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THE NITRATION OF SOME PHENYL SUBSTITUTED INDOLES

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Abstract—The products of nitration of 2,3-diphenylindole depend on whether the reaction is carried out in acetic or in sulphuric acid solution. The 6-nitro derivative is the only product in the first case, while in the second case 3-(*p*-nitrophenyl)-2-phenylindole is the first product, which is nitrated further to 5-nitro-3-(*p*-nitrophenyl)-2-phenylindole. Sulphuric acid nitration of 2-methyl-3-phenylindole takes a similar course, while that of 3-methyl-3-phenylindole gives the 5-nitro derivative in 80% yield, no nitration of the 2-phenyl substituent taking place.

PREVIOUS work on the nitration of indole derivatives[1] has been extended to some phenyl substituted indoles, in order to compare the reactivity towards nitronium ions of the indole benzene ring positions and of those of phenyl substituents on the pyrrole ring. The only known case in this field is the nitration of 2,3-diphenylindole (I) with nitric acid in acetic acid medium, which gives the 6-nitro derivative in 25% yield.[2] We have found that even using a milder reagent, $Cu(NO_3)_2$ in acetic acid, the yield is not improved, 6-nitro-2,3-diphenylindole (II, Chart I) being isolated in 21% yield as the only crystalline product. Nitration at the 4- and/or 6-position of the unprotonated indole nucleus has been shown to occur in many other instances.[3] Steric hindrance by the 3-phenyl group no doubt accounts for the lack of reactivity at the 4-position in I.

The nitration of I in conc. sulphuric acid takes a completely different course: 3-(*p*-nitrophenyl)-2-phenylindole (III, 6%) and 5-nitro-3-(*p*-nitrophenyl)-2-phenylindole (IV, 17%) are obtained, but no trace of II is formed. The dinitro derivative (IV) is also obtained on further nitration of III under similar conditions. The structure of III was proved by a stepwise degradation (Chart II), involving oxidation to the keto amide (VI), hydrolysis of the latter to 2-amino-4′-nitrobenzophenone (VII) and Baeyer-Villiger oxidation of VII followed by hydrolysis of the ester (VIII) to give *p*-nitrobenzoic acid (IX). Additional evidence came from the synthesis of III by cyclization of α-(*p*-nitrophenyl)acetophenone phenylhydrazone (V). Elucidation of the structure of IV was obtained by peroxyacetic acid oxidation to 2-benzamido-4′,5-dinitrobenzophenone (X), hydrolysis of the latter to the corresponding amino-compound (XI) and benzoic acid, and conversion of XI by deamination to the known 3,4′-dinitrobenzophenone[4] (XII). The results of this degradative procedure do not preclude *a priori* 6-nitro-3-(*m*-nitrophenyl)-2-phenylindole or 7-nitro-3-(*p*-nitrophenyl)-2-phenylindole as structures for compound IV. These however, were discarded on

[1] Previous publication: G. Berti, A. Da Settimo and O. Livi, *Tetrahedron* **20**, 1397 (1964).

[2] D. A. Kinsley and S. G. P. Plant, *J. Chem. Soc.* 1 (1958).

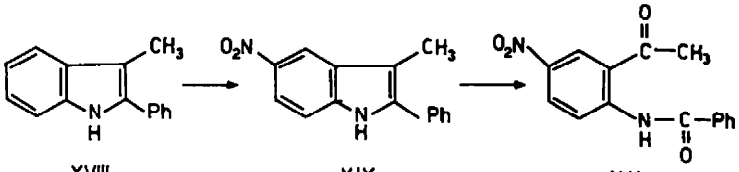
[3] [a] R. De Fazi, G. Berti and A. Da Settimo, *Gazz. Chim. Ital.* **89**, 2238 (1959); [b] G. Berti and A. Da Settimo, *Ibid.* **91**, 728 (1961); [c] A. Da Settimo, *Ibid.* **92**, 150 (1962); [d] W. E. Noland and D. Rieke, *J. Org. Chem.* **27**, 2250 (1962).

[4] L. Gattermann and H. Rüdt, *Ber. Dtsch. Chem. Ges.* **27**, 2293 (1894).

consideration that IV is produced on further nitration of the 3-(*p*-nitrophenyl) derivative (III) and that no examples are reported in the literature of direct nitration of indoles in the 7-position, the 5-position being strongly favoured in sulphuric acid medium.[5]

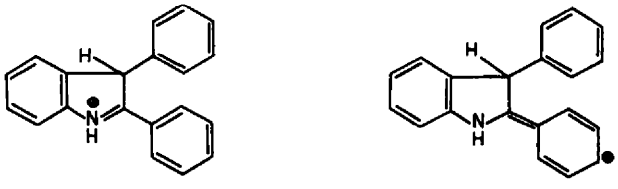
Nitration of 2-methyl-3-phenylindole (XIII) with KNO_3 in conc. sulphuric acid (Chart III) gives, as in the case of I, a mixture of a mono- and dinitro derivatives, identified as 2-methyl-3-(*p*-nitrophenyl)- (XIV, 13%) and 2-methyl-5-nitro-3-(*p*-nitrophenyl)indole (XV, 2%). Further nitration of XIV in conc. sulphuric acid gives XV. The structures of XIV and XV were established by peroxyacetic acid oxidation to the keto amides (XVII and XVI), these give on hydrolysis the products already obtained in the degration of III and IV, namely, 2-amino-4'-nitrobenzophenone (VII) and 2-amino-4',5-dinitrobenzophenone (XI) respectively.

Nitration of 3-methyl-2-phenylindole (XVIII) in conc. sulphuric acid gives in good yield (80%) the 5-nitro derivative (XIX) as the only crystalline reaction product, the structure of which was proved by its identity with an authentic sample prepared according to Atkinson *et al.*,[6] and by peroxyacetic acid oxidation to the known 2-benzamido-5-nitroacetophenone[6] (XX).



XVIII XIX XX

The present results indicate that while the 3-phenyl group is less reactive than the indole benzene ring towards an electrophilic reagent in unprotonated indoles (acetic acid solution), it is more reactive in protonated ones (sulphuric acid solution). The fact that the 2-phenyl group is not nitrated in any case, may be rationalized on the following basis. 3-Protonation of indole derivatives in conc. sulphuric acid is well-established.[7] Therefore, in strongly acidic media 3-arylindoles should assume the structure XXI, where the 3-phenyl group may be expected to show the reactivity of an alkyl substituted benzene ring, steric reasons strongly favouring the *p*- over the *o*-position. The positively charged nitrogen should deactivate both the indole aromatic



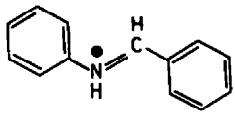
XXI XXII

[5] cf. e.g. W. E. Noland, L. R. Smith and D. C. Johnson, *J. Org. Chem.* **28**, 2262 (1963). For details on a recent procedure for nitration of indoles in the 7-position (the "indoline method"), see W. E. Noland and K. R. Rush, *Ibid.* **29**, 947 (1964); and Refs. therein.

[6] C. M. Atkinson, J. C. E. Simpson and A. Taylor, *J. Chem. Soc.* 165 (1954).

[7] [a] G. Berti, A. Da Settimo and D. Segnini, *Gazz. Chim. Ital.* **91**, 571 (1961); [b] R. L. Hinman and J. Lang, *Tetrahedron Letters* No 21, 12 (1960); [c] R. L. Hinman and E. B. Whipple, *J. Amer. Chem. Soc.* **84**, 2534 (1962).

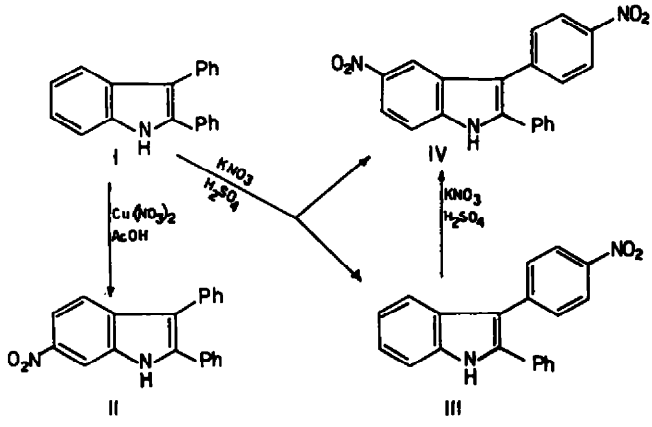
nucleus and the 2-phenyl group, but a larger degree of deactivation of the 2-substituent, due to the conjugation with the positive group (as e.g. in XXII), is to be expected. The 5-position has been reported by several Authors[3b,5,8] to be the usual site of electrophilic attack in protonated indoles and this has been confirmed. A parallel has been drawn[3b] between 3-protonated indoles and protonated N-benzylideneaniline (XXIII),



XXIII

which also undergoes nitration at the *p*-position of the aniline ring,[9] in spite of the adjacent positive charge. A recent investigation on the nitration of some indolenines,[10] which may be considered as analogs of 3-protonated indoles, shows nitration to occur in 77–88% yield at the 5-position, thus lending further support to the theory involving participation of structures such as XXI in the 5-nitration of indoles in sulphuric acid.

CHART I



EXPERIMENTAL[11]

Nitration of 2,3-*diphenylindole* (I) *in acetic acid*

To a solution of I[12] (1·0 g) in 7 ml glacial acetic acid was added a solution of $Cu(NO_3)_2$ (0·54 g) in 5 ml glacial acetic acid. The mixture was heated 10 min on a steam-bath, then poured onto crushed ice. The orange precipitate (0·95 g) was filtered off, washed with water, dried, and repeatedly extracted with pet. ether. The insoluble part (0·5 g) was dissolved in benzene and chromatographed

[8] H. Bauer and E. Strauss, *Ber. Dtsch. Chem. Ges.* **65**, 308 (1932).

[9] F. Arnall and T. Lewis, *J. Soc. Chem. Ind.* **48T**, 159 (1929).

[10] K. Brown and A. R. Katritzky, *Tetrahedron Letters* No. 14, 803 (1964).

[11] M.ps were determined on a Kofler apparatus, and are not corrected. IR spectra were recorded on a Perkin–Elmer Infracord Model 137 spectrophotometer, in Nujol mulls. UV spectra were obtained using a Beckman Model DU spectrophotometer. Analyses were performed by Alfred Bernhardt Microanalytical Laboratory, Mülhein, Germany. Pet. ether refers to the fraction b.p. 40–60°. Identity of compounds was proved by mixture m.ps and comparison of IR spectra.

[12] Prepared according to F. R. Japp and T. S. Murray, *J. Chem. Soc.* 889 (1894).

CHART II

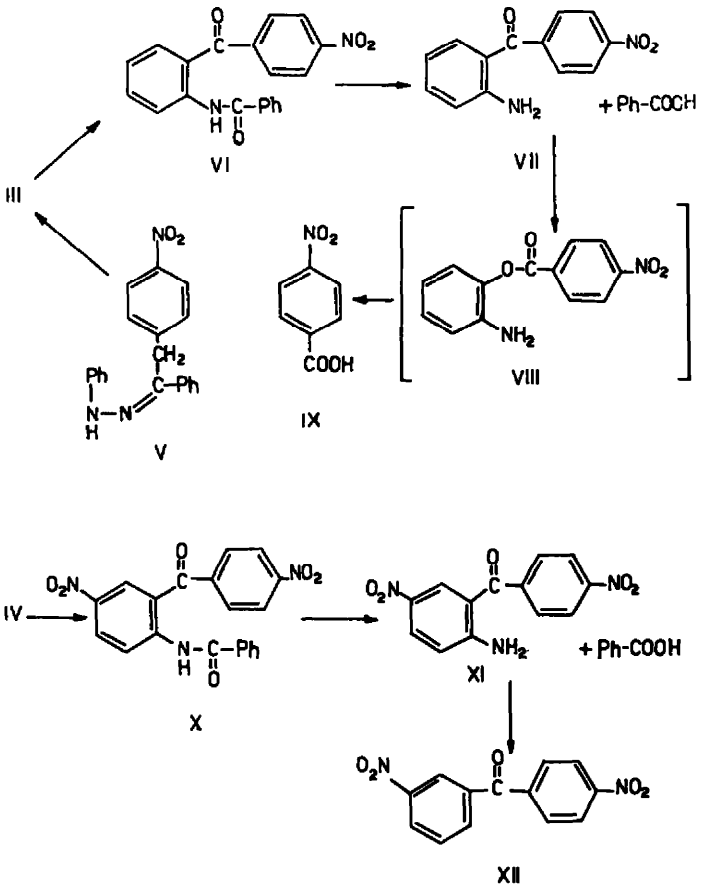


CHART III

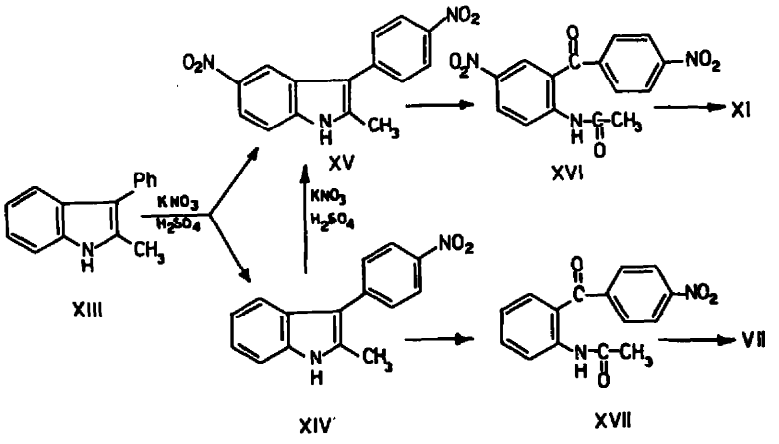


TABLE 1. ULTRAVIOLET ABSORPTION MAXIMA[a] OF THE NITROINDOLES IN 95% ETHANOL

II	III	IV	XIV	XV
252 (4·35)	239 (4·43)	220[b]	223 (4·50)	230[b]
295 (4·08)	304 (4·24)	292 (4·52)	268 (4·05)	270 (4·34)
346 (4·01)	405 (3·94)	330[b]	396 (4·05)	344 (4·10)
401 (4·12)				

[a] λ_{max}, mμ (log ε);
[b] inflection

on a 20 × 1·1 cm column of neutral Al_2O_3 (act. I). Elution with benzene gave 0·25 g (21%) pure II, m.p. 227–228° after recrystallization from 95% EtOH. This material was identical with an authentic sample prepared by the method of Schofield and Theobald.[13] Further elution with benzene and with more polar solvents produced only amorphous, non-identified material.

Nitration of I *in sulphuric acid*

To a solution of I (5 g) in 45 ml of conc H_2SO_4, cooled below 0° in a salt-ice bath, a solution of KNO_3 (1·9 g) in 10 ml conc H_2SO_4 was slowly added, with stirring. The mixture was stirred at room temp for an additional 40 min, then poured onto crushed ice. The yellow precipitate was filtered off, washed with water, dried, and extracted with 600 ml boiling benzene, 1·0 g of tarry material remaining insoluble. The benzene solution, concentrated to 400 ml, deposited on standing at 0° overnight 1·0 g crystalline material. This was recrystallized twice from 1:1 benzene–EtOH to give 0·6 g IV as yellow plates, m.p. 300–302°. (Found: C, 67·14; H, 3·70; N, 11·70. $C_{20}H_{12}N_2O_4$ requires: C, 66·85; H, 3·65; N, 11·70%.) The filtrate from IV was chromatographed through a 49 × 3·6 cm column of neutral Al_2O_3, using benzene as eluent, to give 0·33 g (5·6%) III as orange prisms from benzene, m.p. 234–235°. (Found: C, 76·47; H, 4·61; N, 8·65. $C_{20}H_{14}N_2O_2$ requires: C. 76·42; H, 4·49; N, 8·91%.) Further elution yielded 0·3 g of an unidentified compound, m.p. 321–323°. (Found: C, 82·12; H, 4·81; N, 7·43%), and 0·53 g of IV (overall yield of IV, 16·5%).

Nitration of 3-(p-*nitrophenyl*)-2-*phenylindole* (III)

A solution of KNO_3 (37 mg) in 0·5 ml conc. H_2SO_4 was slowly added with stirring to a solution of III (70 mg) in 1·0 ml conc. H_2SO_4, while cooling in a salt–ice bath. The mixture was kept 30 min at room temp, then poured onto crushed ice. The precipitate was filtered, washed with water, dried, and extracted with boiling benzene, 25 mg of tarry material remaining insoluble. The benzene extract was chromatographed through a 28 × 1·0 cm column of neutral Al_2O_3 and eluted with benzene to yield 25 mg pure IV.

Structure proof of 3-(p-*nitrophenyl*)-2-*phenylindole* (III)

(a) *Degradation to* p-*nitrobenzoic acid.* To a suspension of III (0·15 g) in 5 ml glacial acetic acid was added 3·5 ml 35% H_2O_2. The mixture was kept at room temp until the color of the suspended product turned from dark orange to yellow (about 30 days), it then was filtered. The residue was washed with water, dried, and crystallized from MeOH to yield 0·12 g VI as yellow needles, m.p. 187–189°, λ_{NH} 3·01; λ_{CO} 5·96, 6·11 μ. (Found: C, 69·28; H, 4·21; N, 8·27. $C_{20}H_{14}N_2O_4$ requires: C, 69·36; H, 4·07; N, 8·09%.) A suspension of VI (70 mg) in a mixture of water, conc. H_2SO_4 and glacial acetic acid (2·0:2·2:2·5 ml), was refluxed for 20 min. The resulting solution was poured onto crushed ice and filtered. The filtrate was buffered to pH 5 with sodium acetate, causing precipitation of a solid (50 mg). This was crystallized from EtOH to give VII as orange needles, m.p. 156–157°. (Found: C, 64·17; H, 4·40; N, 11·50. $C_{13}H_{10}N_2O_3$ requires: C, 64·46; H, 4·16; N, 11·57%.) The mother liquor of VII on acidification and extraction with ether gave 25 mg pure benzoic acid. A solution of VII (40 mg) in a mixture of glacial acetic acid (4 ml) and 35% H_2O_2 (1·0 ml) was heated 40 min on a steam-bath. The solution was filtered, evaporated to dryness, and the residue saponified by refluxing 1 hr in 3 ml of 2 N NaOH. Acidification of the cooled reaction mixture afforded IX, identical with an authentic sample.[5]

[13] K. Schofield and R. S. Theobald, *J. Chem. Soc.* 1505 (1950).

(b) *Fischer synthesis.* A hot solution of α-(p-*nitrophenyl*)*acetophenone*[14] (0·5 g) in 50 ml of 95% EtOH was treated with water until the solution was faintly turbid. Phenylhydrazine (0·5 g) and glacial acetic acid (0·2 ml) were then added, and the mixture was heated 30 min on a steam-bath. Water (50 ml) was added to the cooled solution, and the product which separated (0·55 g) was filtered and recrystallized from EtOH to give V as orange needles, m.p. 137–138°. (Found: C, 72·54; H, 5·24; N, 12·71. $C_{20}H_{17}N_3O_2$ requires: C, 72·49; H, 5·17; N, 12·68%.) A solution of V (50 mg) in 1·5 ml glacial acetic acid and 1·0 ml conc. HCl was heated 10 hr under reflux, then allowed to cool and filtered. The residue was washed with water, dried (34 mg), and recrystallized from benzene to yield pure III, identical with the product previously obtained.

*Structure proof of 5-nitro-*3-(p-*nitrophenyl*)-2-*phenylindole* (IV)

A mixture of IV (0·5 g), glacial acetic acid (15 ml), and 35% H_2O_2 (10 ml), was heated 4 hr on a steam bath, cooled, and filtered. The residue (0·48 g) was crystallized from 1:1 benzene–EtOH to give X as almost colorless needles, m.p. 262–264°, λ_{NH} 3·08; λ_{CO} 5·91, 6·11 μ. (Found: N, 10·60. $C_{20}H_{13}N_3O_6$ requires: N, 10·74%.) A suspension of X (0·38 g) in a mixture of water, conc. H_2SO_4, and glacial acetic acid (10:10:12 ml) was refluxed until the solid was completely dissolved (ca. 2 hr), then poured onto crushed ice and filtered. The residue (0·27 g) was crystallized from 1:1 benzene–EtOH to yield XI as small prisms, m.p. 279–281°. (Found: C, 53·99; H, 3·23; N, 14·73. $C_{13}H_9N_3O_5$ requires: C, 54·36; H, 3·16; N, 14·63%.) The acid mother liquor of XI gave, on extraction with ether, 55 mg benzoic acid. To a suspension of XI (0·19 g) in 0·9 ml 83% H_2SO_4 and 1·8 ml glacial acetic acid cooled in an ice-bath, 85 mg $NaNO_2$ was gradually added. Stirring at 0° was continued until all the solid had dissolved, then water (8 ml) and 40% NaH_2PO_2 (4 ml) were added. The mixture was kept at 0° overnight and filtered. The residue (0·17 g) was purified by crystallization from dil. acetic acid (charcoal), followed by sublimation at 155°/4 mm. The pure product, m.p. 169–171° was identical with an authentic sample of XII prepared by the method of Gattermann and Rüdt.[4]

Nitration of 2-*methyl*-3-*phenylindole* (XIII)

To a solution of XIII[15] (5 g) in 50 ml conc. H_2SO_4 a solution of KNO_3 (2·9 g) in 20 ml conc. H_2SO_4 was added dropwise with stirring while the flask was cooled in a salt–ice bath. The mixture was kept 45 min at room temp, then poured onto crushed ice. The yellow ppt. was filtered, washed with water, dried and extracted with three 150-ml portions of boiling benzene, 1g of tarry material remaining insoluble. The benzene solution was chromatographed through a 53 × 3·5 cm column of neutral Al_2O_3 (act. I), using benzene as eluent. A first yellow band yielded 0·8 g of a product (yellow needles, m.p. 214–216° after 2 recrystallizations from EtOH), which was identified as XIV. (Found: C, 71·22; H, 4·72; N, 11·10. $C_{15}H_{12}N_2O_2$ requires: C, 71·41; H, 4·80; N, 11·11%.) A second orange band yielded a semicrystalline material which was crystallized once from benzene and twice from 1:1 benzene–EtOH to yield 0·15 g XV, as yellow prisms, m.p. 305–307°. (Found: C, 61·01; H, 3·82; N, 14·26. $C_{15}H_{11}N_3O_4$ requires: C, 60·60; H, 3·73; N, 14·14%.)

Nitration of 2-*methyl*-3-(p-*nitrophenyl*)*indole* (XIV)

To a solution of XIV (0·1 g) in 1·0 ml conc. H_2SO_4 was added a solution of KNO_3 (50 mg) in 0·5 ml of conc. H_2SO_4, while cooling the reaction mixture in a salt-ice bath. After 30 min at room temp, the mixture was poured onto crushed ice and worked up as described for the nitration of III, yielding as the only product, XV (45 mg), identical with that obtained previously.

Structure proof of 2-*methyl*-3-(p-*nitrophenyl*)*indole* (XIV)

A mixture of XIV (0·15 g), glacial acetic acid (6 ml), and 35% H_2O_2 (3·5 ml), was kept at room temp for 4 days, then evaporated under red press. The residue yielded on crystallization from EtOH aq, 70 mg crude XVII, λ_{NH} 3·06; λ_{CO} 5·91, 6·10 μ. This was directly saponified by refluxing for 15 min in a mixture of water, conc. H_2SO_4 and glacial acetic acid (2:2:1·5 ml). Addition of sodium acetate to the cooled and diluted reaction mixture caused precipitation of a solid. This was filtered off and crystallized from EtOH aq to yield 40 mg VII, identical with the material obtained previously.

[14] Prepared according to E. B. Womack, N. Campbell and G. B. Dodds, *J. Chem. Soc.* 1402 (1938).
[15] Prepared according to D. W. Ockenden and K. Schofield, *J. Chem. Soc.* 612 (1953).

Structure proof of 2-*methyl*-5-*nitro*-3-(p-*nitrophenyl*)*indole* (XV)

A mixture of XV (35 mg), glacial acetic acid (2 ml), and 35% H_2O_2 (1·0 ml), was heated 2 hr on a steam-bath. Evaporation of the solution under red. press. followed by crystallization of the residue from EtOH aq yielded 35 mg crude XVI, λ_{NH} 3·10; λ_{CO} 5·87; 6·08 μ; which was used without purification in the following step. XVI (25 mg) was saponified by refluxing for 25 min in a mixture of water, conc. H_2SO_4 and glacial acetic acid (1:1:1 ml). Dilution of the cooled reaction mixture gave a ppt (15 mg), which was crystallized from 1:1 benzene–EtOH to yield XI, identical with the material obtained previously.

Nitration of 3-*methyl*-2-*phenylindole* (XVIII)

To a solution of XVIII[16] (1·0 g) in 10 ml conc. H_2SO_4 was added dropwise and with stirring a solution of KNO_3 (0·54 g) in 2·5 ml conc. H_2SO_4. The temp of the reaction mixture was kept below 0° by cooling in a salt–ice bath. After stirring 30 min at 0° and 15 min at room temp, the mixture was poured onto crushed ice, and the yellow ppt filtered, washed with water, and dried. Crystallization from benzene (charcoal) afforded XIX (0·97 g; 80%), m.p. 194–195°. This was identical with an authentic sample prepared according to Atkinson *et al.*[6] A mixture of XIX (0·1 g), glacial acetic acid (3·5 ml) and 35% H_2O_2 (2 ml) was heated 1 hr on a steam-bath, cooled, and filtered. Crystallization of the residue from benzene afforded 0·1 g XX, m.p. 196–197°, (lit.[6] m.p. 194–195°).

Acknowledgment—We wish to thank Prof. Giancarlo Berti for many helpful discussions, and Mr. E. Nannipieri for performing part of the experimental work.

[16] Prepared by the method of H. M. Kissman, D. W. Farnsworth and B. Witkop, *J. Amer. Chem. Soc.* **74**, 3948 (1952).