requires N, 12·5%). A solution of the base (0·5 g.) in glacial acetic acid (50 c.c.) which had been treated at 0° with a solution of sodium nitrite (2*N* ; 3·4 c.c.) deposited a brownish-red precipitate after 48 hours. The product (0·44 g.), isolated by extracting the mixture with benzene, crystallised from alcohol in fine, red needles, m. p. 173—174°. Analysis showed it to be 7-*nitro*-6-*methoxyindazole* (Found : N,* 21·3. $C_8H_7O_3N_3$ requires N, 21·8%).

Action of Methyl-alcoholic Ammonia on 2 : 3-*Dinitro*-4-*methoxytoluene.*—Four separate quantities of the dinitro-compound (2·1 g.) were each treated with methyl alcohol (27 c.c.) and ammonium hydroxide (*d* 0·880 ; 5 c.c.) at 145—150° for 7 hours. The residue after removal of methyl alcohol by distillation was extracted with hot concentrated hydrochloric acid (400 c.c.) in order to separate unchanged material (0·5 g.) from the basic product (6·8 g.), which was recovered from the acid solution in the usual manner. When a portion of this (1·3 g.) was dissolved in glacial acetic acid (66 c.c.) and treated at 0° with sodium nitrite solution (4·5 c.c.), it yielded crude 7-nitro-6-methoxyindazole (0·35 g.), which crystallised from alcohol in red needles, m. p. 165—166°, and was identified by comparison with the authentic compound. The yield of indazole, in comparison with that attained in the preparation described above, indicated the presence of 30% of 3-nitro-4-methoxy-*o*-toluidine in the basic mixture. When a further quantity (4 g.) of this was repeatedly extracted with hot light petroleum (b. p. 40—60°), a red solid was obtained. By crystallisation from methyl alcohol, this was obtained in orange needles (0·7 g.), m. p. 49—50° (Found : N,* 15·5. $C_8H_{10}O_3N_2$ requires N, 15·4%). Since the compound depressed the melting point of authentic 3-nitro-4-methoxy-*o*-toluidine, it was *2-nitro-4-methoxy-*m*-toluidine.* Its *acetyl* derivative (Found : N,* 12·3. $C_{10}H_{12}O_4N_2$ requires N, 12·5%) crystallised from benzene in small, white needles, m. p. 170—171°, and depressed the melting point of 3-nitro-4-methoxyaceto-*o*-toluidide.

When 2 : 5-dinitrotoluene (8·4 g.) was treated in the same manner for 14 hours at 150—160°, there were obtained a black deposit (0·65 g.), unchanged material (1 g.), and red semi-solid material (2 g.), precipitated from dilute mineral acid solution, and an oily mixture of bases (2·5 g.), which furnished a semi-solid acetyl derivative.

2 : 3-*Dinitro*-4-*methoxybenzoic acid* was prepared by boiling a mixture of 2 : 3-dinitro-4-methoxytoluene (10 g.) with a solution of potassium permanganate (20 g.) and magnesium sulphate (15·6 g.) in water (900 c.c.) for 4 hours. Unchanged dinitro-compound (4 g.) was recovered, and the acid (4·9 g.) isolated in the usual manner. It crystallised from water in needles, m. p. 248—250° (decomp.) (Found : N, 11·8; equiv., 243·6. $C_8H_6O_7N_2$ requires N, 11·6%; equiv., 242). The *methyl* ester separated from methyl alcohol in needles, m. p. 156° (Found : N, 11·1. $C_9H_8O_7N_2$ requires N, 10·9%). A solution of the acid (1 g.) in methyl alcohol (15 c.c.) was heated with a solution of sodium (0·2 g.) in methyl alcohol (12 c.c.) for 14 hours at 120°; the resulting neutral solution furnished 3-*nitro*-2 : 4-*dimethoxybenzoic acid* (0·75 g.) on acidification. This crystallised from water in needles, m. p. 210—212° (Found : N,* 6·4; equiv., 225·7. $C_9H_9O_6N$ requires N, 6·1%; equiv., 227). The *methyl* ester crystallised from methyl alcohol in large prisms, m. p. 118—119° (Found : N,* 6·0. $C_{10}H_{11}O_6N$ requires N, 5·8%). The acid and its ester were shown by direct comparison to be distinct from authentic 2-nitroveratric acid, m. p. 201—202°, and its methyl ester, m. p. 127—128° (Pschorr and Sumuleanu, *loc. cit.*).

Action of Sodium Methoxide on 2 : 3-*Dinitro*-4-*methoxytoluene*.—Whether the dinitro-compound (3 g.) was heated with a solution of sodium (0·3 g.) in methyl alcohol (12 c.c.) for 8 hours at 125° or for 20 hours at 110—115°, a quantity remained unchanged and crystallised when the solution was concentrated. When the residues from a number of such experiments were fractionated, a mixture of nitrodimethoxytoluenes passed over at 132—136°/2 mm., leaving a further quantity of dinitromethoxytoluene behind. The distillate (6 g.) was completely oxidised in 4 hours by a boiling, mechanically agitated solution of potassium permanganate (16 g.) in water (800 c.c.).

The acid so obtained (4·5 g.) crystallised from water in needles, m. p. 172—177° (Found : equiv., 223·2), and on esterification furnished a mixture of methyl esters, m. p. 105—110°, from which methyl 2-nitroveratrate, m. p. 125—126°, was separated by recrystallisation from methyl alcohol. Its identity was established by direct comparison with an authentic specimen, and it was similarly shown to be distinct from methyl 3-nitro-2 : 4-dimethoxybenzoate.

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