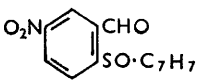
537. *Abnormal Nucleophilic Substitution of 3-Nitrobenzylidene Dichlorides.*

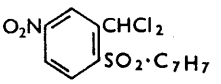
By J. D. Loudon and D. M. Smith.

Attack by methoxide or ethoxide ion on 5-nitro-2-toluene-*p*-sulphonylbenzylidene dichloride (II) occurs mainly at position 4 and, with departure of a chloride ion from the side-chain, leads to a 4-alkoxybenzyl chloride, *e.g.*, (IV). Piperidine displaces both chloro-substituents in the dichloride (II), yielding a mixture of the normal product, which is hydrolysable to the aldehyde (II; CHO for $CHCl_2$), and the abnormal product (III). The abnormal reaction is not observed for methoxide attack on the acetal (X), whereby replacement of the nitro or sulphonyl substituent occurs.

As shown in the preceding Paper 5-nitro-2-toluene-*p*-sulphinylbenzaldehyde (I) reacts with hydrogen chloride, giving 5-nitro-2-toluene-*p*-sulphonylbenzylidene dichloride (II) as part-product. Before the structure of this product was established, attempts to characterise its two chloro-substituents had shown that these resisted hydrolysis by acid, and survived oxidation (which merely converted the methyl into a carboxyl group), but suffered replacement under nucleophilic attack. In the light of the established structure (II), however, these replacement reactions were seen to present anomalies.[1]



(I)



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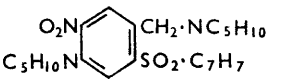

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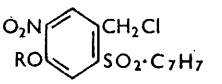


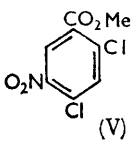
(IV)

It was consistent with structure (II) that, by reaction with piperidine and subsequent acid hydrolysis, the dichloride gave some of the corresponding aldehyde, but this normal course was concurrent with another leading to a dipiperidino-compound which, although formally derived by replacement of the two chloro-substituents, was stable towards acids. The orange colour and marked basicity of the abnormal product suggested that it contained structural units derived, respectively, from *N-o*-nitrophenylpiperidine and *N*-benzylpiperidine; these and steric considerations make (III) the most probable structure.

Results of greater significance were obtained from the interaction of the dichloride (II) and ethoxide ions, for here the abnormal course predominated and the double replacement was separated into distinct steps. The first step afforded the benzyl chloride (IV; R = Et) in 70% yield; further reaction gave the benzyl ethyl ether (IV; R = Et, OEt for Cl). Consistent with this interpretation, the benzyl chloride reacted with piperidine, forming a product which was colourless and basic, as required for the *N*-benzylpiperidine (IV; R = Et, NC_5H_{10} for Cl). Similar but, because of the incidence of side-reactions, less sharply defined results were obtained from the action of methoxide ions on the dichloride (II), whereby the appropriate benzyl chloride (IV; R = Me) (60% yield) and the derived methyl ether (IV; R = Me, OMe for Cl) were again isolated.

Confirmation of the structures assigned to these abnormal products, and with it proof of the 1,2,4,5- (as against the possible 1,2,3,4-)tetrasubstitution pattern in the significant

[1] Preliminary communication, Loudon and Smith, *Proc. Chem. Soc.*, 1963, 182.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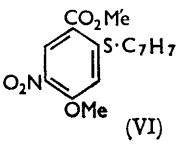
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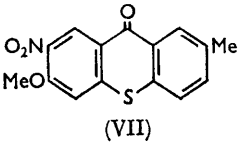
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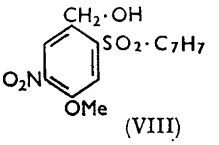
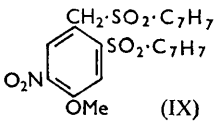

(VIII)

benzene ring, was secured by synthesis of the methoxybenzyl chloride (IV; R = Me). Successive treatment of methyl 2,4-dichloro-5-nitrobenzoate (V) with sodium methoxide and the potassium salt of *p*-methyl(thiophenol) afforded a product (VI) with the required orientation, as was shown by its conversion into the thioxanthone derivative (VII). Oxidation of the sulphide (VI) to the sulphone, followed by reduction of the derived acid chloride, gave the benzyl alcohol (VIII), and hence, by treatment with phosphorus pentachloride, the benzyl chloride (IV; R = Me).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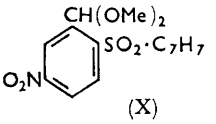
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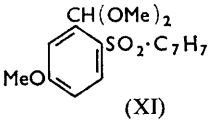
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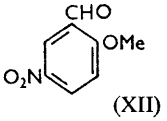
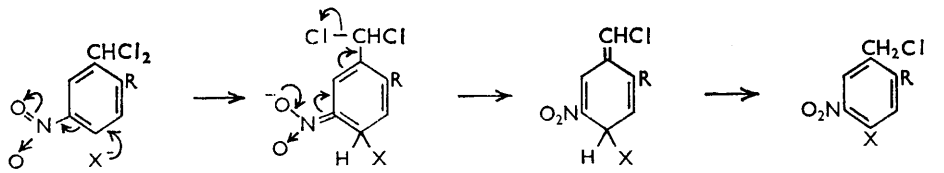

(XII)

The bis-sulphone (IX) was one of a mixture of by-products formed, together with the benzyl chloride (IV; R = Me) (17%), when the dichloride (II) was heated with sodium carbonate in aqueous methanol. At some stage, therefore, replacement of a sulphonyl substituent must occur, affording sodium toluene-*p*-sulphinate which, as was independently shown, reacts with the methoxybenzyl chloride to form the bis-sulphone. Although the source of the toluene-*p*-sulphinate was not directly established, it is known that both the nitro- and sulphonyl groups are mobile in derivatives of *o*- and *p*-nitrodiphenyl sulphone.[2] Because of this mobility the abnormal reaction course observed with the dichloride (II) is largely superseded when, as in the acetal (X), the side-chain substituent is much inferior to chloride as a leaving group. Thus, from the interaction of the acetal (X) and sodium methoxide there were isolated (i), by acidification of a water-soluble fraction, di(toluene-*p*-sulphonyl)hydroxylamine, $(C_7H_7SO_2)_2NOH$, a product indicating formation and combination of nitrous and toluene-*p*-sulphinic acid, (ii) the methoxy-acetal (XI), formed by displacement of the nitro-group, and (iii), after hydrolysis and isolation as the anil, 2-methoxy-5-nitrobenzaldehyde (XII), representing the product from displacement of the toluene-*p*-sulphonyl group; there was no evidence of an abnormal reaction. It is, therefore, probable that, together with the benzyl chloride (IV; R = Me), some of the acetal (X) is formed from the dichloride (II), and gives rise to the sulphinate by which the bis-sulphone (IX) is produced.

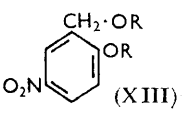
The mechanism shown, which plausibly accounts for the abnormal replacement reactions, presents a novel and interesting variant of nucleophilic substitution at an aromatic centre. The overall result, *i.e.*, entry of the attacking anion at a site remote from that



occupied by the leaving group, recalls a number of S_N2' reactions which are mainly aliphatic in type [3] but include formation of 2-cyano- and 2-methoxy-5-methylfuran from furfuryl chloride by cyanide [4] and methoxide [5] attack, respectively. In the present case, however,

[2] Loudon and Shulman, *J.*, 1941, 722.
[3] DeWolfe and Young, *Chem. Rev.*, 1956, **56**, 769.
[4] Reichstein, *Ber.*, 1930, **63**, 749; Runde, Scott, and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 1284.
[5] Kland-English and Wilson, Abstr. 119th Meeting Amer. Chem. Soc., New York, 1951, p. 48-M.

it can hardly be doubted that the nitro-group plays an important part, and a search of the literature discloses only one report of a truly cognate reaction. Kliegl and Hölle [6] noted that normal formation of 3-nitrobenzylidene acetals (XV) by the action of sodium alkoxide on 3-nitrobenzylidene dichloride was accompanied by abnormal formation of the mixed 2-alkoxy-5-nitro- and 4-alkoxy-3-nitro-benzyl alkyl ethers, (XIII) and (XIV). The proportion of abnormal products isolated was always small, but increased with alkoxides in ascending order ($MeO^- < EtO^- < Pr^nO^-$) and, for the reaction with ethoxide, was doubled (XIII, 6·5% yield; XIV, 16% yield) when 3-nitrobenzylidene dibromide was used in place of the dichloride. Kliegl and Hölle's work has been overlooked in current surveys of nucleophilic aromatic substitution. Analogy with the reaction (II) ⟶ (IV) now disposes of the possibility that the abnormal course proceeds through an acetal type of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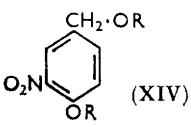
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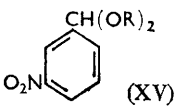
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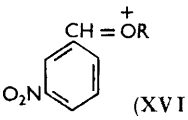
(XVI)

intermediate, as (XV), and a highly electrophilic entity such as (XVI). It is, therefore, to be expected that circumstances which operate against direct replacement of halogen will favour the abnormal course. In particular, the large favourable influence of the sulphonyl substituent in (II) could well combine a steric effect with a contribution to the general electrophilic character of the nucleus. The latter contribution, however, is probably the more significant, since the rate of hydrolysis of benzylidene dichloride in aqueous alkali is independent of the concentration of alkali [7] and is diminished by electron-withdrawing substituents in the ring.[8]

The dipiperidino-compound (III) is similarly regarded as the product of a two-stage reaction from the dichloride (II), but here the intermediate benzyl chloride was not isolated, the use of a deficiency of piperidine merely leading to the same products together with unchanged dichloride. Compared with ethoxide, piperidine as reagent gave a smaller proportion of abnormal product. Indeed, in experiments made by Mr. H. Clark, no abnormal product was found from its action with 3-nitrobenzylidene dichloride, in contrast with reactions of the S_N2' type, where uncharged reagents are usually more effective than anions.

Experimental

Light petroleum had b. p. 60—80°.

4-(2-Dichloromethyl-4-nitrophenylsulphonyl)benzoic acid.—A solution of sodium dichromate (0·4 g.) in water (1 ml.) and concentrated sulphuric acid (0·5 ml.) was added to a solution of 5-nitro-2-toluene-*p*-sulphonylbenzylidene dichloride [9] (II) (0·1 g.) in acetic acid (3 ml.), and the mixture heated under reflux for 2 hr., cooled, and poured into water. The precipitated *acid* (69%) was filtered off, m. p. 250° (from acetic acid) (Found: C, 43·2; H, 2·4; Cl, 18·2; N, 3·8. $C_{14}H_9Cl_2NO_6S$ requires C, 43·1; H, 2·3; Cl, 18·2; N, 3·6%).

Reaction of the Dichloride (II) *with Piperidine.*—The dichloride (0·3 g.) was heated for 5 min. with piperidine (3 ml.) at 100° and the cooled mixture added to crushed ice, to give an orange-yellow solid.

(*a*) The colourless solution, obtained by dissolving this solid in concentrated hydrochloric acid, was gently heated, whereupon 5-nitro-2-toluene-*p*-sulphonylbenzaldehyde,[9] m. p. and mixed m. p. 140—142°, was precipitated. Basification of the acidic filtrate gave N-(*5-nitro-4-piperidino-2-toluene*-p-*sulphonylbenzyl*)*piperidine* (III), m. p. 154° (from light petroleum–benzene) (Found: C, 63·1; H, 6·8; N, 8·8. $C_{24}H_{31}N_3O_4S$ requires C, 63·0; H, 6·8; N, 9·2%).

(*b*) Separation of the crude product by chromatography in benzene on silica gel gave the sulphone-aldehyde (33%) eluted with benzene, and the orange dipiperidino-compound (43%) eluted with 10% ether–benzene.

[6] Kliegl and Hölle, *Ber.*, 1926, **59**, 901.
[7] Olivier and Weber, *Rec. Trav. chim.*, 1934, **53**, 869.
[8] Asinger and Lock, *Monatsh.*, 1933, **62**, 323.
[9] Loudon and Smith, preceding Paper.

4-Ethoxy-5-nitro-2-toluene-p-sulphonylbenzyl Chloride (IV; R = Et).—(*a*) 5-Nitro-2-toluene-*p*-sulphonylbenzylidene dichloride (II) (360 mg.) was suspended in a solution of sodium ethoxide (from sodium, 23 mg.) in dry ethanol (5 ml.), and the mixture heated under reflux for 1 hr.

(*b*) The dichloride (II) (500 mg.), AnalaR sodium carbonate (500 mg.), ethanol (40 ml.), and water (10 ml.) were heated together under reflux for 1½ hr. In each case the *benzyl chloride* (68—70%) crystallised as the reaction proceeded, m. p. 194° (from benzene–light petroleum) (Found: C, 52·2; H, 4·3; N, 4·0. $C_{16}H_{16}ClNO_5S$ requires C, 52·0; H, 4·4; N, 3·9%).

4-Ethoxy-5-nitro-2-toluene-p-sulphonylbenzyl ethyl ether, m. p. 116° (from ethanol), was formed when a solution of the chloride (IV; R = Et) and sodium ethoxide (1 equiv.) in ethanol was boiled for 30 min. It was purified by chromatography in benzene on alumina (Found: C, 56·75; H, 5·6; N, 3·7. $C_{18}H_{21}NO_6S$ requires C, 57·0; H, 5·6; N, 3·7%).

N-(4-Ethoxy-5-nitro-2-toluene-p-sulphonylbenzyl)piperidine, produced when the chloride (IV; R = Et) (0·1 g.) and piperidine (1 ml.) were heated together at 100° for 5 min., had m. p. 136° (from ethanol) (Found: C, 60·4; H, 6·4; N, 6·7. $C_{21}H_{26}N_2O_5S$ requires C, 60·3; H, 6·3; N, 6·7%).

4-Methoxy-5-nitro-2-toluene-p-sulphonylbenzyl chloride (IV; R = Me), m. p. 160° (from acetic acid–methanol), was formed in 58% yield by the interaction of the dichloride (II) and sodium methoxide (1 equiv.) in methanol, as for the ethoxy-analogue (Found: C, 50·7; H, 4·0; N, 4·1. $C_{15}H_{14}ClNO_5S$ requires C, 50·6; H, 4·0; N, 3·9%). The derived *benzyl methyl ether* had m. p. 104° (from methanol) (Found: C, 54·4; H, 5·05; N, 4·0. $C_{16}H_{17}NO_6S$ requires C, 54·7; H, 4·9; N, 4·0%), and the *N-benzylpiperidine* had m. p. 134° (from methanol) (Found: C, 59·2; H, 5·9; N, 7·0. $C_{20}H_{24}N_2O_5S$ requires C, 59·4; H, 6·0; N, 6·9%).

Reaction of the dichloride (II) with sodium carbonate in aqueous methanol gave a mixture of products which was chromatographed in benzene on silica gel. Elution with benzene gave the chloride (IV; R = Me) (17%). A solid obtained by elution with 10% ether–benzene was identified (mixed m. p. and infrared spectrum) as 4-methoxy-5-nitro-2-toluene-*p*-sulphonyl benzyl *p*-tolyl sulphone (IX) (see below).

Methyl 2,4-Dichloro-5-nitrobenzoate (V).—A solution of 2,4-dichloro-5-nitrobenzoic acid (25 g.) in methanol (125 ml.) and concentrated sulphuric acid (12·5 ml.) was heated under reflux for 5 hr. and concentrated until it became turbid. The methyl ester (88%) crystallised from the cooled solution, m. p. 62° (from methanol) (lit.,[10] 62°).

Methyl 2-Chloro-4-methoxy-5-nitrobenzoate.—A solution of sodium methoxide (from sodium, 1·85 g.) in dry methanol (50 ml.) was added to a warm solution of the above ester (V) (20 g.) in dry methanol (250 ml.), and the mixture heated under reflux for 1 hr., concentrated to *ca.* 200 ml., and cooled. The *methoxy-ester* (12·4 g., 63%) had m. p. 133° (from methanol) (Found: C, 43·9; H, 3·4. $C_9H_8ClNO_5$ requires C, 44·0; H, 3·3%). The mother-liquors were combined and concentrated, affording a solid, m. p. 60—78°, a portion of which was chromatographed in benzene on alumina (Grade I). A fraction eluted with benzene and repeatedly crystallised from methanol gave methyl 4-chloro-2-methoxy-5-nitrobenzoate, m. p. 103° (lit.,[10] 107·5°) (Found: C, 43·9; H, 2·9%). Elution with 25% benzene–ether gave methyl 2,4-dimethoxy-5-nitrobenzoate, m. p. 149° (from methanol) (lit.,[11] 150°) (Found: C, 49·8; H, 4·85. Calc. for $C_{10}H_{11}NO_6$: C, 49·8; H, 4·6%).

Methyl 4-Methoxy-5-nitro-2-(p-tolylthio)benzoate (VI).—To a warm solution of methyl 2-chloro-4-methoxy-5-nitrobenzoate (12·3 g.) and *p*-methyl(thiophenol) (6·2 g.) in dry methanol (200 ml.) was added AnalaR potassium carbonate (3·5 g.), and the mixture heated under reflux for 2 hr. and filtered hot. The pale yellow solid was washed with hot water and recrystallised from acetic acid. The *sulphide-ester* (VI) had m. p. 213° (Found: C, 57·5; H, 4·5; N, 4·3. $C_{16}H_{15}NO_5S$ requires C, 57·65; H, 4·5; N, 4·2%). Unreacted chloro-ester (3 g.) crystallised from the cooled filtrate; it was treated with the appropriate quantities of *p*-methyl(thiophenol) and potassium carbonate, so giving more of the sulphide-ester (total yield, 12·7 g.).

4-Methoxy-5-nitro-2-(p-tolythio)benzoic acid, m. p. 263° (from acetic acid), was obtained when the ester (VI) (0·5 g.) was heated with acetic acid (20 ml.), water (10 ml.), and concentrated sulphuric acid (10 ml.) for 5 hr., and the cooled solution was poured into water (Found: C, 56·5; H, 3·9; N, 4·4. $C_{15}H_{13}NO_5S$ requires C, 56·4; H, 4·1; N, 4·4%). When heated with concentrated sulphuric acid (15 min. at 100°) it was cyclised to *3-methoxy-7-methyl-2-nitrothioxanthone* (VII), m. p. 293° (from dimethylformamide) (Found: C, 59·9; H, 3·75; N, 4·7. $C_{15}H_{11}NO_4S$ requires C, 59·8; H, 3·7; N, 4·65%).

[10] Goldstein and Schaaf, *Helv. Chim. Acta*, 1957, **40**, 369, 1187.
[11] Goldstein and Jaquet, *Helv. Chim. Acta*, 1941, **24**, 34.

4-Methoxy-5-nitro-2-toluene-p-*sulphonylbenzoic Acid.*—A solution of the sulphide-ester (VI) (10 g.) in acetic acid (300 ml.) at 100° was treated with 30% hydrogen peroxide (100 ml.), and the solution heated at 100° for 30 min., cooled, and added to ice–water, to give *methyl 4-methoxy-5-nitro-2-toluene*-p-*sulphonylbenzoate* (9·64 g., 88%), m. p. 165° (from acetic acid) (Found: C, 52·85; H, 4·3; N, 4·1. $C_{16}H_{15}NO_7S$ requires C, 52·6; H, 4·1; N, 3·8%). It was hydrolysed by sulphuric–acetic acid to the corresponding *benzoic acid*, m. p. 242° (from acetic acid–water) (Found: C, 51·2; H, 3·9; N, 4·2. $C_{15}H_{13}NO_7S$ requires C, 51·3; H, 3·7; N, 4·0%).

4-Methoxy-5-nitro-2-toluene-p-*sulphonylbenzyl Alcohol* (VIII).—Thionyl chloride (15 ml.) was added to a suspension of 4-methoxy-5-nitro-2-toluene-*p*-sulphonylbenzoic acid (1 g.) in benzene (20 ml.), and the mixture heated under reflux until the acid had dissolved and gas evolution ceased (*ca.* 1½ hr.). Evaporation of the solution *in vacuo* gave the *acid chloride* as a colourless crystalline solid which was dissolved in AnalaR dioxan (30 ml.) and added dropwise to a stirred suspension of sodium borohydride (1 g.) in the same solvent (25 ml.). The mixture was stirred at room temperature for 30 min., heated under reflux for 1 hr., cooled, and poured into ice–water. Crystallisation of the solid product from methanol gave the *alcohol* (VIII) (0·68 g., 70%), m. p. 157° (Found: C, 53·25; H, 4·5; N, 4·2. $C_{15}H_{15}NO_6S$ requires C, 53·4; H, 4·5; N, 4·15%).

A mixture of the alcohol (0·2 g.) and phosphorus pentachloride (1 g.) was heated (violent reaction) until a clear melt was obtained. This was maintained for 10 min. at 100°, cooled, and added to ice–water. The solid product was extracted with benzene, and the extract dried ($MgSO_4$) and evaporated, giving 4-methoxy-5-nitro-2-toluene-*p*-sulphonylbenzyl chloride, m. p. and mixed m. p. 156—158°.

4-Methoxy-5-nitro-2-toluene-p-*sulphonylbenzyl* p-*Tolyl Sulphone* (IX).—A solution of the benzyl chloride (IV; R = Me) (180 mg.) and sodium toluene-*p*-sulphinate (150 mg.) in dimethylformamide (2·5 ml.) and water (0·5 ml.) was heated at 100° for 2 hr., and diluted with water (1 ml.). The *bis-sulphone* (IX) crystallised from the cooled solution, m. p. 166° (from methanol) (Found: C, 55·3; H, 4·3; N, 3·0. $C_{22}H_{21}NO_7S_2$ requires C, 55·6; H, 4·5; N, 2·95%).

αα-Dimethoxy-5-nitro-2-toluene-p-*sulphonyltoluene* (X).—A suspension of 5-nitro-2-toluene-*p*-sulphonylbenzaldehyde [9] (1 g.) in methanol (2 ml.) was treated with concentrated sulphuric acid (0·3 ml.). After a few minutes, the suspension became sticky, and a crystalline solid gradually separated. This was washed with dilute sodium carbonate then water, dried, and recrystallised from methanol, affording the *acetal* (X) (0·7 g.), m. p. 107° (Found: C, 54·8; H, 4·7; N, 4·4. $C_{16}H_{17}NO_6S$ requires C, 54·7; H, 4·9; N, 4·0%).

Reaction of the Acetal (X) *with Sodium Methoxide.*—A solution of the acetal (350 mg.) and sodium methoxide (from sodium, 25 mg.) in dry methanol (4 ml.) was heated under reflux for 2 hr.; the methanol was evaporated, and the residue extracted with ether. The ether-insoluble solid was dissolved in water, and acidified; the white precipitate was identified as di(toluene-*p*-sulphonyl)hydroxylamine, by m. p. and mixed m. p. 120—122° (decomp.) (from methanol) and by infrared spectroscopy (Found: C, 49·25; H, 4·2. Calc. for $C_{14}H_{15}NO_5S_2$: C, 49·3; H, 4·4%). Evaporation of the ether extract at room temperature gave a mixture of colourless crystals and a yellow gum. The crystals, washed free from gum with ether gave *5,αα-trimethoxy-2-toluene*-p-*sulphonyltoluene* (XI), m. p. 105° (from methanol) (Found: C, 60·2; H, 5·9. $C_{17}H_{20}O_5S$ requires C, 60·7; H, 6·0%). The gum was hydrolysed by boiling with 6N-sulphuric acid (3 ml.) and acetic acid (2 ml.) for 1 hr., and the product poured into water and extracted with ether. The washed ($NaHCO_3$, H_2O) and dried ($MgSO_4$) extract, on evaporation, afforded a mixture, one component of which was sparingly soluble in ether. It was identified (m. p. and infrared spectrum) as 5-nitro-2-toluene-*p*-sulphonylbenzaldehyde. The ether-soluble portion was extracted with boiling water, affording a low-melting solid whose infrared spectrum was almost identical with that of 2-methoxy-5-nitrobenzaldehyde (XII). It was converted, by heating for a few minutes with a solution of *p*-toluidine in ethanol, into *N*-(2-methoxy-5-nitrobenzylidene)-*p*-toluidine,[12] m. p. and mixed m. p. 163—165° (from ethanol).

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[12] Chakravarti, *Current Sci.*, 1935, **4**, 26.