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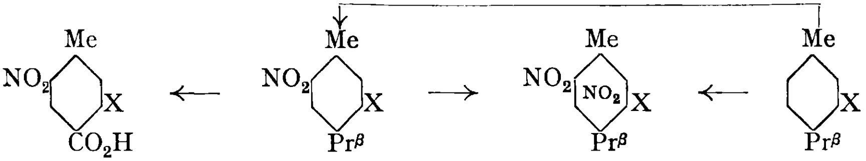
182. *Volume Effects of Alkyl Groups in Aromatic Compounds. Part III. The Dinitration of 3-Chloro- and 3-Bromo-p-cymene.*

By SAMARENDRA N. GANGULY and RAYMOND J. W. LE FÈVRE.

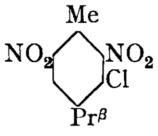
ACCORDING to Fileti and Crosa (*Gazzetta*, 1888, **18**, 289) fuming nitric acid converts 3-chloro-*p*-cymene into two chlorodinitrocymenes, m. p. 100—101° and 80°, and 3-bromo-*p*-cymene into two bromodinitrocymenes, m. p. 125—126° and 94°. Using nitric acid of *d* 1·48, however, they obtained halogenomononitrocymenes, which gave the corresponding 5-halogeno-2-nitro-*p*-toluic acids on oxidation and therefore were formulated as (I, X = Cl or Br). The mononitro-derivatives on further nitration gave the above-mentioned dinitro-derivatives. The constitutions allotted to (I) are supported by the results of interaction with piperidine (present paper).



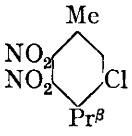
(I.) (II.)
(X = Cl or Br)

The Italian authors did not discuss the position of the second nitro-group in the chloro- and bromo-dinitrocymenes (II) and were apparently unaware that Ladenburg and Engelbricht (*Ber.*, 1877, **10**, 1220) had obtained 3-chloro-2 : 6-dinitro-*p*-cymene, m. p. 100—101°, from dinitrothymol by the action of phosphorus pentachloride.

In the chloro-series, therefore, it was evident to Beilstein (" Handbuch," 4th Edn, V, 425) that the higher-melting isomeride was (III) and the lower-melting form either (IV) or (V)—in view of the alleged formation from (I), (IV) is to be preferred.



(III.)



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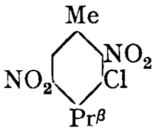

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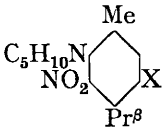

(VI.)

We have re-examined the above substitutions because of the possibility that these alleged isomerides might have a relationship of the type sought unsuccessfully in Part I of this series.

In Parts I and II (J., 1933, 977, 980) the interactions of *p*-cymene derivatives with piperidine were shown to obey the rules that hold for simpler aromatic compounds (Le Fèvre and Turner, J., 1927, 1113). Since, *e.g.*, 1 : 2-dichloro-4 : 5-dinitrobenzene on treatment with this reagent loses a nitro-group rather than a halogen atom (Le Fèvre

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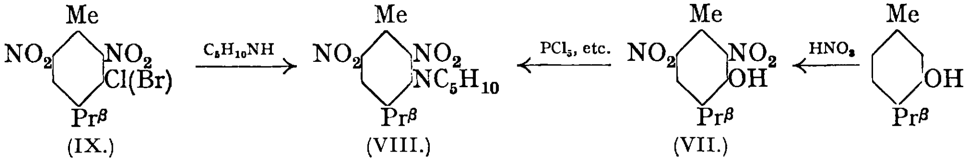
and Turner, *loc. cit.*), yielding 4 : 5-dichloro-2-nitro-1-piperidinobenzene, it is clear that piperidine should react with (III) and with *one* of the 3-bromodinitrocymenes to give 2 : 6-dinitro-3-piperidinocymene (VIII), and with the lower-melting chlorodinitro- and the other bromodinitro-cymene to produce a chloro- and a bromo-nitropiperidinocymene respectively (possibly VI).

3-Chloro- and 3-bromo-*p*-cymene, prepared from thymol to ensure freedom from the similar 2-isomerides, were both dinitrated as described by the Italian authors. Each product was separated into a higher- and a lower-melting substance: the former raised the m. p. of the latter. The two higher-melting substances both reacted with piperidine with production of the same 2 : 6-dinitro-3-piperidino-*p*-cymene (VIII), which was also obtained from the 3-chloro-2 : 6-dinitrocymene prepared from dinitrothymol (VII):

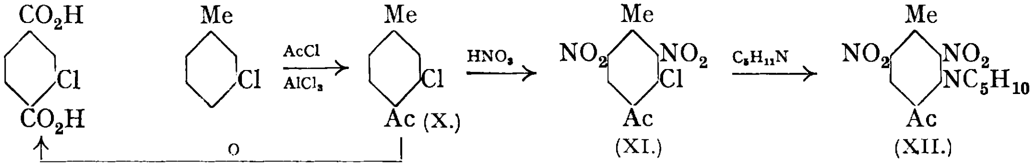


The two lower-melting substances were changed by hot piperidine into products from which, by crystallisation, considerable quantities of (VIII) were isolated. The amounts of (IX) isolated directly and also as the piperidino-derivative from the lower-melting substances show that the dinitration of each 3-halogenocymene proceeds *mainly* to give the 2 : 6-dinitro-derivative (IX).

The lower-melting substances of Fileti and Crosa thus seem to be mixtures of (IX) with other compounds having similar physical properties. If these compounds resemble (IX) in solubility and, admixed with it, have fusion-point diagrams with very flat minima (compare mercuric bromide and iodide; Reinders, *Z. physikal. Chem.*, 1900, **32**, 494), separation of the mixtures corresponding approximately to the minima will be slow. In accordance with this, specimens of the lower-melting substances, *of the same m. p.*, can have considerably different carbon and hydrogen contents.

Since *p*-methylacetophenone is formed during the nitration of *p*-cymene (J., 1933, 981), the most likely impurity in (II) is the oxidation product of (IX), namely, 2-chloro- or 2-bromo-3 : 5-dinitro-4-methylacetophenone (XI); indeed, only the two lower-melting substances gave positive ketonic reactions with *o*-nitrobenzaldehyde and alkali (Le Fèvre and Pearson, *J. Soc. Chem. Ind.*, 1932, **51**, 433T).

The chloro-ketone (XI) was therefore synthesised from *m*-toluidine for comparison with the chloro-compound (IX):



Its constitution was established by (a) analysis, (b) the ready formation of a *piperidino*-derivative (XII), and (c) the oxidation of the intermediate ketone (X) to chloroterephthalic acid. The last proof was necessary because Claus (*J. pr. Chem.*, 1891, **43**, 355) by similar treatment obtained a ketone which yielded a derivative of *o*-phthalic acid on oxidation: possibly he oxidised a sample contaminated with the simultaneously formed 4-chloro-2-methylacetophenone and thus obtained the chloro-*o*-phthalic acid, which is more easily isolated than the chloroterephthalic acid.

The parallel reactions starting from *m*-bromotoluene were attempted, but so much 4-bromo-2-methylacetophenone was produced that the synthesis of the bromo-analogue of (XI) was not completed.

Both (XI) and (XII) closely resembled (IX) and (VIII) respectively in m. p. and solubility; a mixed m. p. curve was roughly determined for (XI) and (IX) (chloro-series)

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and displayed the anticipated shape. From this and from the analytical data it appears that the " chlorodinitrocymene " of m. p. 80° may contain 50—80% of the corresponding chlorodinitro-*p*-tolyl methyl ketone. By inference, the same is true, ***mutatis mutandis***, for the analogous bromo-compounds. In confirmation of this we isolated an analytically pure specimen of (XII) from the total crude piperidino-derivatives prepared from a deliberately unpurified sample of the direct dinitration product (II) of 3-bromocymene.

Conclusion.—3-Chloro- and 3-bromo-*p*-cymene both undergo dinitration, by the methods prescribed in the literature, to give the 2 : 6-dinitro-derivatives. This simple conclusion has previously been masked by complications arising from the facile oxidation of the *iso*propyl to the acetyl group. Such a result is entirely in accord with expectations based on the electropolar and volume effects of the groups concerned.

EXPERIMENTAL.

3-*Chloro- and* 3-*Bromo*-p-*cymene*.—Thymol (100 g.) was mixed with phosphorus pentachloride (50 g.) or with phosphorus tribromide (45 g.) which had previously been treated with bromine (26 g.). The mixtures were refluxed for 2 hours and then steam-distilled. The oily distillate was extracted in ether, washed, dried over sodium sulphate, and distilled : chloro-compound, b. p. 120—122°/20 mm. (20 g.) ; bromo-compound, b. p. 130°/35 mm. (30 g.).

Mononitration of 3-*Chloro- and* 3-*Bromo*-p-*cymene*.—The halogeno-hydrocarbons (6 g.) were each shaken with nitric acid (*d* 1·48, 36 g.) below 15° for 3—4 hours. Dilution with water gave oily products, which were washed with alkali and water, dried over calcium chloride, and distilled ; the chloro-derivative had b. p. 142—150°/13 mm., and the bromo-derivative, b. p. 210—211°/100 mm.

The halogenonitro-compounds (4·5 g.) were each heated with piperidine (10 g.) for 30 minutes at 100°. On cooling, piperidine hydrohalide (about 0·7 g.) separated. Dilution with water produced an oil which was largely soluble in dilute sulphuric acid. From the solution, aqueous ammonia liberated the nitropiperidino-*p*-cymene, which was isolated as a yellow oil, b. p. 146—148°/32 mm.

Dinitration of 3-*Chlorocymene*.—The chlorocymene (20 g.) was added to nitric acid (*d* 1·5 ; 200 g.) below — 5° during 15 minutes, and the solution poured on ice. The white solid obtained (25 g.) had m. p. 75—80° (Found : C, 43·1 ; H, 3·4%). Crystallisation from acetic acid (100 c.c.) gave white needles (20 g.), m. p. 75—80° (Found : C, 44·2 ; H, 3·8%) ; from the mother-liquor, after heating and admixture with hot water (25 c.c.), 3 g. of the same material, m. p. 75—80°, were isolated. The whole 23 g., recrystallised from acetic acid (400 c.c.) and water (100 c.c.), gave long white needles (8 g.), m. p. 100—103°, and 102·5—103·5° (6·5 g.) after a further crystallisation from acetic acid (40 c.c.) (Found : C, 46·3 ; H, 4·1. Calc. for $C_{10}H_{11}O_4N_2Cl$: C, 46·4 ; H, 4·25%). The mother-liquor of the 8 g. gave on dilution with water 13 g., m. p. 79—81° (Found : C, 42·7 ; H, 3·1%). These were recrystallised from acetic acid (200 c.c.) and water (50 c.c.), producing 3·5 g., m. p. 75—80° ; the heated filtrate, diluted with hot water, gave 6·5 g. of long needles, m. p. 80—83° (unaltered by further crystallisation and giving a strong ketonic reaction with *o*-nitrobenzaldehyde and alkali) (Found : C, 43·0 ; H, 3·3%).

In other experiments the crude dinitro-derivative (30 g.) was allowed to crystallise slowly from methyl alcohol (120 c.c.) so that a mass of long needles and smaller crystals was produced (23 g.). The longest needles, separated by hand-picking, had m. p. 99—101° and, after recrystallisation from acetic acid, 102·5—103·5° (Found : C, 46·3 ; H, 4·2%). The smaller crystals had m. p. 75—77° (only slightly changed by ordinary crystallisation).

Dinitration of 3-*Bromocymene*.—A mixture of nitric acid (*d* 1·42 ; 70 c.c.) and concentrated sulphuric acid (70 c.c.) was added to 3-bromocymene (14 g.) at such a rate that the temperature did not rise above 10°. After ½ hour's shaking, the oil produced solidified. Dilution with ice, filtration, washing, and drying then afforded *ca.* 17 g. of a white solid, m. p. 80—100° (Found : C, 36·9 ; H, 3·1%). Crystallisation of 16 g. of this product from acetic acid (90 c.c.) gave white needles (5 g.), m. p. 119—122°, raised by two further crystallisations to 125—126° (2·5 g.) (Found : C, 39·7 ; H, 3·6. Calc. for $C_{10}H_{11}O_4N_2Br$: C, 39·6 ; H, 3·6%). Addition of water to the mother-liquors of this series of crystallisations produced 2·5 g. of white solid, m. p. 95—96° (Found : C, 34·9 ; H, 2·5%).

The mother-liquor of the first 5 g. of pure substance above, by treatment with hot water and subsequent cooling, yielded stout white needles (8 g.), m. p. 63—95° ; this specimen, twice recrystallised from acetic acid and once from methyl alcohol, yielded 1·5 g., m. p. 95—96°

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Found: C, 35·0; H, 2·6%). The material precipitated from all the filtrates was dissolved, together with the solids, m. p. 95—96°, obtained in the previous crystallisations, in much hot acetic acid; white needles (0·5 g.), m. p. 120—122° (raised by another crystallisation to 125°) were obtained on cooling.

Piperidino-derivatives.—(a) The chlorodinitrocymene, m. p. 102·5—103·5°, and the bromodinitrocymene, m. p. 125—126°, were separately heated with piperidine (5 parts) for 1½ hours on a steam-bath. Dilution with water gave products, m. p. 112—120° and 110—113°, respectively, both raised to 123—124° by one crystallisation from alcohol. 2 : 6-*Dinitro*-3-*piperidino*-p-*cymene* formed long, pale yellow needles (Found: C, 58·7; H, 6·8; N, 13·9. $C_{15}H_{21}O_4N_3$ requires C, 58·6; H, 6·8; N, 13·7%). A mixture with the same weight of 3 : 5-dinitro-2-piperidinocymene (m. p. 123—124°; Le Fèvre, J., 1933, 980) became liquid at 110°.

(b) The "bromodinitrocymene" of m. p. 95—96° (11 g.) was heated with piperidine (25 c.c.) at 95° for 4 hours. Dilution produced a substance (11 g.) which formed yellow needles (9·5 g.), m. p. 85—90°, on crystallisation from acetic acid (70 c.c.) (Found: C, 56·2; H, 6·0; N, 14·0%). This solid, recrystallised four times from acetic acid, gave bright yellow needles (1·8 g.), m. p. 123—124° (Found: C, 58·7; H, 6·8%). A mixed m. p. determination with 2 : 6-dinitro-3-piperidinocymene (above) proved the identity. Complete precipitation of the mother-liquors with water produced a yellow substance, m. p. 95—98°, giving analytical results (Found: C, 55·3; H, 6·0%) in better agreement with (XII), which requires C, 54·7; H, 5·5%, than with (VIII).

By an analogous process the lower-melting "chlorodinitrocymene" was transformed into a mixture of piperidino-derivatives containing (VIII) in isolable quantity.

Dinitration of Thymol.—A solution of thymol (10 g.) in acetic acid (100 c.c.) was kept as cold as possible without freezing, and treated during 1 hour with nitric acid (20 c.c., *d* 1·42) diluted with acetic acid (50 c.c.). Addition of water precipitated an oil which, after solidifying, was pressed on a porous plate (m. p. 50—53°; yield, 8 g.) and then crystallised from light petroleum, forming yellow-white prisms, m. p. 80—81° (Found: N, 11·7. Calc. for $C_{10}H_{12}O_5N_2$: N, 11·5%). Mazzara (*Gazzetta*, 1890, **20**, 141), who prepared the substance by the action of dilute nitric acid on thymol, gives m. p. 81°.

Action of Phosphorus Pentachloride on the Preceding Substance.—The dinitrothymol (20 g.) and the pentachloride (40 g.) were gently warmed in a wide-mouthed flask until reaction began (110—120°). Dilution with water, washing with soda solution, and dissolution in hot alcohol (charcoal) yielded 4 g. of white needles, m. p. 100°, which, reacting with piperidine as described above, formed a piperidino-derivative identical (mixed m. p.) with (VIII).

2-*Chloro*-4-*methylacetophenone* (X).—Acetyl chloride (20 g.) was added drop by drop to a mechanically stirred mixture of *m*-chlorotoluene (25 g.) and anhydrous aluminium chloride (50 g.) heated under reflux on a steam-bath. After 2 hours, the mass was cooled, shaken with dilute hydrochloric acid, and extracted with ether. The extract was washed successively with water, aqueous sodium carbonate, and water, dried (calcium chloride), and distilled, giving the ketone (20 g.), b. p. 260—262°/760 mm.

Oxidation. The ketone (5 g.) was added to a mixture of 10% sodium hydroxide solution (40 c.c.), water (200 c.c.), and 5% aqueous potassium permanganate (250 c.c.). After 10 hours' boiling, decoloration with sulphur dioxide, and cooling, a white solid, m. p. 228° (after two crystallisations from toluene), was obtained. This acid, which appears to be 3-*chloro*-4-*acetylbenzoic acid* (Found: C, 54·1; H, 3·3. $C_9H_7O_3Cl$ requires C, 54·4; H, 3·5%), was boiled (0·5 g.) with a mixture of 10% sodium hydroxide solution (4 c.c.), water (25 c.c.), and 5% potassium permanganate solution (25 c.c.) for 5 hours and gave chloroterephthalic acid, m. p. 320° (Fileti and Crosa, *loc. cit.*, give m. p. 300°; Ahrens, *Ber.*, 1886, **19**, 1637, records m. p. "oberhalb 300°").

2-*Chloro*-3 : 5-*dinitro*-4-*methylacetophenone* (XI).—2-Chloro-4-methylacetophenone (10 g.) was added during ½ hour to nitric acid (*d* 1·5, 150 g.) at — 10°. Dilution with ice produced a white solid, m. p. 76—80°, which after crystallisation from acetic acid (*ca.* 20 c.c.) formed white needles (4 g.), m. p. 91—92° (Found: C, 39·5; H, 2·1. $C_9H_7O_5N_2Cl$ requires C, 41·7; H, 2·7%).

Rough determinations of solubility showed that, at 20°, 100 parts of methyl alcohol dissolve *ca.* 3 g. of both (XI) and (IX) and 100 parts of acetic acid dissolve 9—10 parts of (XI) and slightly less of (IX).

The following m. p.'s were observed for mixtures of (IX) and (XI):

(IX), %	100	67·8	49·5	38	29·8	15·1	0
M. p.	102·5—103·5°	88°	78°	76°	79°	84°	91—92°

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3 : 5-*Dinitro-2-piperidino-4-methylacetophenone* (XII).—The ketone (XI) (1 g.) was gently refluxed with piperidine (5 g.) for ½ hour; dilution with water and two crystallisations of the product from methyl alcohol gave yellow needles, m. p. 108—109° (Found: C, 54·2; H, 5·2. $C_{14}H_{17}O_5N_3$ requires C, 54·7; H, 5·5%).

Direct Isolation of (XII) *from the Crude Dinitration Product* (II).—The total nitration product (12 g., from bromocymene) was heated with piperidine (60 g.) for 2 hours on the steam-bath. The substance precipitated by water was crystallised by allowing a solution in hot methyl alcohol to cool slowly. The crystals deposited first (60° to 80°), which differed in shape and colour from those following, were recrystallised three or four times from methyl alcohol; they then had m. p. 108—109° (alone or mixed with XII above) (Found: C, 54·6; H, 5·3. Calc.: C, 54·7; H, 5·5%).

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