For conversion to the sulfate XI, the purified dihydrochloride (5 g.) was dissolved in 8 ml. of water and treated with 12 ml. of 9 *N* sulfuric acid. Addition of 160 ml. of 2-propanol gave the sulfate XI as an oil which crystallized on standing and, after trituration with methanol, had m.p. 222–224° dec. Recrystallization, by the addition of absolute ethanol to a concentrated aqueous solution, did not change the melting point. This pure salt (XI) showed $\nu_{NH_3}^{Nujol}$ 2120, 2500–3200 cm.$^{-1}$; $\lambda_{max}^{H_2O}$ 222 mμ (ε 15,600), 308 mμ (ε 8950).

Anal. Calcd. for $C_8H_{12}N_4O_4S$: C, 36.92; H, 4.65; N, 21.55. Found: C, 36.96; H, 4.85; N, 21.47.

Acknowledgment.—The authors are indebted to Mrs. U. Zeek for the elemental analyses, to Mr. R. Puchalski for spectral data, and to Mr. George Conrad for the preparation of substantial quantities of some of the intermediates described herein.

Nitration of Indoles. III. Polynitration of 2-Alkylindoles[1]

WAYLAND E. NOLAND, LOWELL R. SMITH,[2a] AND KENT R. RUSH[2b]

School of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received February 15, 1965

Nitration in concentrated nitric acid of 2-methylindole and 1,2-dimethylindole gives the corresponding 3,6-dinitroindoles **5** and **16**; **5** was also obtained from 2-methylindole-3-carboxaldehyde and 2-methyl-6-nitroindole (**3**). 2-Methyl-3-nitroindole (**1**) and 2-methyl-3H-indol-3-one oxime (**2**) gives both **5** and 3,4-dinitro-2-methylindole (**6**); **6** was also obtained from 2-methyl-4-nitroindole (**4**). Further nitration of **5** and **16** or their precursors gives the 3,4,6-trinitroindoles **7** and **17**; 3-acetyl-2-methyl-4-nitroindole (**9**) and **4** also gave **7**. Nitration in concentrated nitric acid of 2-methyl-5-nitroindole (**20**) and 1,2-dimethyl-5-nitroindole (**27**) gives the corresponding 3,5-dinitroindoles **22** and **28**. Further nitration of **22** and **28** (or **27**) gives the 3,5,6-trinitroindoles **24** and **31**; **24** was also obtained from the 1-acetyl derivative (**21**) or **20**. Dimethylation of **22** gave 3,5-dinitro-2-*ethyl*-1-methylindole (**36**), as proved by preparation from 2-ethylindole *via* the 5-nitro (**34**) and 3,5-dinitro (**35**) derivatives and methylation to **36**. Nitration in concentrated sulfuric acid of 1,2,3-trimethylindole and 2,3,3-trimethyl-3H-indole gives the corresponding 5-nitro derivatives **41** and **43**. The differing mechanisms of nitration of indoles in sulfuric acid and in nitric or acetic acids are discussed, and a set of orientation rules for nitration of 2-alkylindoles is presented.

In this paper the nitration in concentrated nitric acid of 2-methylindole and its derivatives (including the 1-methyl, 3-acetyl, 3-formyl, and 3-, 4-, 5-, and 6-mononitro derivatives), which leads to dinitro and ultimately to trinitroindoles, is described. The structures of all the nitration products are rigorously proved, and the results are correlated with plausible interpretations of the differing mechanisms of nitration of indoles in concentrated sulfuric acid and in nitric or acetic acids. A set of generalizations concerning the orientation of nitration of 2-alkylindoles is then presented.

2-Methyl-3,4,6-trinitroindole Series.—Nitration of 2-methylindole with cold fuming nitric acid (*d* 1.50),[3] or by warming to about 50° with a large excess of concentrated nitric acid (*d* 1.38–1.42) until a vigorous reaction begins (accompanied by evolution of NO_2 fumes),[4,5] gives a dinitro derivative (**5**). Nitration of 2-methylindole or of **5** past the dinitro stage by heating with nitric acid on a steam bath for 30 min. gives a trinitro derivative[5] (**7**). Nitration of 2-methyl-3-nitroindole (**1**) and of 2-methyl-3H-indol-3-one oxime (**2**, accompanied by oxidation) is also reported[6] to give **5**, although no details of the comparison were reported. Nitration of 2-methylindole-3-carboxaldehyde in acetic acid has recently been reported[7] to give 2-methyl-6-nitroindole-3-carboxaldehyde (47%), the deformylated by-products 3,6-dinitro-2-methylindole and **1**, and a small amount of an unidentified compound, m.p. 268–271°.

We have confirmed the isolation of **5**[8] from nitration with nitric acid of 2-methylindole, of **1**, and of **2** (Chart I), and have also isolated it (as a product of deformylation) from a similar nitration of 2-methylindole-3-carboxaldehyde. In the nitrations of **1** and **2** we have also isolated an isomeric dinitro-2-methylindole (**6**).[9] Chromic acid oxidation of **5** gave N-acetyl-4-nitroanthranilic acid[10] (**10**). Since **5** has been derived from **1** and **2**, this proves that **5** is 3,6-dinitro-2-methylindole.

Nitration of 3-acetyl-2-methylindole in acetic acid at 0° gave **1** (a product of deacetylation[11]) and two mononitro-3-acetyl-2-methylindoles **8** and **9**. Chromic

---

(1) Paper II: W. E. Noland, L. R. Smith, and D. C. Johnson, *J. Org. Chem.*, **28**, 2262 (1963).

(2) Taken in part from (a) L. R. Smith, Ph.D. Thesis, University of Minnesota, May 1960; *Dissertation Abstr.*, **21**, 1766 (1961) [it is a pleasure to acknowledge support of this portion of the work through a Frederick Gardner Cottrell Grant from the Research Corporation (1958–1959), to the Upjohn Co. for a summer fellowship (1959), and to the Dow Chemical Co. for an academic year fellowship (1959–1960)]; and (b) K. R. Rush, Ph.D. Thesis, University of Minnesota, Sept. 1963; *Dissertation Abstr.*, **25**, 2241 (1964); National Science Foundation Graduate Fellow, June 1961–Sept. 1963.

(3) C. Zatti, (a) *Gazz. chim. ital.*, **19**, 260 (1889); *J. Chem. Soc. Abstr.*, **58**, 897 (1890); (b) *Atti reale accad. Lincei, Rend. classe sci. fis. mat. nat.*, [4] **5**, I, 376 (1889); *Chem. Ber.*, **23**, Referate, 155 (1890).

(4) R. von Walther and J. Clemen, *J. prakt. chem.*, [2] **61**, 249 (1900).

(5) F. C. Mathur and R. Robinson, *J. Chem. Soc.*, 1415 (1934).

(6) (a) A. Angeli and F. Angelico, *Atti reale accad. Lincei, Rend. classe sci. fis. mat. nat.*, [5] **12**, I, 344 (1903); (b) F. Angelico and G. Velardi, *Gazz. chim. ital.*, **34**, II, 57 (1904); *Atti reale accad. Lincei, Rend. classe sci. fis. mat. nat.*, [5] **13**, I, 241 (1904); (c) A. Angeli, *Samml. Chem. Chem.-Tech. Vortr.*, **17**, 311 (1912).

(7) G. Berti, A. Da Settimo, and O. Livi, *Tetrahedron*, **20**, 1397 (1964).

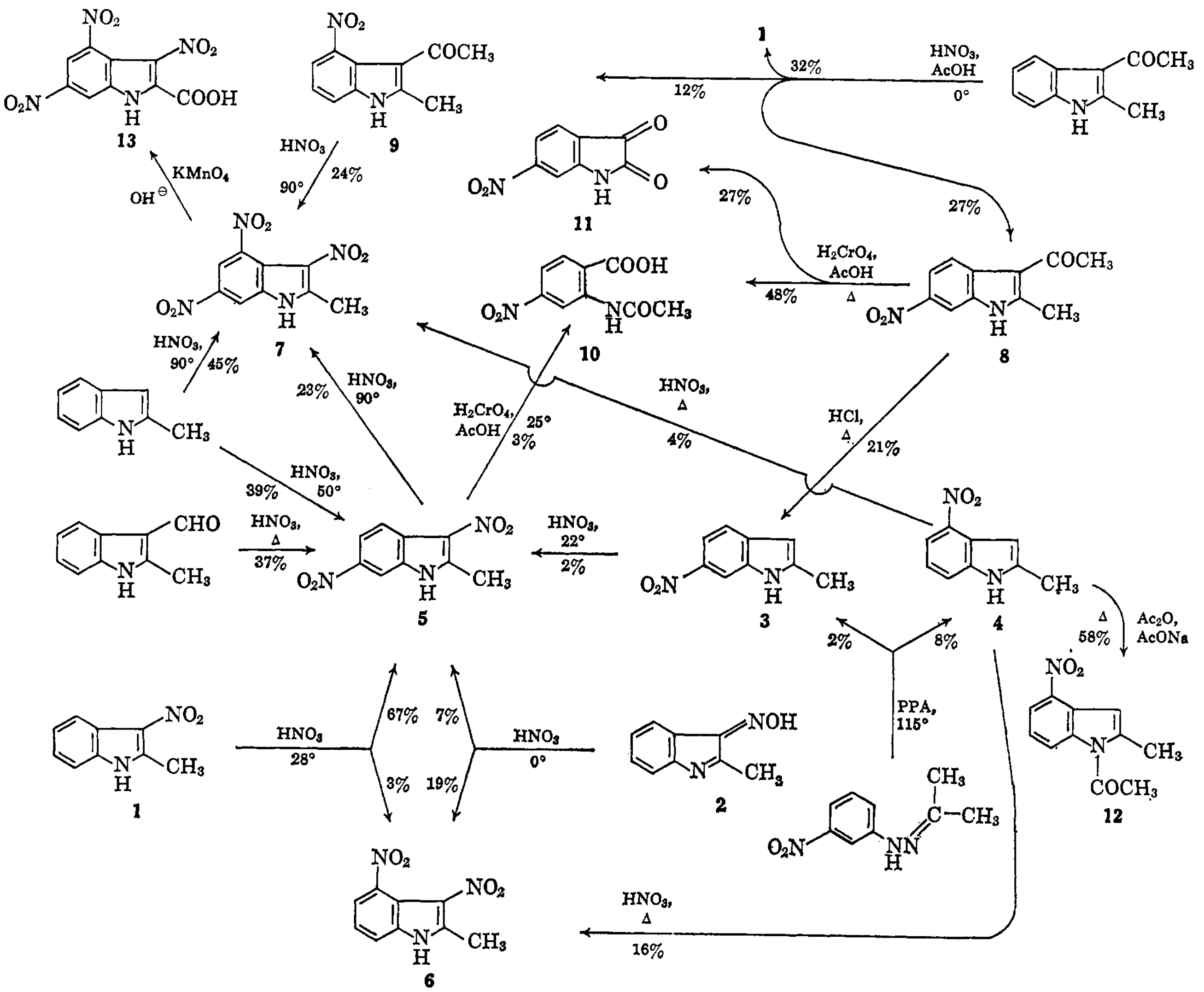
(8) Compound **5** sublimed on the hot stage at about 260°, darkened at 290°, and melted at 305° with decomposition. When the melting point was taken in a capillary tube, a wide range of melting points was observed between 250 and 305°, depending upon the rate of heating, as the compound sublimes. Hence, it is not surprising that a wide range of melting points has been reported: dec. upon heating,[3] m.p. 260° dec.,[6b] 265–267°,[5] 268°,[4] 300–302°.[7]

(9) It seems possible to us that the unidentified compound, m.p. 268–271°,[7] isolated from nitration of 2-methylindole-3-carboxaldehyde in acetic acid may be an impure sample of **6** (3,4-dinitro-2-methylindole, m.p. 284–285° dec.).

(10) S. Hillers, A. Lokenbachs, and L. Majs, *Latvijas PSR Zinatnu Akad. Vestis*, No. 3 (Whole No. 32), 7 (1950); *Chem. Abstr.*, **48**, 9965 (1954).

(11) Analogous to the deformylation which occurred during the nitration of 2-methylindole-3-carboxaldehyde. The probable mechanism of this displacement by nitronium ion has already been discussed.[7]

CHART I



acid oxidation of **8** gave **10**[10] and 6-nitroisatin[12,13] (**11**), proving that **8** is 3-acetyl-2-methyl-6-nitroindole. Deacetylation of **8** in refluxing hydrochloric acid gave 2-methyl-6-nitroindole[14] (**3**). Nitration of **3** gave **5**, again proving that **5** is 3,6-dinitro-2-methylindole.

A proof of structure of the isomeric dinitro-2-methylindole (**6**) was obtained by the synthesis and nitration of 2-methyl-4-nitroindole (**4**). In contrast to the complete failure of acetone *p*-nitrophenylhydrazone to undergo the Fischer indole synthesis,[15] acetone *m*-nitrophenylhydrazone gave with polyphosphoric acid a mixture of **3** and **4**. Acetylation of **4** in the presence of sodium acetate gave an N-acetyl derivative (**12**), different from **9** and having no NH band in its infrared spectrum. Nitration of **4** gave **6**. Since **6** has been derived from **1** and **2**, this proves that **6** is 3,4-dinitro-2-methylindole.

It had been shown earlier that **7** is different from 2-methyl-3,5,7-trinitroindole[16] (**37**). We found **7** to be resistant to chromic acid or acidic permanganate oxidation, but oxidation with alkaline permanganate has been shown to give a trinitroindole-2-carboxylic acid[5] (**13**). Dinitration of **4** gave **7**; since nitration of **5** also gives **7**, this proves that **7** is 2-methyl-3,4,6-trinitroindole.[17] The acid **13** derived from **7** must, therefore, be 3,4,6-trinitroindole-2-carboxylic acid, and the condensation product from **7** and *p*-dimethylaminobenzaldehyde in the presence of piperidine must be 2-(*p*-dimethylaminostyryl)-3,4,6-trinitroindole. Nitration of **9** (accompanied by deacetylation[11,18]) also gave **7**; since **8** is the 6-nitro derivative, this proves that **9** is 3-acetyl-2-methyl-4-nitroindole.

---

[12] (a) E. Giovannini and P. Portmann, *Helv. Chim. Acta*, **31**, 1375 (1948); (b) W. E. Noland and R. D. Rieke, *J. Org. Chem.*, **27**, 2250 (1962).

[13] A. P. Terent'ev, M. N. Preobrazhenskaya, A. S. Bobkov, and G. M. Sorokina, *J. Gen. Chem. USSR*, **29**, 2504 (1959).

[14] Previously reported[13] as the product of dehydrogenation of the corresponding indoline.

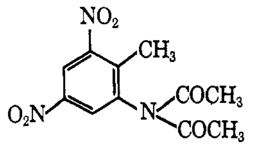
[15] The vigorous reaction produced by heating acetone *p*-nitrophenylhydrazone with excess zinc chloride to 185° gave no 2-methyl-5-nitroindole [E. Bamberger and H. Sternitzki, *Chem. Ber.*, **26**, 1306 (1893)], a failure which has also been noted elsewhere [V. Colo, B. Asero, and A. Vercellone, *Farmaco* (Pavia), *Ed. Sci.*, **9**, 611 (1954)]. In our hands, attempted cyclization with boron fluoride etherate in acetic acid or hydrochloric acid in ethanol gave unchanged starting material, while heating with polyphosphoric acid or zinc chloride at temperatures above 160–170° produced vigorous reactions from which only black tars were isolated. An attempt to cyclize 4'-nitro-*o*-acetotoluidide by heating with sodamide in the Madelung syntheses (C. F. H. Allen and J. Van Allan, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 597) produced an explosion and evolution of nitrogen oxides when the reactants were heated to slightly over 100°.

[16] G. Bendz, C. C. J. Culvenor, L. J. Goldsworthy, K. S. Kirby, and R. Robinson, *J. Chem. Soc.*, 1130 (1950).

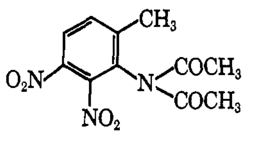
[17] This is in agreement with the guess of R. Robinson and co-workers.[16]

[18] Analogous to the deacetylation which occurred during the formation of **1** from 3-acetyl-2-methylindole.

An attempt to extend Robinson's procedure[16] for the synthesis of 2-methyl-3,5,7-trinitroindole[16] (**37**) to the synthesis of 4,6-dinitro-2-methylindole and 6,7-dinitro-2-methylindole was unsuccessful. Heating of 3,5-dinitro-*o*-toluidine and 5,6-dinitro-*o*-toluidine in acetic anhydride containing a catalytic amount of sulfuric acid did not produce ring closure, but gave instead 3′,5′-dinitro-*o*-diacetotoluidide (**14**) and 5′,6′-dinitro-*o*-diacetotoluidide (**15**). The use of catalysts other than sulfuric acid, such as polyphosphoric acid, sodium methoxide, and sodium ethoxide, also failed to effect ring closure of **14** and **15**.



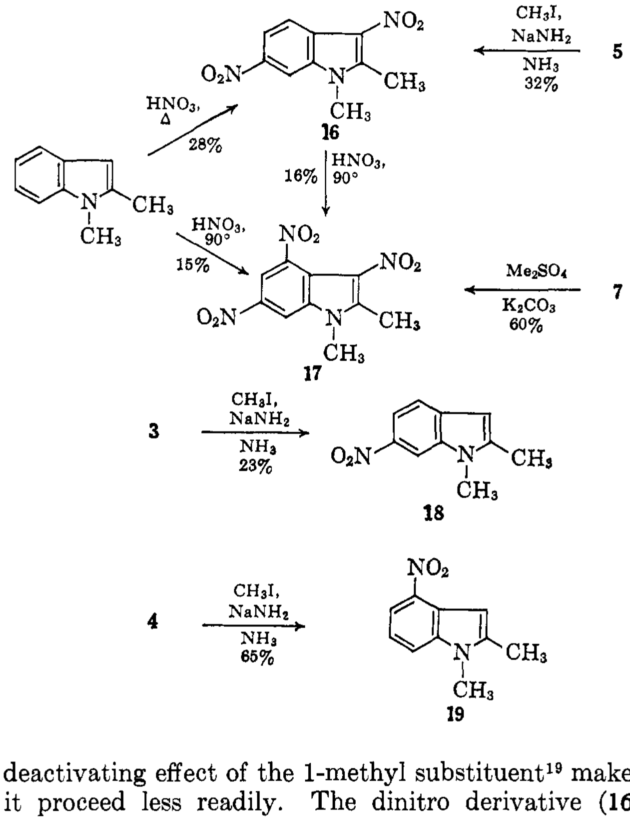
14



15

1,2-Dimethyl-3,4,6-trinitroindole Series.—Polynitration of 1,2-dimethylindole proceeds similarly to that of 2-methylindole (Chart II), although the usual deactivating effect of the 1-methyl substituent[19] makes it proceed less readily. The dinitro derivative (**16**) was identical with a sample of 1,2-dimethyl-3,6-dinitroindole prepared by methylation of **5**. Berti, Da Settimo, and Livi[7] isolated **16** as a by-product (3%) in the nitration of 1,2-dimethylindole-3-carboxaldehyde in acetic acid, along with 1,2-dimethyl-3-nitroindole (both products resulting from deformylation[11,18]) and three pyrrole ring-fission nitration products. The structure of their **16** was proved[7] by peracetic acid oxidation to N-acetyl-N-methyl-4-nitroanthranilic acid.

Chart II



The trinitro derivative (**17**), obtained from 1,2-dimethylindole and from **16**, was identical with a sample of 1,2-dimethyl-3,4,6-trinitroindole prepared by methylation of **7**. Methylation of **3** and **4** gave the corresponding 1,2-dimethylindole derivatives, **18** and **19**.

2-Methyl-3,5,6-trinitroindole Series.—Nitration of 2-methyl-5-nitroindole[1] (**20**) by warming with nitric acid (*d* 1.42) for 3 min. on a steam bath gave 3,5-dinitro-2-methylindole (**22**), as shown by chromic acid oxidation to N-acetyl-5-nitroanthranilic acid[10] (**23**) (Chart III). Nitration of **22** by warming with nitric acid for 30 min. on a steam bath gave 2-methyl-3,5,6-trinitroindole (**24**), as shown by chromic acid oxidation to N-acetyl-4,5-dinitroanthranilic acid (**26**), prepared by permanganate oxidation of 4′,5′-dinitro-*o*-acetotoluidide[20] (**25**). A better yield of the trinitroindole **24** was obtained by direct nitration under trinitro conditions (accompanied by N-deacetylation) of the N-acetyl derivative[1] (**21**) of **20**.

1,2-Dimethyl-3,5,6-trinitroindole Series.—Nitration of 1,2-dimethyl-5-nitroindole (**27**) (Chart III) by warming with nitric acid (*d* 1.42) at about 50° for 2 min. gave 1,2-dimethyl-3,5-dinitroindole (**28**), identical with a sample prepared by methylation of **22**. Chromic acid oxidation of **28** gave 1-methyl-5-nitroisatin[7,21] (**29**) and N-methyl-5-nitroanthranilic acid[22,23] (**30**). The trinitro derivative (**31**), obtained from **27** and **28**, was identical with a sample of 1,2-dimethyl-3,5,6-trinitroindole prepared by methylation of **24**. Chromic acid oxidation of **31** gave 4,5-dinitro-N-methylanthranilic acid (**32**).

It is perhaps significant that chromic acid oxidation of the 2-methylindole derivatives **22** and **24** gave *N-acetyl*nitroanthranilic acids (**23** and **26**), while similar oxidation of the 1,2-dimethylindole derivatives **28** and **31** gave *deacetylated* nitroanthranilic acids (**30** and **32**) and, in the case of **28**, also the isatin **29**. This suggests either that *N-methyl*-N-acetylanthranilic acids hydrolyze more rapidly[24] than the corresponding N-acetylanthranilic acids or that the 2-methyl group is more easily oxidized in the 1,2-dimethylindole derivatives than in the 2-methylindole derivatives—a hypothesis in accord with formation of the isatin **29**. A possibly related observation is the fact that attempted methylation of **22** to **28** (Chart IV) with methyl iodide and excess sodium hydride in N,N-dimethylformamide gave a *dimethyl* derivative (**36**, presumably formed *via* the anion **33** of **28**), which was proved to be 3,5-dinitro-2-ethyl-1-methylindole by the sequence: 2-ethylindole → 2-ethyl-5-nitroindole (**34**) → 3,5-dinitro-2-ethylindole (**35**) → **36**.

2-Methyl-3,5,7-trinitroindole Series.—2-Methyl-3,5,7-trinitroindole[16] (**37**) has been prepared by a synthesis involving ring closure of a substrate already containing all three nitro groups, and what appears to

---

[19] W. E. Noland and R. F. Lange, *J. Am. Chem. Soc.*, **81**, 1203 (1959).

[20] (a) O. L. Brady and P. N. Williams, *J. Chem. Soc.*, **117**, 1138 (1920); (b) G. T. Morgan and T. Glover, *ibid.*, **119**, 1702 (1921).

[21] W. Borsche, H. Weussmann, and A. Fritzsche, *Chem. Ber.*, **57**, 1149 (1924).

[22] Our sample was obtained by sublimation at 190° (1 mm.) as small white needles, m.p. 217–218°. The reported melting points are 259° dec.[23] and 271–273°.[7]

[23] (a) P. Thieme, *J. prakt. chem.*, [2] **43**, 451 (1891); (b) J. J. Blanksma, *Rec. trav. chim.*, **21**, 275 (1902).

[24] In this connection, *N-methyl*trifluoroacetanilide is reported to hydrolyze more rapidly, under alkaline conditions, than trifluoroacetanilide: S. S. Biechler and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **79**, 4927 (1957).

CHART III

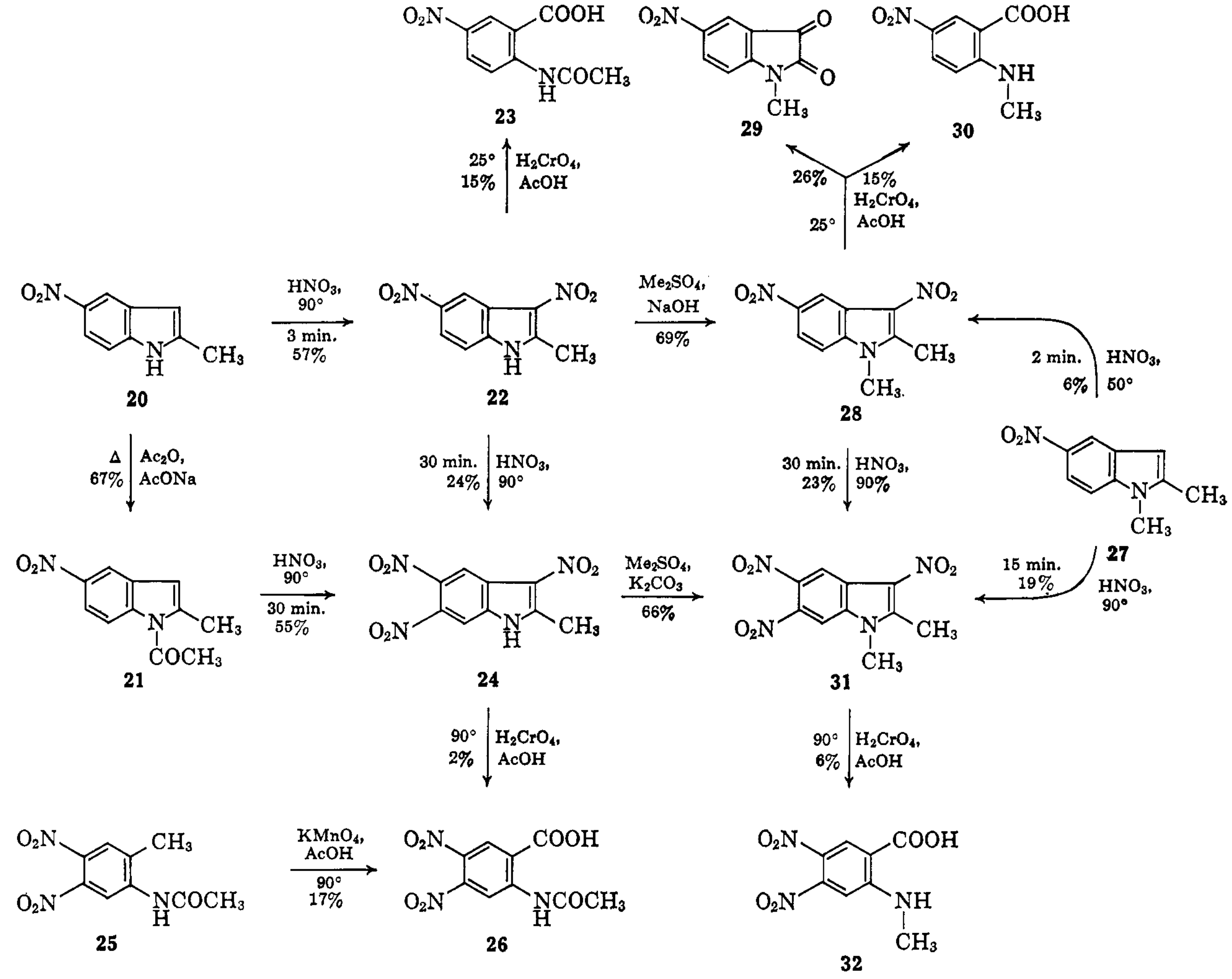
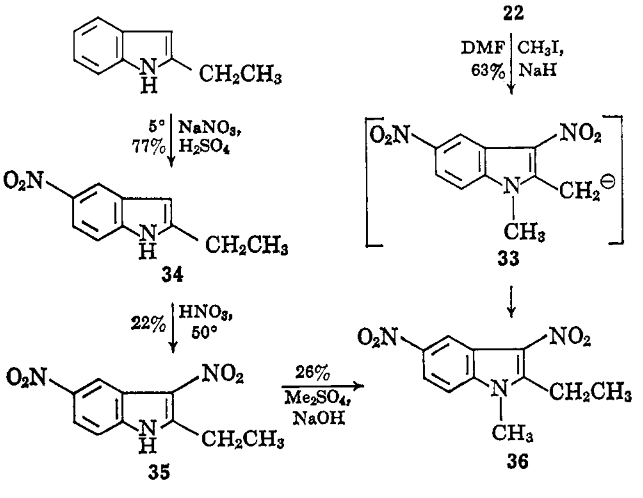
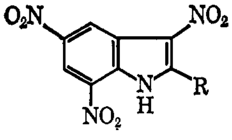


CHART IV



be 3,5,7-trinitroindole[25] (38) has been prepared by nitration of 1-acetyl-5-nitroindoline (accompanied by dehydrogenation and deacetylation). It appears very unlikely that these compounds will ever be prepared by direct nitration in the 7-position of an *indole* (in contrast to an indoline[21]). In the absence of complete protonation of the 3-position,[1] it is clear that nitration of 2-methylindoles follows 3,6,4- or 3,4,6-orientation [see, for example, formation of **1**, **5–9**, **16**, **17**, **22**, **24**, **28**, and **31**; also, Berti and Da Settimo[26] have shown that nitration in acetic acid occurs in the 6-position with 2-methyl- and 1,2-dimethylgramine, and with 3,3′-methylenebis(2-methylindole)]. Complete protonation of the 3-position is effected in concentrated sulfuric acid, permitting nitration at the 5-position of 2-methylindole (to **20**) and 1,2-dimethylindole (to **27**) at 0–15°.[1] Attempted 5-nitrations of 3-acetyl-2-methylindole and 2-methylgramine, or 7-nitration of 2-methyl-5-nitroindole (**20**), under similar conditions, with sodium nitrate in concentrated sulfuric acid at 0–5°, were unsuccessful, giving amorphous dark brown solids or a black tar. Raising the temperature under otherwise similar conditions was also unsuccessful; attempted 5,7-dinitration of 2-methylindole at 70° for 15 min. gave a black tar, while attempted 7-nitration of 3,5-dinitro-2-methylindole (**22**) at 70–90° gave unchanged **22** (45%) as the only water-insoluble product.



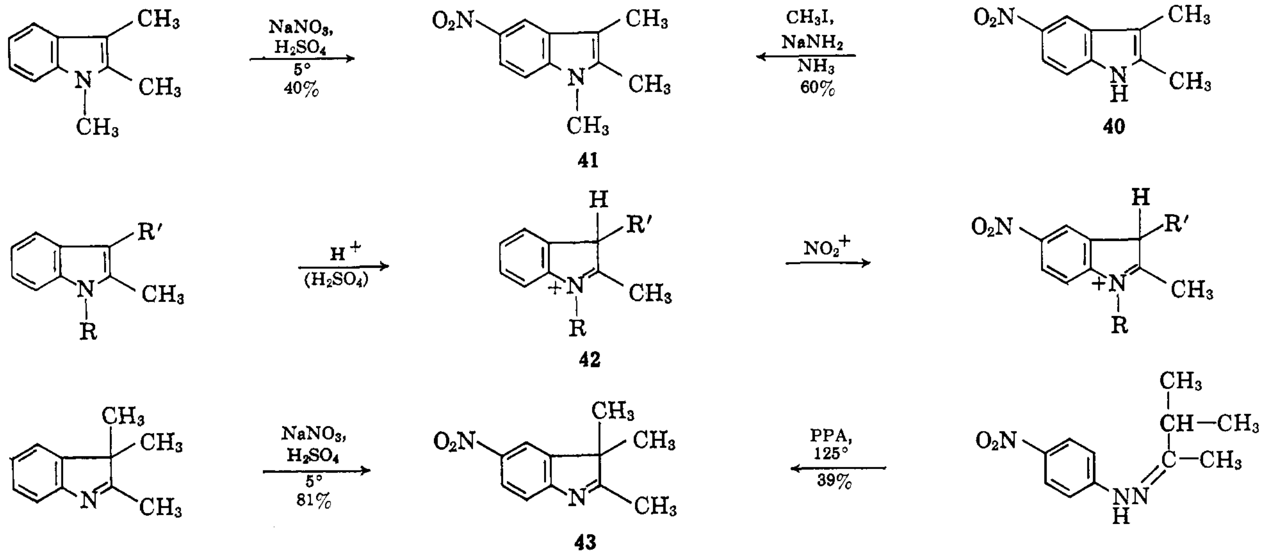
37, R=CH_3
38, R=H

---

[25] W. E. Noland and K. R. Rush, *J. Org. Chem.*, **29**, 947 (1964).

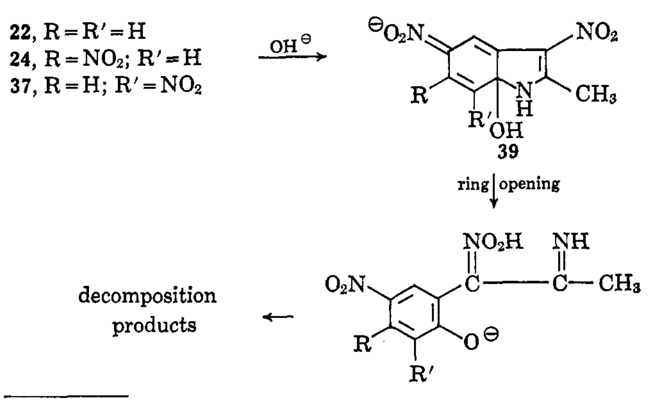
[26] G. Berti and A. Da Settimo, *Gazz. chim. ital.*, **90**, 525 (1960).

Chart V



Properties of the Polynitro-2-methylindoles.—The three trinitro-2-methylindoles **7**, **24**, and **37** are sufficiently strong acids that the dilute solutions (2.5–12.7 $\times$ 10^{-5} M) in ethanol used to determine their ultraviolet spectra do not obey Beer's law, indicating a significant degree of dissociation.[27] Their pK_a values are all very similar: 3,4,6 (**7**), pK_a = 7.3; 3,5,6 (**24**), pK_a = 7.4; and 3,5,7 (**37**), pK_a = 7.3. Since all three compounds have three nitro groups conjugated with the indole nitrogen, the slightly lower acidity of the 3,5,6 isomer (**24**), to the extent that it is significant is attributed to steric inhibition of the resonance interaction of the *o*- (5,6-) nitro groups with the indole nitrogen.

A noteworthy difference among the polynitro-2-methylindoles is in their relative sensitivity to being warmed in strong sodium hydroxide solution. Alkaline solutions of **5** and **7** can be warmed at length on a steam dath without apparent reaction, and the compounds can be recovered upon acidification. In contrast, alkaline solutions of **22**, **24**, and **37** turn black in less than 30 sec. of warming on a steam bath. The great difference in reactivity between the *m*-nitroaniline (**5**) and *m,m'*-dinitroaniline (**7**) derivatives on the one hand, and the *p*-nitroaniline (**22**) and *o,p*-dinitroaniline derivatives (**24** and **37**) on the other hand, is attributed to the ease of nucleophilic displacement of the indole nitrogen (*via* the intermediate **39**) in the latter types. Ample precedent for such a reaction is to be found in the *o*- and *p*-nitroaniline series[28]; for example, 2,4-dinitroaniline undergoes displacement of the amino group by alkali to give 2,4-dinitrophenol,[28b] while 3,5-dinitroaniline is relatively inert to hydroxide ion.



Nitration of 1,2,3-Trimethylindole.—Nitration of 1,2,3-trimethylindole with sodium nitrate in concentrated sulfuric acid follows the pattern of 5-nitration already established for the closely related compounds, 1,2-dimethylindole (to **27**[1]) and 2,3-dimethylindole (to **40**[29]). Thus, nitration of 1,2,3-trimethylindole at 5° gives 5-nitro-1,2,3-trimethylindole[30a] (**41**), identical with a sample prepared by methylation of 2,3-dimethyl-5-nitroindole (**40**).

Attempted nitration of 1,2,3-trimethylindole in acetic acid at ice-bath temperature gave an unstable, greenish solid, which decomposed upon attempted recrystallization.

The Differing Mechanisms of Nitration of Indoles in Sulfuric and in Nitric or Acetic Acids.—It has been proposed[1] that the 5-nitration of indoles in concentrated sulfuric acid proceeds by an initial, complete protonation at the 3-position, through an intermediate 2-alkyl-3H-indolium cation, such as **42** (Chart V). Nitration of 2,3,3-trimethyl-3H-indole (the protonated form of which would be an analog of **42**) with sodium nitrate in concentrated sulfuric acid at 5° gave 5-nitro-2,3,3-trimethyl-3H-indole (**43**), identical with a sample[30] prepared by the Fischer indolenine synthesis. An almost identical result has been reported in a recent communication,[31] which also reports the nitration under comparable conditions of 1,2,3,3-tetramethyl-

---

[27] For a careful study of the electronic spectra of nitroindoles and their dissociation products in alkaline solution, see G. Berti, A. Da Settimo, and D. Segnini, *Gazz. chim. ital.*, **90**, 539 (1950).

[28] (a) L. F. Fieser and M. F. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, p. 713; (b) C. Willgerodt, *Chem. Ber.*, **9**, 979 (1876).

[29] (a) H. Bauer and E. Strauss, *ibid.*, **65**, 308 (1932); (b) S. G. P. Plant and M. L. Tomlinson, *J. Chem. Soc.*, 955 (1933); (c) C. M. Atkinson, J. C. E. Simpson, and A. Taylor, *ibid.*, 165 (1954); (d) S. N. Nagaraja and S. V. Sunthankar, *J. Sci. Ind. Res.* (India), **B17**, 457 (1958); *Chem. Abstr.*, **53**, 11340 (1959); (e) W. E. Noland and K. R. Rush, *J. Org. Chem.*, **28**, 2921 (1963).

[30] (a) E. Shaw and D. W. Woolley, *J. Am. Chem. Soc.*, **75**, 1877 (1953); (b) D. S. Deorha and S. S. Joshi, *J. Org. Chem.*, **26**, 3527 (1951).

[31] K. Brown and A. R. Katritzky, *Tetrahedron Letters*, 803 (1964).

3H-indolium sulfate (a quaternary analog of **41**) to 5-nitro-1,2,3,3-tetramethyl-3H-indolium cation, also prepared by methylation of **43** with methyl iodide. As Brown and Katritzky[31] noted, these results strongly support the hypothesis[1] that the 5-nitration of indoles proceeds *via* an intermediate 2-alkyl-3H-indolium cation.

Nitration of 2-alkylindoles in concentrated nitric acid or in acetic acid proceeds by a different mechanism than in concentrated sulfuric acid. In nitric acid or acetic acid 5-nitration is never observed; the orientation is 3,6,4 or 3,4,6, and thermal initiation is often required. For example, the highly nucleophilic 2-methylindole was recovered unchanged in excellent yield after 30 min. in concentrated nitric acid (*d* 1.42) at room temperature (22–28°); warming the solution to about 50° causes the reaction to "take off" with almost uncontrollable vigor and copious evolution of NO_2 fumes, yielding Ia. Similarly, attempted nitration of 2-methylindole with nitric acid in acetic acid at 0° gave unchanged 2-methylindole in 90% recovery.

Nitration in concentrated nitric acid or in acetic acid is believed to involve the free indole. The relative slowness of the nitration in these media is attributed to two factors: (1) a low concentration of active nitrating agent, as nitric acid alone is known to be a much poorer source of nitronium ions than is nitric acid in concentrated sulfuric acid[32]; and (2) a low concentration of free indole, as nitric acid is still a strong enough acid to protonate most of the indole. Since heating should favor dissociation of the protonated indole, it is assumed that at least a small concentration of the unprotonated indole will be present in equilibrium with its relatively unreactive conjugate acid[33] (**42**), especially at the elevated temperatures which seem to favor the start of the reaction in nitric acid. As soon as an indole molecule is nitrated, almost certainly first at the most nucleophilic 3-position, the basicity[34] of the resulting mononitroindole will be markedly reduced, leaving a relatively large proportion of the nitroindole unprotonated and available for further nitration in competition with the small amount of unprotonated indole. Consequently, once the first nitro group has entered, the second nitro group can enter very rapidly, and the exothermic reaction can become thermally autocatalytic.

The nitration of 2-methylindole in concentrated nitric acid (*d* 1.42) solution at room temperature is catalyzed by sodium nitrite, but not by sodium acetate. Consequently, the catalytic effect of nitrite ion does not appear to be that of a base diminishing the acidity of the medium to a point where the resulting higher concentration of unprotonated indole would lead to a more rapid onset of the vigorous dinitration reaction. The results do suggest, however, that the usually thermally initiated, vigorously exothermic dinitration of 2-methylindole may involve an initial nitrosation[35] at the 3-position (to give **2**) of whatever unprotonated indole is present. In this event, the warming to about 50° usually used to start the reaction promptly could be interpreted partly as an induction period during which the necessary nitrosating agent is being formed by reduction of nitric acid through an oxidation reaction of the 2-methylindole which competes with nitration (thus, the usual yields of **5** and **16** are only 39 and 28%, and copious amounts of NO_2 are evolved). Once 3-nitrosation of the small amount of unprotonated indole has begun, the nitrosation can become a chain reaction as more nitrosating agent is produced by reduction of the nitric acid as it oxidizes the nitrosation product (such as **2**). As the temperature rises and more NO_2 is formed, more and more oxidation of the 2-methylindole could occur, with production of more nitrosating agent, so that a chain-branching reaction could take place—an observation which is consistent with the very rapid buildup of the reaction once it gets started. The second nitration would then proceed rapidly on the unprotonated mononitroindole, as already described above.

Because of the vigor of the reaction, we have not isolated any 3-nitroindoles, only 3,6-dinitroindoles (**5**, **16**), from the nitration of 2-methylindole and 1,2-dimethylindole in concentrated nitric acid. 3-Nitroindoles have been isolated only from the milder nitration of 3-acylindoles (in which the nitro group is introduced[7] at a relatively deactivated and sterically hindered 3-position) in acetic acid. Thus, we isolated 2-methyl-3-nitroindole (**1**, 32%), along with the 6- and 4-mononitration products (**8** and **9**) from nitration of 3-acetyl-2-methylindole in acetic acid at 0°. Nitration in acetic acid of the 2-methyl-, 1,2-dimethyl-, and 1-methylindole-3-carboxaldehydes is also reported to give, besides other nitration products, 3-nitroindoles in yields of 1 (**1**), 33, and 10%, respectively, as well as the 3,6-dinitroindoles **5** (5%) and **16** (3%) in the first two cases.[7]

Some evidence that the 3-nitroindole (**1**), and not the 6-nitroindole (**3**), is the mononitro intermediate in the formation of **5** from 2-methylindole may exist in the yields of **5** obtained. Thus, although the nitration conditions are not wholly comparable, **1** gave 67% of **5** and 2-methylindole gave 39% of **5**, while **3** gave 2% of **5**. 3,4-Dinitroindoles have not been isolated from the direct nitration of 2-methylindole or 1,2-dimethylindole, but we have isolated 3,4-dinitro-2-methylindole (**6**) from the nitric acid nitration of **1** (3%) and **2** (19%), as well as from **4** (16%).

Nitration of 5-nitroindoles in concentrated nitric acid follows the same orientation rules as proposed for the free 2-methylindoles themselves, first 3- and then 6-, leading to introduction of the third (6-) nitro group *ortho* to the already present 5-nitro group. No introduction of the third nitro group into the relatively

---

(32) (a) R. J. Gillespie and D. J. Millen, *Quart Rev.* (London), **2**, 277 (1948); (b) E. D. Hughes, C. K. Ingold, and R. I. Reed, *J. Chem. Soc.*, 2400 (1950); (c) E. S. Halberstadt, E. D. Hughes, and C. K. Ingold, *ibid.*, 2441 (1950); (d) R. J. Gillespie, J. Graham, E. D. Hughes, C. K. Ingold, and E. R. A. Peeling, *ibid.*, 2504 (1950); (e) R. J. Gillespie, E. D. Hughes, and C. K. Ingold, *ibid.*, 2552 (1950); (f) C. K. Ingold and D. J. Millen, *ibid.*, 2612 (1950).

(33) A referee has noted that, while one feels intuitively that the unprotonated indole should undergo electrophilic substitution more rapidly than the "relatively unreactive conjugate acid," the facts are that the completely protonated species is nitrated at 5°, whereas in solvents which are less effective proton donors heat is required. This is *probably* a result of low concentration of nitronium ions or other active nitrating agent, but one could also infer that perhaps the protonated species is *more readily* substituted.

(34) For a thorough discussion of the basicity of indoles, see R. L. Hinman and J. Lang, *J. Am. Chem. Soc.*, **86**, 3796 (1964).

(35) The nitrosation mechanism for nitration of electron-rich benzene derivatives has been carefully examined: (a) C. A. Bunton, E. D. Hughes, C. K. Ingold, D. I. H. Jacobs, M. H. Jones, G. J. Minkoff, and R. I. Reed, *J. Chem. Soc.*, 2628 (1950); (b) E. L. Blackall, E. D. Hughes, and C. K. Ingold, *ibid.*, 28 (1952).

more sterically hindered 4-position, between the 3- and 5-nitro groups, has been observed. Introduction of a third nitro group into the indole nucleus (to form **7**, **17**, **24**, or **31**) is a mild and controllable reaction, requiring heating of the dinitro or mononitro substrate in concentrated nitric acid on the steam bath for 15–30 min. In no case has a fourth nitro group been introduced into the indole nucleus, nor has 7-nitration of an indole been observed.

In the nitration of unprotonated 2-alkylindoles, the 2-alkyl substituent appears to release sufficient electrons so that electronic activation of the benzene ring by the indole nitrogen *via* the 2,3 double bond is completely dominant over direct aniline-type activation. An electronically closely analogous example of nitration outside the indole series, which is capable of the same interpretation as for 2-methylindole, is the nitration of 1-phenylpyrrole, which yields 1-(*p*-nitrophenyl)pyrrole in concentrated sulfuric acid and a mixture of 2- and 3-nitro-1-phenylpyrroles in acetic anhydride.[36]

Conclusion

The orientation rules for nitration of 2-alkylindoles arising from the work summarized in this and the preceding paper[1] are presented below.

(1) Nitration of 2-alkylindoles (and their alkyl derivatives: 1,2- and 2,3-dialkylindoles, 1,2,3-trialkylindoles, and 2,3,3-trialkyl-3H-indoles) at acidities sufficiently high so that protonation (at the 3-position) is complete and the concentration of nitronium ions is very high, as in concentrated sulfuric acid, yields 5-nitroindoles below room temperature (usually 0–15°). Attempted further nitration in the same medium, by heating above room temperature, leads to decomposition.

(2) Nitration of 2-alkylindoles and 1,2-dialkylindoles under conditions such that the concentration of active nitrating agent is very low and protonation is not complete, as in concentrated nitric acid above room temperature, or in acetic acid, once thermally initiated, proceeds rapidly and vigorously. Initial attack occurs at the 3-position, and the resulting 3-nitro group stabilizes the indole against oxidative destruction, permitting further nitration, which occurs very rapidly, in the 6- or 4-positions. Raising the temperature to about 90°, by warming on the steam bath in concentrated nitric acid, permits the entrance of a third nitro group, at the 4- or 6-position, whichever is still open. An electronegative substituent in the 3-position serves the same purpose as the 3-nitro group in protecting the indole from oxidative attack, permitting nitration in the 6- and 4-positions. Frequently, the electronegative 3-substituent, if capable of departing as a cation or its equivalent such as formyl or acetyl, is displaced by a nitro group, either before or after the first nitration elsewhere (6- or 4-). 2,3-Dialkylindoles can be stabilized sufficiently against oxidative destruction, by acylation at the 1-position, to permit some 6- and 4-nitration. If a nitro group is already present in the 4-, 5-, or 6-positions of a 2-alkylindole, the next nitro group will enter the open 3-position, just as with 2-alkylindoles. Thus, 2-alkyl-5-nitroindoles nitrate with nitric acid first in the 3- and then in the 6-position (*ortho* to the 5-nitro group already present), but nitration stops when three nitro groups are present, and 4-nitration has not been observed.

(3) Neither 7-nitration nor tetranitration of an indole nucleus have been observed.

Experimental Section

Melting points were determined on calibrated hot stages. Where not specified, the drying agent used for organic solutions was anhydrous magnesium sulfate. Except where otherwise specified, the petroleum ether used was the fraction, b.p. 60–68° (Skellysolve B).

Nitration of 2-Methyl-3-nitroindole (**1**).[2a]—A mixture of 2-methyl-3-nitroindole (1.16 g., 0.00658 mole, prepared by nitration of 3-acetyl-2-methylindole) and concentrated nitric acid (*d* 1.42, 30 ml.) was kept at 28° for 30 min., and then ice–water (60 ml.) was added, causing formation of a tan precipitate. The precipitate was filtered off and crystallized from ethanol, with charcoal giving first 3,6-dinitro-2-methylindole (0.86 g.), m.p. 305° dec. Concentration of the ethanol mother liquor and addition of an equal volume of water precipitated a yellowish solid (0.24 g.), m.p. 220–280°. Recrystallization of this solid from ethanol–water gave first more **3,6-dinitro-2-methylindole** (**5**) [0.11 g., total 0.97 g. (67%)], m.p. 305° dec. There was no depression in mixture melting point with the sample prepared directly from 2-methylindole, and the infrared spectra in Nujol were identical.

Concentration of the ethanol–water mother liquor and addition of an equal volume of water caused separation of a second crop as a yellowish solid. Recrystallization from ethanol–water gave **3,4-dinitro-2-methylindole** (**6**) (0.04 g., 3%), m.p. 284–285° dec. There was no depression in mixture melting point with the sample prepared from 2-methyl-4-nitroindole, and the infrared spectra in Nujol were identical.

2-Methyl-3H-indol-3-one Oxime (**2**).[2a]—The procedure of Spica and Angelico[37] was modified by use of commercial sodium methoxide instead of metallic sodium, by using a reaction time of 48 hr. (not specified previously), and by neutralizing the sodium salt with solid carbon dioxide (Dry Ice) instead of boric acid. A solution of 2-methylindole[38] (6.0 g., 0.0457 mole) and sodium methoxide (2.7 g., 0.0500 mole) in absolute ethanol (25 ml.) was cooled to 0° and stirred for 5 min. Amyl nitrite[39] (5.4 g., 0.0461 mole) was added dropwise, with stirring, at 0°. A small portion of the solution was treated with water and Dry Ice, causing separation of a yellowish solid, which was found to be largely unchanged 2-methylindole. Therefore, the main portion of the reaction solution was kept in a refrigerator for 48 hr., and then water (30 ml.) and Dry Ice were added, causing separation of a bright yellow solid. Recrystallization from ethanol–water gave yellow crystals (6.4 g., 87%): dec. pt. 198–200° (lit.[37] yield unstated, m.p. 198° dec.); $\lambda_{\max}$, mμ (log ϵ), in 95% ethanol 236 infl. (4.20), 240 (4.25), 253 (4.29), 277 (3.55), 314 (3.68), 355 infl. (3.37); ν_{OH} ~2460 (m, broad), $\nu_{\mathrm{C=N}}$ 1648 (w) cm.$^{-1}$ in Nujol.

Attempted preparation of the compound by nitrosation of 2-methylindole with an equimolar portion of sodium nitrite in aqueous acetic acid at 2° gave no crystalline product. Similar observations have been reported previously.[40]

Nitration of 2-Methyl-3H-indol-3-one Oxime (**2**).[2a]—Ice-cold concentrated nitric acid (*d* 1.42, 30 ml.) was added to 2-methyl-3H-indol-3-one oxime (1.6 g., 0.010 mole) and the mixture was shaken in an ice bath for 2 min. Ice-water (70 ml.) was then added, and the precipitated light brown solid was filtered off. Recrystallization of the solid from ethanol–water, with charcoal, gave first 3,6-dinitro-2-methylindole (0.05 g.), m.p. 305° dec. Concentration of the ethanol–water mother liquor and addition of an equal volume of water caused separation of a yellowish solid (0.74 g.) having a wide melting point range. Recrystallization of this solid from ethanol–water gave first more **3,6-dinitro-2-**

---

[36] J. Dhont and J. P. Wibaut, *Rec. trav. chim.*, **62**, 177 (1943).

[37] M. Spica and F. Angelico, *Gazz. chim. ital.*, **29**, II, 49 (1899).

[38] C. F. H. Allen and J. VanAllan, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 597; *Org. Syn.*, **22**, 94 (1942).

[39] Prepared by a modification of the procedure for *n*-butyl nitrite described by W. A. Noyes, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 108; *Org. Syn.* **16**, 7 (1936).

[40] (a) O. R. Jackson, *Chem. Ber.*, **14**, 880 (1881); (b) E. Fischer, *Ann. Chem.*, **236**, 126 (1886).

methylindole (5) [0.11 g., total 0.16 g. (7%)], m.p. 305° dec. There was no depression in mixture melting point with the sample prepared directly from 2-methylindole, and the infrared spectra in Nujol were identical.

Concentration of the ethanol–water mother liquor and addition of an equal volume of water caused separation of a second crop as a yellowish solid. Recrystallization from ethanol–water gave **3,4-dinitro-2-methylindole** (6) (0.41 g., 19%), m.p. 284–285° dec. There was no depression in mixture melting point with the sample prepared from 2-methyl-4-nitroindole, and the infrared spectra in Nujol were identical.

3,6-Dinitro-2-methylindole (5). A. **From 2-Methylindole.**[2a]—The procedure is essentially that of von Walther and Clemen[4] as improved by Mathur and Robinson,[5] except that conditions favorable for the reaction and subsequent work-up have been more specifically defined. 2-Methylindole[38] (10.0 g., 0.076 mole) was dissolved in concentrated nitric acid (*d* 1.42, 100 ml.) in a 2-l. beaker, the beaker was covered with a large watch glass to prevent splattering, and the solution was warmed to about 50° until the reaction, which appears to involve an induction period, began. Warming was stopped and a very vigorous reaction ensued, with copious evolution of fumes of nitrogen dioxide. After the reaction had subsided the mixture was cooled and filtered through a sintered-glass funnel. The resulting solid was washed with water and recrystallized from ethanol–water, with charcoal, yielding a light yellow solid (6.6 g., 39%): m.p. 305° dec.[8,41]; λ_{max}, mμ (log ϵ), in 95% ethanol 225 (4.01), 291 infl. (4.14), 306 (4.15), 341 (4.17); ν_{NH} 3280 (m), ν_{NO_2} 1517 (s), 1381 (s) or 1338 (s) cm.$^{-1}$ in Nujol.

B. **Effect of Nitrite Ion on the Preparation from 2-Methylindole at Room Temperature** (with S. P. Hiremath, 1965).—Two identical solutions were prepared by adding concentrated nitric acid (*d* 1.42, 10 ml.) at room temperature (25°) to 2-methylindole[38] (1.00 g., 0.0076 mole) in each of two 250-ml. beakers. The mixtures were swirled to complete solution and then treated as follows.

1. **Nitrite Ion Catalyzed Reaction.**—Sodium nitrite (0.0525 g., 0.00076 mole) was added to one of the solutions and the resulting mixture was swirled, causing most of the sodium nitrite to dissolve. Immediate darkening and a slight warming of the solution were noted. The solution continued to darken rapidly and between observations at 27.5 and 33.5 min. a vigorous reaction took place, with evolution of NO_2 fumes and precipitation of crystalline 3,6-dinitro-2-methylindole. The mixture was then kept overnight without visible change and, after a total of 21 hr., was poured into ice–water (250 ml.), with stirring, causing separation of a crude yellow precipitate, which was filtered, washed with water, and dried (1.19 g.), sublimed at 230–235°, darkened at 270°, and melted completely at 280–285° dec. Recrystallization from ethanol–water gave yellow crystals (0.71 g., 42%) that sublimed at 255°, darkened at 285°, and melted completely at 298–300° dec. There was no depression in mixture melting point with the sample prepared as described in part A, and the infrared spectra in Nujol were identical.

In another run, the vigorous reaction took place between 51 and 89 min. of reaction time. The crude yellow precipitate (1.20 g.), obtained by work-up after 22.5 hr., gave yellow crystals (0.72 g., 43%), which melted completely at 298–300° dec.

2. **Uncatalyzed Reaction.**—The solution without sodium nitrite darkened more slowly, without detectable warming, but eventually became darker than the catalyzed solution ever had. After a total of 5 hr., the solution was left unobserved overnight. The next day, after a total of 20.5 hr., a vigorous reaction was found to have taken place during the night; brown fumes of NO_2 and a crystalline precipitate were present, although the reaction mixture was darker than that from the catalyzed reaction. After a total of 21 hr., the mixture was poured into ice–water (250 ml.), with stirring, causing separation of a crude, dark yellow precipitate, which was filtered, washed with water, and dried (1.41 g.); it sublimed at 220–225°, darkened at 260°, and melted completely at 275–285° dec. Recrystallization from ethanol–water gave yellow crystals (0.65 g., 39%) that sublimed at 250–255°, darkened at 280–285°, and melted completely at 298–300° dec. The infrared spectrum in Nujol was identical with the spectrum of the sample prepared as described in part A above.

In another run, to which was added sodium acetate trihydrate (0.0624 g., 0.00076 mole), brown fumes and a crystalline precipitate formed between 8.4 and 18.4 hr. of reaction time. The crude yellow precipitate (1.44 g.) obtained by work-up after 20.3 hr., gave yellow crystals (0.71 g., 42%), which melted completely at 298–300° dec. The infrared spectrum in Nujol was identical with that of the sample prepared from the nitrite ion catalyzed reaction.

C. **From 2-Methyl-6-nitroindole** (3).[2a]—A solution of 2-methyl-6-nitroindole (0.035 g., 0.000198 mole) in concentrated nitric acid (*d* 1.42, 10 ml.) was kept at 22° for 20 min. Ice–water (30 ml.) was then added, and the mixture was cooled and filtered. The brown solid was washed with ice–water and recrystallized from ethanol–water, with charcoal, giving a light yellow solid (1 mg., 2%), m.p. 305° dec. There was no depression in mixture melting point with the sample prepared from 2-methylindole, and the infrared spectra in Nujol were identical

D. **From 2-Methylindole-3-carboxaldehyde.**[2b]—A solution of 2-methylindole-3-carboxaldehyde[42] (prepared in 87% yield by the method[43] for indole-3-carboxaldehyde; m.p. 207–207.5°, 6.05 g., 0.0380 mole) in concentrated nitric acid (*d* 1.42, 100 ml.) was stirred at 5° for 15 min. and then warmed on a steam bath until a vigorous reaction occurred. The resulting mixture was cooled and poured into water. The precipitate was filtered off, washed with water and sodium bicarbonate solution, and crystallized from acetone–ethanol, with charcoal, giving a crude solid (3.58 g.). This solid was dissolved in ethyl acetate and placed on a column of alumina (100 g.) which had been packed wet with petroleum ether (b.p. 60–68°). Elution with ethyl acetate yielded short pale yellow needles (3.07 g., 37%), m.p. 301–303.5° dec. There was no depression in mixture melting point, 301–303.5° dec., with a sample prepared from 2-methylindole, and the infrared spectra in Nujol were identical.

Oxidative Degradation of 3,6-Dinitro-2-methylindole (5).[2a]—A solution of chromium(VI) oxide (1.2 g., 0.012 mole) in water (1.5 ml.) and acetic acid (20 ml.) was added dropwise, with stirring, to a solution of 3,6-dinitro-2-methylindole (0.60 g., 0.00272 mole) in acetic acid (50 ml.). The mixture was stirred for 48 hr., and then water was added and the aqueous solution was extracted with chloroform and ether. The chloroform and ether extracts were washed with water and extracted with aqueous saturated sodium bicarbonate solution until carbon dioxide was no longer evolved. The sodium bicarbonate extracts were acidified to pH 2 with sulfuric acid and extracted with chloroform and ether. The chloroform and ether extracts were washed with water, dried, treated with charcoal, and evaporated to a small volume. Addition of petroleum ether (b.p. 40–75°) caused separation of **N-acetyl-4-nitroanthranilic acid** (10) (0.02 g., 3%), m.p. 216–218°. There was no depression in mixture melting point with a sample of m.p. 216–217° prepared[10] by oxidation of 5′-nitro-*o*-acetotoluidide, and the infrared spectra of the two samples in dioxane and Nujol were very similar.

Attempted Nitration of 2-Methylindole in Acetic Acid Solution.[2a]—Concentrated nitric acid (*d* 1.42, 15 ml.) was added dropwise, with stirring, to a solution of 2-methylindole[38] (5.0 g.) in acetic acid (75 ml.) cooled in a salt–ice bath. Stirring was continued for a total of 1 hr. and then the solution was poured onto ice, causing precipitation of unchanged 2-methylindole (4.49 g., 90%).

Nitration of 3-Acetyl-2-methylindole.[2a]—Concentrated nitric acid (*d* 1.42, 25 ml.) was added dropwise, with stirring, to a solution of 3-acetyl-2-methylindole[40a,44] (5.90 g., 0.0340 mole) in acetic acid (100 ml.) cooled in a salt–ice bath. The solution was stirred at 0° for 1 hr. and then poured into ice–water. The precipitated yellow solid was filtered off, giving a mixture of mononitration products (6.50 g.). Crystallization of the solid from 95% ethanol yielded first **3-acetyl-2-methyl-6-nitroindole** (8) as a bright yellow solid (2.02 g., 27%): m.p. 298–300°; λ_{max}, mμ (log ϵ), in 95% ethanol 260 infl. (4.11), 283 (4.33), 351 (4.00); ν_{NH} or ν_{CH} 3100 (m, broad, diffuse), $\nu_{C=O}$ 1635 (s), ν_{NO_2} 1510 (s), 1335–1322s cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$ (218.21): C, 60.54; H, 4.62; N, 12.84. Found: C, 60.38; H, 4.46; N, 13.26.

---

(41) We have obtained satisfactory analyses (within ±0.4% of the calculated) for C, H, and N on these compounds, for which similar analyses have previously been reported in the references cited.

(42) E. Leete, *J. Am. Chem. Soc.*, **81**, 6025 (1959).

(43) P. N. James and H. R. Snyder, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 539; *Org. Syn.*, **39**, 30 (1959).

(44) E. Fischer, *Ann. Chem.*, **242**, 378 (1887).

The mother liquor was evaporated to a small volume, and slightly more than an equal volume of water was added, giving a yellow solid mixture of mononitration products (3.82 g.). The mixture was slurried with ice-cold aqueous 10% sodium hydroxide solution and filtered. Crystallization of the filtered solid from ethanol–water yielded **3-acetyl-2-methyl-4-nitroindole** (**9**) as light yellow crystals (0.87 g., 12%): m.p. 248–249°; λ_{max}, mμ (log ϵ), in 95% ethanol 228 (4.27), 250 infl. (4.11), 280 (3.87), 366 (3.54); ν_{NH} 3200 (m, broad), $\nu_{C=O}$ 1630 (s), ν_{NO_2} 1537 (s), 1374 (ms) or 1358 (ms) or 1327 (m) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$ (218.21): C, 60.54; H, 4.62; N, 12.84. Found: C, 60.71; H, 4.64; N, 13.04.

The alkaline filtrate was acidified to pH 2 with sulfuric acid. The precipitated solid was filtered and recrystallized from ethanol–water, yielding **2-methyl-3-nitroindole** (**1**) as yellow crystals (1.93 g., 32%): m.p. 252–253°[41]; lit. m.p. 237°,[45] 243° dec.,[46] 247°,[7] 248° dec.[6b]; λ_{max}, mμ (log ϵ), in 95% ethanol 242 infl. (3.97), 248 (4.00), 253 (4.01), 269 (3.96), 276 (3.99), 352 (4.05); ν_{NH} 3230 (ms), ν_{NO_2} 1538 (m), 1366 (s) cm.$^{-1}$ in Nujol. The product was soluble in aqueous 10% sodium hydroxide solution.

Anal. Calcd. for $C_9H_8N_2O_2$ (176.17): C, 61.36; H, 4.58; N, 15.90. Found: C, 61.66; H, 4.68; N, 15.87.

Attempted nitration of 3-acetyl-2-methylindole with sodium nitrate in concentrated sulfuric acid at 0° gave no crystalline product.

Oxidative Degradation of 3-Acetyl-2-methyl-6-nitroindole (8)[2a].—A solution of chromium(VI) oxide (8.0 g., 0.080 mole) in water (20 ml.) and acetic acid (30 ml.) was added to a solution of 3-acetyl-2-methyl-6-nitroindole (2.47 g., 0.0113 mole) in refluxing acetic acid (100 ml.). The solution was stirred at room temperature for 48 hr., and then water (200 ml.) was added. The resulting mixture was filtered yielding **6-nitroisatin** (**11**) as an orange solid (0.58 g., 27%): m.p. 281–284°[41]; lit. m.p. 288–290° dec.,[12] 300° dec.[13] The infrared spectrum in Nujol was identical with that of a sample prepared by oxidation of 6-nitroindole-3-carboxaldehyde.[12b]

The filtrate was diluted further with water (100 ml.) and the resulting solution was extracted with ether. The ether extracts were washed with water and extracted with aqueous saturated sodium bicarbonate solution until carbon dioxide was no longer evolved. The sodium bicarbonate extract was acidified to pH 2 with sulfuric acid, and the resulting mixture was filtered. The filtered solid was recrystallized from ether–petroleum ether yielding **N-acetyl-4-nitroanthranilic acid** (**10**) (1.22 g., 48%), m.p. 216–217°. There was no depression in mixture melting point with the sample of m.p. 216–217° prepared[10] by oxidation of 5′-nitro-*o*-acetotoluidide, and the infrared spectra in Nujol were identical.

2-Methyl-6-nitroindole (3). From Hydrolysis of 3-Acetyl-2-methyl-6-nitroindole (8).[2a]—A solution of 3-acetyl-2-methyl-6-nitroindole (0.40 g., 0.00183 mole) in concentrated hydrochloric acid (50 ml.) was refluxed for 4 hr. Water (100 ml.) was then added and the dark brown mixture was extracted with ether. The ether extracts were dried and treated with charcoal. Evaporation of the ether to a small volume and addition of petroleum ether caused separation of 2-methyl-6-nitroindole (0.067 g., 21%), m.p. 107–109.5°. There was no depression in mixture melting point with the sample prepared by the Fischer indole synthesis from acetone *m*-nitrophenylhydrazone, and the infrared spectra in Nujol were identical.

Fischer Indole Synthesis of 2-Methyl-4-nitroindole (4) and 2-Methyl-6-nitroindole (3).[2a]—A mixture of acetone *m*-nitrophenylhydrazone[47] (m.p. 123–125°, 18.0 g., 0.0932 mole) and polyphosphoric acid (200 g.) was heated at 110–115° for 30 min. The resulting solution was cooled and ice–water (400 ml.) was added. After the polyphosphoric acid had hydrolyzed, the gray-green solid precipitate was filtered off. Basification of the filtrate with aqueous saturated potassium hydroxide solution gave unchanged acetone *m*-nitrophenylhydrazone (9.0 g., 50%), m.p. 123–124°.

The gray-green solid was boiled with benzene (200 ml.), and a quantity of insoluble, black, amorphous material was filtered off. The yellow filtrate was diluted with petroleum ether (100 ml.) and the resulting solution was chromatographed on alumina which had been packed wet with petroleum ether. Elution with 2:1 benzene–petroleum ether yielded first **2-methyl-4-nitroindole** (**4**) as yellow-orange crystals (0.66 g., 8% based on unrecovered starting material): m.p. 198–199°; λ_{max}, mμ (log ϵ), in 95% ethanol 240 (4.09), 248 infl. (4.05), 392 (3.85); ν_{NH} 3320 (s), ν_{NO_2} 1508 (s) or 1484 (s, stronger), 1326 (vs) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_9H_8N_2O_2$ (176.17): C, 61.36; H, 4.58; N, 15.90. Found: C, 61.54; H, 4.68; N, 15.77.

Further elution with 2:1 benzene–petroleum ether yielded **2-methyl-6-nitroindole** (**3**) as yellow crystals (0.13 g., 2% based on unrecovered starting material): m.p. 107–109.5°; lit.[13] m.p. 113.5–114.5°; λ_{max}, mμ (log ϵ), in 95% ethanol 247 (4.05), 266 infl. (3.76), 336 diffuse infl. (3.89), 376 (4.00); ν_{NH} 3330 (m), ν_{NO_2} 1545 (m) or 1505 (m) or 1466 (vs) (partly Nujol), 1320 (s) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_9H_8N_2O_2$ (176.17): C, 61.36; H, 4.58; N, 15.90. Found: C, 61.54; H, 4.68; N, 15.77.

1-Acetyl Derivative of 4. 1-Acetyl-2-methyl-4-nitroindole (12).[2a]—A solution of 2-methyl-4-nitroindole (0.28 g., 0.00159 mole) and sodium acetate trihydrate (2.00 g., 0.0147 mole) in acetic anhydride (40 ml., 0.42 mole) was refluxed for 40 hr. Ice–water (200 ml.) was added and the precipitated solid was filtered. Recrystallization from ethanol–water, with charcoal, yielded the analytical sample (0.20 g., 58%): m.p. 111–112°; ν_{NH} none, $\nu_{C=O}$ 1697 (s), ν_{NO_2} 1511 (s) or 1463 (s) (partly Nujol), 1370 (s) or 1345 (s) or 1326 (s) or 1304 (s) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$ (218.21): C, 60.54; H, 4.62; N, 12.84. Found: C, 60.26; H, 4.34; N, 13.03.

3,4-Dinitro-2-methylindole (6). From 2-Methyl-4-nitroindole (4).[2a]—A solution of 2-methyl-4-nitroindole (0.10 g., 0.00057 mole) in concentrated nitric acid (*d* 1.42, 20 ml.) was kept at 24° for 30 min. and then warmed gently on a steam bath for 2 min. Ice–water (30 ml.) was added and the resulting mixture was filtered, giving a brown solid. The solid was washed with ice-water and recrystallized twice from ethanol–water, with charcoal, yielding a yellowish solid (0.02 g., 16%): m.p. 284–285° dec.; λ_{max}, mμ (log ϵ), in 95% ethanol 233 (4.08), 300 broad plateau (3.94), 338 (4.00); ν_{NH} 3230 (m) (broad), ν_{NO_2} 1527 (s), 1386 (s) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_9H_7N_3O_4$ (221.18): C, 48.87; H, 3.19; N, 19.00. Found: C, 49.08; H, 3.72; N, 18.95.

2-Methyl-3,4,6-trinitroindole (7).[2a] **A. From 2-Methylindole.**—The procedure, essentially that of Mathur and Robinson,[5] is identical with that described above for preparation of 3,6-dinitro-2-methylindole, except that after the initial vigorous reaction had subsided the mixture was warmed further on the steam bath for 30 min. until all of the solids dissolved. The solution was then cooled and filtered through a sintered-glass funnel, and the filtered solid was washed with water. One recrystallization of the solid from concentrated nitric acid (*d* 1.42) at steam-bath temperature, and one recrystallization from 95% ethanol, gave cream-colored needles (4.6 g., 23%): m.p. 259–262° dec.; lit.[5] 20% yield, m.p. 254–256° dec.; λ_{max}, mμ (log ϵ), in 95% ethanol (does not obey Beer's law) at c 1.270 × 10^{-4} M, ~277 (~4.14), 318 (4.10); at c 2.539 × 10^{-5} M, 281 (4.04), 313 (4.12), 384 (4.15); ν_{NH} 3320 (m), ν_{NO_2} 1528 (s), 1340 (s) cm.$^{-1}$ in Nujol; pK_a = 7.3.

In contrast to the successful oxidative degradation of the isomeric 2-methyl-3,5,6-trinitroindole, attempted oxidative degradation of the compound with chromium(VI) trioxide in acetic acid, or with sodium permanganate in aqueous acetic–sulfuric acid, gave unchanged starting material as the only crystalline product, in yields of 40–84%.

B. From 3,6-Dinitro-2-methylindole (5).—A mixture of 3,6-dinitro-2-methylindole (1.65 g., 0.00746 mole) and concentrated nitric acid (*d* 1.42, 30 ml.) was warmed on a steam bath for 30 min. The resulting deep red solution was cooled in an ice bath and filtered through a sintered-glass funnel. The filtered solid was washed with water and recrystallized from 95% ethanol, giving cream-colored needles (0.44 g.). Cold water was added to the nitric acid filtrate, and the precipitated solid was filtered off and recrystallized from 95% ethanol, giving additional product (0.45 g.; total 0.89 g., 45%), m.p. 259–262° dec. There was no depression in mixture melting point with the sample prepared directly from 2-methylindole, and the infrared spectra in Nujol were identical.

C. From 2-Methyl-4-nitroindole (4).—A solution of 2-methyl-4-nitroindole (0.12 g., 0.00068 mole) in concentrated nitric acid (*d* 1.42, 20 ml.) was warmed on a steam bath for 30 min. Ice–water (about 30 ml.) was then added, and the mixture was cooled and filtered. The filtered solid was recrystallized from

---

(45) A. Angeli and F. Angelico, *Gazz. chim. ital.*, **30**, II, 268 (1900).

(46) L. Alessandri and M. Passerini, *ibid.*, **51**, I, 262 (1921).

(47) W. A. Van Ekenstein and J. J. Blanksma, *Rec. trav. chim.*, **24**, 36 (1907).

ethanol–water, with charcoal, giving cream-colored needles (7 mg., 4%), m.p. 259–260° dec. There was no depression in mixture melting point with the sample prepared from 2-methylindole, and the infrared spectra in Nujol were identical.

D. **From 3-Acetyl-2-methyl-4-nitroindole** (**9**).—A mixture of 3-acetyl-2-methyl-4-nitroindole (0.10 g., 0.00046 mole) and concentrated nitric acid (*d* 1.42, 20 ml.) was treated as described (in part C) for 2-methyl-4-nitroindole, giving cream-colored needles (0.03 g., 24%), m.p. 259–260° dec. There was no depression in mixture melting point with the same prepared from 2-methylindole, and the infrared spectra in Nujol were identical.

3′,5′-Dinitro-*o*-diacetotoluidide (**14**).[2a]—Concentrated sulfuric acid (1 drop) was added to a solution of 3,5-dinitro-*o*-toluidine[48,49] (m.p. 135–137°, 1.0 g., 0.0051 mole) in acetic anhydride (15 ml., 0.16 mole), and the solution was warmed on a steam bath for 15 min. Work-up as described for 5′,6′-dinitro-*o*-diacetotoluidide and recrystallization from 95% ethanol yielded white crystals (0.7 g., 49%): m.p. 123–126°; λ_{max}, mμ (log ϵ), in 95% ethanol 239 (4.63), 318 (3.29); ν_{NH} none, $\nu_{C=O}$ 1802 (s), 1711 (s) (slightly stronger), ν_{NO_2} 1554 (vs), 1378 (s) or 1325 (ms) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{11}H_{11}N_3O_6$ (281.22): N, 14.94. Found: N, 14.41.

Hydrolysis of the compound with aqueous 20% sulfuric acid at 100° gave **3′,5′-dinitro-*o*-acetotoluidide**, m.p. 224°, lit.[48a] m.p. 224°.

5′,6′-Dinitro-*o*-diacetotoluidide (**15**).[2a]—Concentrated sulfuric acid (3 drops) was added to a solution of 5,6-dinitro-*o*-toluidine[20] (m.p. 129–130°, 4.0 g., 0.0203 mole) in acetic anhydride (50 g., 0.49 mole). The solution was refluxed for 30 min. and then poured into ice–water. After the acetic anhydride had hydrolyzed, the mixture was filtered, and the filtered solid was recrystallized from ethanol–water, yielding white platelets (2.2 g., 38%): m.p. 122–123°; λ_{max}, mμ (log ϵ), in 95% ethanol 264 (3.88), 336 diffuse infl. (2.85); ν_{NH} none, $\nu_{C=O}$ 1738 (s, stronger), 1710 (s), ν_{NO_2} 1555 (s), 1373 (s) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{11}H_{11}N_3O_6$ (281.22): C, 46.98; H, 3.94; N, 14.94. Found: C, 47.20; H, 3.85; N, 15.15.

A longer reaction reflux time produced only decomposition.

Hydrolysis to 5′,6′-Dinitro-*o*-acetotoluidide.[2a]—Treatment of 5′,6′-dinitro-*o*-diacetotoluidide (1) with sodium methoxide in ethanol at room temperature for 24 hr., (2) with sodium ethoxide in boiling ethanol for 1 hr., or (3) with polyphosphoric acid at 110° for 0.5 hr. all gave 5′,6′-dinitro-*o*-acetotoluidide, m.p. 187–189°, lit.[20b] m.p. 186°. There was no depression in mixture melting point with a sample prepared[20] by acetylation of 5,6-dinitro-*o*-toluidine.

Hydrolysis to 5,6-Dinitro-*o*-toluidine.[2a]—Hydrolysis of 5′,6′-dinitro-*o*-diacetotoluidide with aqueous 20% sulfuric acid at 100° for 1 hr. gave 5,6-dinitro-*o*-toluidine: m.p. 129–130°; lit. m.p. 130°,[20b] 131–131.5°.[20a] There was no depression in mixture melting point with a sample of m.p. 129–130° prepared[20] from 5-nitro-*o*-toluidine.

1,2-Dimethyl-3,6-dinitroindole (**16**).[2b] A. **From 1,2-Dimethylindole.**—A solution of 1,2-dimethylindole[50] (5.14 g., 0.0353 mole) in concentrated nitric acid (*d* 1.42, 50 ml.) was warmed on a steam bath (in the manner described for the preparation of 3,6-dinitro-2-methylindole, except that the present reaction is milder and can be controlled in an erlenmeyer flask) until a vigorous reaction occurred. The mixture was cooled and the precipitate was filtered off and crystallized from acetonitrile, with charcoal, yielding white crystals (2.36 g., 28%): m.p. 299°; lit.[7] m.p. 293–295° dec.; λ_{max}, mμ (log ϵ), in 95% ethanol 223 infl. (3.95), 273 infl. (3.95), 303 (4.18), 339 (4.20), ν_{NO_2} 1515 (s), 1337 (s), or 1323 (s) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{10}H_9N_3O_4$ (235.20): C, 51.06; H, 3.86; N, 17.87. Found: C, 51.15; H, 3.58; N, 17.79.

B. **From 3,6-Dinitro-2-methylindole** (**5**).—A slurry of 3,6-dinitro-2-methylindole (1.04 g., 0.00470 mole) in anhydrous ether (10 ml.) was added dropwise, with stirring, to a solution of sodamide (from sodium, 0.20 g., 0.0087 g.-atom, and ferric nitrate nonahydrate, 0.05 g.) in liquid ammonia (10 ml.). After 15 min., methyl iodide (1.00 g., 0.00705 mole) was added dropwise and stirring was continued for 15 min. The ammonia was allowed to evaporate and the residue was recrystallized from acetonitrile, yielding white crystals (0.37 g., 32%), m.p. 299°. There was no depression in mixture melting point, 299°, with the sample prepared from 1,2-dimethylindole, and the infrared spectra in Nujol were identical.

1,2-Dimethyl-3,4,6-trinitroindole (**17**).[2b] A. **From 1,2-Dimethylindole.**—A solution of 1,2-dimethylindole[50] (1.14 g., 0.00785 mole) in concentrated nitric acid (*d* 1.42, 30 ml.) was warmed on a steam bath until a vigorous reaction occurred. The solution was cooled until the reaction ceased and then rewarmed at 90° on a steam bath for 30 min. The solution was cooled and poured into water, and the resulting precipitate was filtered off. Three recrystallizations from acetone–ethanol, one with charcoal, gave pale yellow platelets (0.33 g., 15%), m.p. 238–241° dec. Two more similar recrystallizations yielded a sample, m.p. 242–244°. There was no depression in mixture melting point, 242–243.5°, with the sample prepared from 1,2-dimethyl-3,6-dinitroindole, and the infrared spectra in Nujol were identical.

B. **From 1,2-Dimethyl-3,6-dinitroindole** (**18**).—A solution of 1,2-dimethyl-3,6-dinitroindole (1.18 g., 0.00502 mole) in concentrated nitric acid (*d* 1.42, 30 ml.) was warmed at 90° on a steam bath for 30 min. The solution was cooled, and the resulting precipitate was filtered off and recrystallized from acetone–ethanol, yielding pale yellow platelets (0.22 g., 16%): m.p. 243–244°; λ_{max}, mμ (log ϵ), in 95% ethanol 294 (4.20), 347 (4.08); ν_{NO_2} 1538 (s, infl.), 1520 (s), 1353 (s), 1330 (s) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{10}H_8N_4O_6$ (280.20): C, 42.86; H, 2.88; N, 20.00. Found: C, 43.09; H, 3.11; N, 19.98.

The analytical sample described above was obtained as a dimorphic form having an infrared spectrum in Nujol different from the spectra of all other samples of the compound only in that the band usually present at 903 (m) cm.$^{-1}$ was split into two bands at 898 (mw) and 907 (mw) cm.$^{-1}$. Recrystallization of the analytical sample from the same solvent pair (acetone–ethanol) from which it had been obtained yielded the common dimorphic form, of unchanged melting point, but having an infrared spectrum in Nujol identical with those of the samples prepared from 1,2-dimethylindole and 2-methyl-3,4,6-trinitroindole.

Anal. Found: C, 43.12; H, 2.89; N, 19.11.

C. **From 2-Methyl-3,4,6-trinitroindole** (**7**).—Dimethyl sulfate (1.5 g., 0.0119 mole) was added, with stirring, to a solution of 2-methyl-3,4,6-trinitroindole (0.19 g., 0.00071 mole) in aqueous potassium carbonate (5%, 15 ml.) and ethanol (10 ml.). After 1 hr. the resulting precipitate was filtered off and dried. Recrystallization from acetone–ethanol, with charcoal, gave pale yellow platelets (0.12 g., 60%), m.p. 235–239° dec. One more recrystallization yielded a sample, m.p. 242–244°. There was no depression in mixture melting point, 242–243.5°, with the sample prepared from 1,2-dimethyl-3,6-dinitroindole, and the infrared spectra in Nujol were identical.

1,2-Dimethyl-6-nitroindole (**18**).[2b]—By the method used for the preparation of 1,2-dimethyl-4-nitroindole, 2-methyl-6-nitroindole was converted in 23% yield to fluffy bright yellow needles (from methylene chloride–petroleum ether): m.p. 106–107.5°; λ_{max}, mμ (log ϵ), in 95% ethanol 213 (4.35), 252 (4.01), 267 infl. (3.86), 338 (3.92), 384 (3.95); ν_{NO_2} 1534 (m) or 1497 (s), 1337 (s) or 1311 (s, stronger) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$ (190.20): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.24; H, 5.19; N, 14.89.

1,2-Dimethyl-4-nitroindole (**19**).[2b]—A solution of 2-methyl-4-nitroindole (0.60 g., 0.00340 mole) in anhydrous ether (50 ml.) was added dropwise, with stirring, to a solution of sodamide (from sodium, 0.15 g., 0.0065 g.-atom, and ferric nitrate nonahydrate, 0.10 g.) in liquid ammonia (250 ml.). Stirring was continued for 30 min., methyl iodide (1.00 g., 0.00705 mole) was added dropwise, and stirring was continued for an additional 30 min. The ammonia was allowed to evaporate, water was added to the solid residue, and the resulting mixture was extracted with methylene chloride. The methylene chloride extracts were dried, treated with charcoal, and concentrated. Addition of petroleum ether and cooling yielded fluffy orange needles (0.42 g., 65%): m.p. 94–97°; λ_{max}, mμ (log ϵ), in 95% ethanol 212 (4.41), 243 (4.08), 396 (3.84); ν_{NO_2} 1534 (m) or 1499 (s), 1314 (s) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$ (190.20): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.11; H, 5.41; N, 14.86.

---

(48) K. Brand and T. Eisenmenger: (a) *J. prakt. chem.*, [2] **87**, 487 (1913); (b) *Chem. Ber.*, **49**, 673 (1916).

(49) R. Anschütz and W. Zimmerman, *ibid.*, **48**, 152 (1915).

(50) (a) K. T. Potts and J. E. Saxton, *J. Chem. Soc.*, 2641 (1954); (b) W. E. Noland, W. C. Kuryla, and R. F. Lange, *J. Am. Chem. Soc.*, **81**, 6010 (1959).

3,5-Dinitro-2-methylindole (22).[2a]—2-Methyl-5-nitroindole (6.0 g., 0.0340 mole) was added to concentrated nitric acid (*d* 1.42, 80 ml.) and the mixture was warmed on a steam bath for 3 min. During this time the solid dissolved, the solution turned maroon, and a new solid precipitated. The mixture was then poured onto crushed ice. The maroon crystals were filtered off and recrystallized from ethanol–water, with charcoal, yielding metallic yellow crystals (4.28 g., 57%): m.p. 285–287°; λ_{max}, mμ (log ϵ), in 95% ethanol 251 (4.37), 314 (4.04), 347 (4.04); ν_{NH} 3280 (s), ν_{NO_2} 1556 (m), 1520 (s), 1336 (s) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_9H_7N_3O_4$ (221.18): C, 48.87; H, 3.19; N, 19.00. Found: C, 49.21; H, 3.27; N, 18.92.

The mixture melting point with the direct dinitration product of 2-methylindole, 3,6-dinitro-2-methylindole, was depressed, m.p. 250–257°, and the infrared spectra in Nujol were different.

The compound was recovered unchanged in 80% yield, m.p. 285–287°, from attempted acetylation for 24 hr. in refluxing acetic anhydride containing sodium acetate trihydrate. In contrast to the successful methylation with dimethyl sulfate and sodium hydroxide solution, attempted methylation of the compound with sodamide and methyl iodide in liquid ammonia gave unchanged starting material in 60% yield, m.p. 288–290°. Attempted nitration of the compound with sodium nitrate in concentrated sulfuric acid at 70–90° gave unchanged starting material in 45% yield as the only water-insoluble product.

Oxidative Degradation of 3,5-Dinitro-2-methylindole (22).[2a]—A mixture of pure 3,5-dinitro-2-methylindole (1.00 g., 0.00452 mole) and acetic acid (45 ml.) was refluxed for 30 min., causing most but not all of the solid to dissolve. The solution was then allowed to cool to room temperature and a solution of chromium(VI) trioxide (2.0 g., 0.020 mole) in water (2 ml.) and acetic acid (15 ml.) was added dropwise, with stirring. The mixture was stirred for 72 hr. and water (150 ml.) was added. The mixture was extracted with chloroform and ether. The combined extracts were washed with water and then extracted with aqueous saturated sodium bicarbonate solution until carbon dioxide was no longer evolved. The chloroform–ether solution was dried over anhydrous sodium sulfate and evaporated to a small volume. Addition of petroleum ether caused precipitation of unchanged 3,5-dinitro-2-methylindole (0.17 g., 17%), m.p. 285–287°, which gave no depression in mixture melting point with starting material.

The sodium bicarbonate extract was acidified to pH 2 with sulfuric acid and extracted with ether. The ether solution was dried over anhydrous sodium sulfate, treated with charcoal, and evaporated to a small volume. Addition of petroleum ether caused precipitation of **N-acetyl-5-nitroanthranilic acid (23)** (0.13 g., 15% based on unrecovered starting material), m.p. 213–214°. There was no depression in mixture melting point with a sample[10] of m.p. 213–214° prepared by oxidation of 4′-nitro-*o*-acetotoluidide,[51] and the infrared spectra in Nujol were identical.

2-Methyl-3,5,6-trinitroindole (24).[2a] **A. From 3,5-Dinitro-2-methylindole (22).**—A mixture of 3,5-dinitro-2-methylindole (0.70 g., 0.00316 mole) and concentrated nitric acid (*d* 1.42, 15 g.) was warmed on a steam bath for 30 min. The resulting deep red solution was cooled and water (75 ml.) was added. The precipitated solid was filtered off and recrystallized from 75% ethanol, yielding a cream-colored solid (0.20 g., 24%): m.p. 265–267°; λ_{max}, mμ (log ϵ), in 95% ethanol (c 3.682 × 10^{-5} *M*, does not obey Beer's law) 230 (4.12), 244 (4.12), 317 (4.05), 386 (3.92); ν_{NH} 3280 (s), ν_{NO_2} 1548 (s), 1362 (s) cm.$^{-1}$ in Nujol; pK_a = 7.4.

Anal. Calcd. for $C_9H_6N_4O_6$ (266.17): C, 40.61; H, 2.27; N, 21.05. Found: C, 40.70; H, 2.44; N, 20.85.

The compound reacts with *p*-dimethylaminobenzaldehyde in the presence of piperidine,[5] giving complex tarry products; in the presence of sulfuric acid, however, it gave a greenish yellow solid, m.p. 154–160°, having a double-bond band in the infrared at 1650 cm.$^{-1}$ in Nujol.

B. From 1-Acetyl-2-methyl-5-nitroindole (21).—A solution of 1-acetyl-2-methyl-5-nitroindole (0.40 g., 0.00183 mole) in concentrated nitric acid (*d* 1.42, 20 ml.) was warmed on a steam bath for 30 min. and then poured into ice–water (50 ml.). The precipitated solid was filtered off and recrystallized from ethanol–water, giving a cream-colored solid (0.27 g., 55%), m.p. 265–267°. There was no depression in mixture melting point with the sample prepared from 3,5-dinitro-2-methylindole, and the infrared spectra in Nujol were identical.

Oxidative Degradation of 2-Methyl-3,5,6-trinitroindole (24).[2a]—A solution of chromium(VI) oxide (12.00 g., 0.120 mole) in water (20 ml.) was added to a solution of 2-methyl-3,5,6-trinitroindole (8.60 g., 0.0323 mole) in acetic acid (150 ml.), and the resulting solution was warmed on a steam bath for 1 hr. and then kept at room temperature for 24 hr. Water (200 ml.) was added and the mixture was cooled in an ice bath. The precipitated solid was filtered off and extracted with aqueous saturated sodium bicarbonate solution, leaving unchanged 2-methyl-3,5,6-trinitroindole (2.20 g.). The filtrate was extracted with ether and the ether extracts were washed with water. The ether solution was then extracted with aqueous saturated sodium bicarbonate solution until carbon dioxide was no longer evolved. Evaporation of the ether solution gave additional unchanged 2-methyl-3,5,6-trinitroindole (1.00 g.; total 3.20 g., 37%), m.p. 265–267°.

Both sodium bicarbonate extracts were combined, acidified to pH 2 with sulfuric acid, and extracted with ether. The ether extracts were washed with water, dried, and treated with charcoal. The ether solution was then evaporated to a small volume and petroleum ether was added, causing separation of **N-acetyl-4,5-dinitroanthranilic acid (26)** (0.13 g., 2% based on unrecovered starting material), m.p. 249–250°. There was no depression in mixture melting point with the sample prepared from 4′,5′-dinitro-*o*-acetotoluidide, and the infrared spectra in Nujol were identical.

N-Acetyl-4,5-dinitroanthranilic Acid (26).—A solution of potassium permanganate (1.70 g., 0.0107 mole) in water (70 ml.) was added to a solution of 4′,5′-dinitro-*o*-acetotoluidide[20] (m.p. 181–182°, 0.82 g., 0.00343 mole) in acetic acid (100 ml.). The mixture was refluxed for 2 hr. until the purple color disappeared. The hot solution was filtered, and the filtrate was diluted with water (50 ml.) and cooled. The precipitated solid was filtered off and found to be unchanged 4′,5′-dinitro-*o*-acetotoluidide (0.29 g.). The filtrate was diluted with more water (50 ml.) and extracted with ether. The ether extracts were washed with water and extracted with aqueous saturated sodium bicarbonate solution until carbon dioxide was no longer evolved. Evaporation of the ether solution gave additional unchanged 4′,5′-dinitro-*o*-acetotoluidide (0.17 g.; total 0.46 g., 56%).

The sodium bicarbonate extracts were acidified to pH 2 with sulfuric acid and extracted with ether. The ether extracts were washed with water, dried, and treated with charcoal. The ether solution was then evaporated to a small volume and petroleum ether was added, causing separation of **N-acetyl-4,5-dinitroanthranilic acid (26)** as light cream-colored crystals (0.07 g., 17% based on unrecovered starting material): m.p. 249–250°; λ_{max}, mμ (log ϵ), in 95% ethanol 234 (4.20), 326 (3.95); ν_{NH} ~3200 (m, broad), $\nu_{NH\ or\ CH}$ 3100 (m), $\nu_{C=O}$ 1700 (s), ν_{NO_2} 1559 (s), 1515 (ms), 1378 (s), 1346 (s) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_9H_7N_3O_7$ (269.17): C, 40.16; H, 2.62; N, 15.61. Found: C, 40.43; H, 2.82; N, 15.13.

1,2-Dimethyl-3,5-dinitroindole (28).[2b] **A. From 1,2-Dimethyl-5-nitroindole (27).**—A solution of 1,2-dimethyl-5-nitroindole[1] (1.00 g., 0.00526 mole) in concentrated nitric acid (*d* 1.42, 5 ml.) was warmed on a steam bath until brown fumes were evolved (about 2 min. at 50°). The solution was cooled and the resulting precipitate was filtered off, dried, and added to the top of a column of alumina (25 g.) which had been packed wet with petroleum ether. Elution with ether–benzene (1:4 by volume) removed a pale yellow solid. Recrystallization from acetone–methanol yielded pale yellow needles (0.07 g., 6%): m.p. 201–203°; λ_{max}, mμ (log ϵ), in 95% ethanol 257 (4.31), 304 broad (3.97), 357 (3.98); ν_{NO_2} 1544 (ms), 1509 (s), 1350 (s), 1332 (s, infl. in KBr), 1541 (m, infl.), 1515 (ms), 1342 (s, infl.) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{10}H_9N_3O_4$ (235.20): C, 51.06; H, 3.86; N, 17.87. Found: C, 51.31; H, 3.99; N, 18.03.

B. From 3,5-Dinitro-2-methylindole (22).—Dimethyl sulfate (5.00 g., 0.0396 mole) was added, with stirring, to a solution of 3,5-dinitro-2-methylindole (1.37 g., 0.00620 mole) in aqueous sodium hydroxide (1%, 80 ml.) and ethanol (65 ml.). After 0.5 hr. the resulting precipitate was filtered off, dried, and recrystallized from acetone, with charcoal, yielding pale yellow needles (1.00 g., 69%), m.p. 199–200.5°. There was no depression in mixture melting point, 198.5–201.5°, with the sample

---

(51) H. Franzel and E. Engel, *J. prakt. chem.*, [2] **102**, 173 (1921).

prepared from 1,2-dimethyl-5-nitroindole, and the infrared spectra in Nujol were identical.

Oxidative Degradation of 1,2-Dimethyl-3,5-dinitroindole (28).[2b]—A solution of chromium(VI) oxide (2.00 g., 0.0200 mole) in water (3 ml.) and acetic acid (15 ml.) was added to a suspension of 1,2-dimethyl-3,5-dinitroindole (0.78 g., 0.00332 mole) in acetic acid (40 ml.). The resulting solution was stirred for 72 hr. and then diluted with water and extracted with chloroform and ether. The organic extracts were washed with water and extracted with aqueous sodium bicarbonate solution until carbon dioxide was no longer evolved The chloroform–ether solution was dried and concentrated to a small volume. Addition of petroleum ether caused precipitation of an orange solid. Recrystallization from methylene chloride–petroleum ether yielded **1-methyl-5-nitroisatin (29)** as small orange needles (0.18 g., 26%): m.p. 202.5–205°; lit. m.p. 203°[21] (yellow-red platelets), m.p. 204–206°[7] (orange needles); λ_{max}, mμ (log ε), in 95% ethanol 223 infl. (4.06), 249 infl. (3.65), 285 infl. (3.65), 331 (3.99); $\nu_{C=O}$ 1752 (s), 1740 (s), stronger), 1614 (s), ν_{NO_2} 1520 (m), 1346 (s) or 1332 (ms) cm.$^{-1}$ in Nujol. There was no depression in mixture melting point, 202.5–205°, with a sample of m.p. 204–205.5° prepared in 68% yield by nitration[21] of 1-methylisatin[52] at 0°, and the infrared spectra in Nujol were identical.

The sodium bicarbonate extracts were acidified with dilute sulfuric acid and extracted with ether. The ether extracts were dried and concentrated to a small volume. Addition of petroleum ether caused separation of a pale yellow solid. Recrystallization from ether–petroleum ether gave small pale yellow needles (0.10 g., 15%), m.p. 211.5–214°. Sublimation at 190° (1 mm.) yielded **N-methyl-5-nitroanthranilic acid (30)** as small white needles: m.p. 217–218°; lit. m.p. 259° dec.,[23] 271–273°[7]; λ_{max}, mμ (log ε), in 95% ethanol 213 (4.26), 243 infl. (3.92), 320 (4.00); ν_{NH} 3430 (vw), 3260 (w, in $CHCl_3$), 3300 (w, in Nujol), $\nu_{C=O}$ 1692 (s, in $CHCl_3$), 1704 (ms), 1674 (s, in Nujol), ν_{NO_2} 1513 (s, partly $CHCl_3$), 1348 (s, in $CHCl_3$), 1506 (s), 1347 (s) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_8H_8N_2O_4$ (196.16): C, 48.98; H, 4.11; N, 14.28. Found: C, 48.73; H, 3.84; N, 14.18.

1,2-Dimethyl-3,5,6-trinitroindole (31).[2b] **A. From 1,2-Dimethyl-5-nitroindole (27).**—A solution of 1,2-dimethyl-5-nitroindole[1] (1.00 g., 0.00526 mole) in concentrated nitric acid (*d* 1.42, 12 ml.) was warmed at 90° on a steam bath for 15 min. The resulting mixture was poured onto crushed ice. The precipitate was filtered off and recrystallized from acetone–ethanol, with charcoal, yielding pale yellow platelets (0.28 g., 19%): m.p. 267–269° dec.; λ_{max}, mμ (log ε), in 95% ethanol 230 (4.09), 272 (4.30), 295 diffuse infl. (4.19), 353 (4.03); ν_{NO_2} 1542 (s), 1530 (s), 1363 (s), 1337 (s) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{10}H_8N_4O_6$ (280.20): C, 42.86; H, 2.88; N, 20.00. Found: C, 42.98; H, 3.15; N, 20.14.

B. From 1,2-Dimethyl-3,5-dinitroindole (28).—A solution of 1,2-dimethyl-3,5-dinitroindole (0.50 g., 0.00213 mole) in concentrated nitric acid (*d* 1.42, 5 ml.) was warmed at 90° on a steam bath for 30 min. The solution was cooled and the resulting precipitate was filtered off, washed with aqueous sodium bicarbonate solution, and recrystallized from acetone–ethanol, giving pale yellow platelets (0.14 g., 23%), m.p. 260–265° dec. One more recrystallization yielded a sample, m.p. 267–269° dec. There was no depression in mixture melting point, 266–269° dec., with the sample prepared from 1,2-dimethyl-5-nitroindole, and the infrared spectra in Nujol were identical.

C. From 2-Methyl-3,5,6-trinitroindole (24).—Dimethyl sulfate (2.50 g., 0.0198 mole) was added, with stirring, to a solution of 2-methyl-3,5,6-trinitroindole (0.55 g., 0.00206 mole) in aqueous potassium carbonate (5%, 30 ml.) and ethanol (15 ml.). After 3 hr. the resulting precipitate was filtered off, dried, and recrystallized from acetone–ethanol, with charcoal, giving pale yellow platelets (0.38 g., 66%), m.p. 263–268° dec. Two more recrystallizations yielded a sample, m.p. 265–268° dec. There was no depression in mixture melting point, 266–268.5° dec., with the sample prepared from 1,2-dimethyl-5-nitroindole, and the infrared spectra in Nujol were identical.

Oxidative Degradation of 1,2-Dimethyl-3,5,6-trinitroindole (31).[2b]—A solution of chromium(VI) oxide (6.00 g., 0.0600 mole) in water (10 ml.) was added to a suspension of 1,2-dimethyl-3,5,6-trinitroindole (4.00 g., 0.0143 mole) in acetic acid (120 ml.). The resulting suspension was warmed at 90° on a steam bath for 1 hr. and then kept at room temperature for 40 hr. Water (200 ml.) was added, causing precipitation of unchanged starting material (2.34 g., 58% recovery). The mother liquor was extracted with ether, and the ether extracts were then extracted with aqueous saturated sodium bicarbonate solution until carbon dioxide was no longer evolved. The sodium bicarbonate extracts were acidified to pH 2 with sulfuric acid and extracted with ether. The ether extracts were dried and evaporated, and the residue was crystallized from methylene chloride–petroleum ether, with charcoal, yielding **4,5-dinitro-N-methylanthranilic acid (32)** as white crystals (0.08 g., 6% based on unrecovered starting material): m.p. 248–249° dec. with gas evolution; λ_{max}, mμ (log ε), in 95% ethanol 210 (4.18), 236 (4.14), 327 (3.91); ν_{NH} 3180 (mw, infl.), $\nu_{C=O}$ 1696 (s), ν_{NO_2} 1556 (s), 1513 (ms), 1372 (ms) (NO_2?), 1344 (s) cm.$^{-1}$ in KBr.

Anal. Calcd. for $C_8H_7N_3O_6$ (241.16): C, 39.84; H, 2.93; N, 17.43. Found: C, 40.30; H, 2.72; N, 17.36.

2-Ethylindole (with James E. Johnson, 1962).—*o*-Propionotoluidide[53] was prepared in 74% yield, m.p. 86–87°, by a procedure[54] described for *o*-acetotoluidide. 2-Ethylindole, m.p. 44–45°, was prepared from it in 91% yield by the procedure[38] for 2-methylindole: lit.[55] 67% yield, m.p. 43°; ν_{NH} 3460 (ms), 3400 (vw, in CCl_4), 3430 (ms), 3380 (vw, in CS_2), ν_{NH} 3380 (s) cm.$^{-1}$ in Nujol.

2-Ethyl-5-nitroindole (34).[2b]—A solution of sodium nitrate (2.34 g., 0.0275 mole) in concentrated sulfuric acid (60 ml.) was added dropwise, with stirring, to a solution of 2-ethylindole (4.00 g., 0.0275 mole) in concentrated sulfuric acid (60 ml.) kept at 5° in an ice bath. The solution was stirred for an additional 5 min. and then poured onto crushed ice. The resulting yellow precipitate was dissolved in benzene and chromatographed on alumina packed wet with petroleum ether. Elution with ether–benzene (1:9 by volume) yielded bright yellow flakes (4.05 g., 77%): m.p. 131–132.5°; λ_{max}, mμ (log ε), in 95% ethanol 208 (4.30), 266 (4.37), 331 (3.99); ν_{NH} 3290 (ms), ν_{NO_2} 1553 (m) or 1499 (ms), 1316 (vs) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$ (190.20): C, 63.15; H, 5.30; N, 14.73. Found: C, 62.88; H, 5.34; N, 14.81.

3,5-Dinitro-2-ethylindole (35).[2b]—A solution of 2-ethyl-5-nitroindole (0.37 g., 0.00195 mole) in concentrated nitric acid (*d* 1.42, 4 ml.) was warmed on a steam bath until effervescence began (about 1 min. at 50°), and then the solution was cooled in an ice bath. The resulting precipitate was filtered off, washed with water and sodium bicarbonate solution, dried, and dissolved in 1:1 ethyl acetate–petroleum ether, and chromatographed on alumina. Elution with 2:1 ethyl acetate–petroleum ether yielded fluffy white needles (0.10 g., 22%): m.p. 229–230° dec.; λ_{max}, mμ (log ε), in 95% ethanol 253 (4.39), 312 (4.05), 349 (4.02); ν_{NH} 3170 (ms), ν_{NO_2} 1548 (m), 1524 (ms), 1355 (s), 1340 (s) cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{10}H_9N_3O_4$ (235.20): C, 51.06; H, 3.86; N, 17.87. Found: C, 50.79; H, 3.93; N, 18.01.

3,5-Dinitro-2-ethyl-1-methylindole (36).[2b] **A. From 3,5-Dinitro-2-methylindole (22).**—A solution of 3,5-dinitro-2-methylindole (2.21 g., 0.0100 mole) in dry[56] N,N-dimethylformamide (100 ml.) was added dropwise, with stirring, to a suspension of sodium hydride (2.00 g., 0.0834 mole) in dry N,N-dimethylformamide (100 ml.). After 5 min., methyl iodide (3.00 g., 0.0211 mole) was added dropwise, and stirring was continued for 0.5 hr. The N,N-dimethylformamide was distilled off at aspirator pressure and water was added to the dark viscous residue. The resulting precipitate was crystallized from acetone–ethanol, with charcoal, giving a mixture, m.p. 212–222°. Extraction of the mixture with aqueous 40% sodium hydroxide solution and recrystallization of the residue from acetone–ethanol yielded pale yellow needles (1.56 g., 63%): m.p. 226–228.5°; λ_{max}, mμ (log ε), in 95% ethanol 256 (4.38), 308 (4.02), 356 (4.02); ν_{NO_2} 1534 (ms), 1515 (s), 1357 (s), 1333 (s) cm.$^{-1}$ in Nujol. There was no depression in mixture melting point, 226–228°, with the sample prepared from 3,5-dinitro-2-ethylindole, and the infrared spectra in Nujol were identical.

Anal. Calcd. for $C_{11}H_{11}N_3O_4$ (249.22): C, 53.01; H, 4.45; N, 16.86. Found: C, 53.18; H, 4.40; N, 16.80.

B. From 3,5-Dinitro-2-ethylindole (35).—Dimethyl sulfate (1.00 g., 0.00793 mole) was added, with stirring, to a solution of

---

(52) M. Kohn and A. Ostersetzer, *Monatsh. Chem.*, **37**, 25 (1916).

(53) A. Pictet and L. Duparc, *Chem. Ber.*, **20**, 3421 (1887).

(54) I. S. Ioffe, *J. Gen. Chem. USSR*, **14**, 812 (1944); *Chem. Abstr.*, **39**, 3786 (1945).

(55) M. A. Verley and J. Beduwé, *Bull. soc. chim. France*, [4] **37**, 189 (1925).

(56) Distilled at atmospheric pressure.

3,5-dinitro-2-ethylindole (0.33 g., 0.00140 mole) in aqueous 1% sodium hydroxide solution (20 ml.) and ethanol (15 ml.). After 1 hr. the resulting precipitate was filtered off and recrystallized twice, once with charcoal, giving a mixture as pale yellow needles (0.15 g.), m.p. 188–210°. Extraction of the mixture with aqueous 40% sodium hydroxide solution, and two recrystallizations from acetone–ethanol yielded pale yellow needles (0.09 g., 26%), m.p. 227–229°.

2-Methyl-3,5,7-trinitroindole (37).—The compound[16] crystallized from ethanol–water as cream-colored crystals: m.p. 213–215°; lit.[16] m.p. 205–206° (anhydrous form[57]); $\lambda_{\max}$, mμ (log ϵ, calculated as the anhydrous form, which is the only form we observed), in 95% ethanol (does not obey Beer's law) at c 1.528 $\times 10^{-4}$ M, intense maximum between 233 and 309, 344 (3.37); at c 3.056 $\times 10^{-5}$ M, 284 (4.24), 350 (3.98); ν_{NH} 3380 (m) and 3330 (m), ν_{NO_2} 1537 (s), 1355 (s) cm.$^{-1}$ in Nujol; pK_a = 7.3.

1,2,3-Trimethylindole (with Norman W. Gill and Frederic J. Baude, 1962).—The compound (which according to previous work[58] should contain 13% 2,3,3-trimethyl-3H-indole) was obtained in 89% yield, $n^{25}\text{D}$ 1.5950, free of NH bands in the infrared spectrum, by methylation of 2,3-dimethylindole[29c,59] with a 15% excess of sodium and methyl iodide in liquid ammonia, according to the procedure used for preparation of 1-methylindole[60] and 1,2-dimethylindole.[50] Redistillation gave a center cut: b.p. 89° (0.75 mm.); $n^{27}\text{D}$ 1.5930; $\lambda_{\max}$, mμ (log ϵ), in 95% ethanol 231 (4.52), 287 (3.83), 293 infl. (3.81).

5-Nitro-1,2,3-trimethylindole (41).[2b] **A. From 1,2,3-Trimethylindole.**—A solution of sodium nitrate (1.60 g., 0.0188 mole) in concentrated sulfuric acid (50 ml.) was added dropwise, with stirring, to a solution of 1,2,3-trimethylindole (3.00 g., 0.0188 mole) in concentrated sulfuric acid (50 ml.) at 5°. The solution was stirred for 5 min. more and then poured onto crushed ice. The resulting dark yellow precipitate was filtered off, dried, dissolved in the minimum amount of benzene, and placed on a column of alumina (100 g.) which had been packed wet with petroleum ether. Elution with 1:1 benzene–petroleum ether removed bright yellow needles (1.54 g., 40%), m.p. 138.5–140.5°. There was no depression in mixture melting point, 139–141.5°, with the sample prepared from 2,3-dimethyl-5-nitroindole, and the infrared spectra in Nujol were identical.

Attempted nitration of 1,2,3-trimethylindole with nitric acid in acetic acid at ice-bath temperature gave an unstable, greenish solid, which decomposed upon attempted recrystallization.

B. From 2,3-Dimethyl-5-nitroindole (40).—A solution of 2,3-dimethyl-5-nitroindole[29] (1.00 g., 0.00525 mole) in anhydrous ether (50 ml.) was added dropwise, with stirring, to a solution of sodamide (from sodium, 0.60 g., 0.0261 g.-atom, and ferric nitrate nonahydrate, 0.10 g.) in liquid ammonia (200 ml.). After the solution had been stirred for 15 min., methyl iodide (1.00 g., 0.00704 mole) was added slowly, and then stirring was continued for 15 min. The ammonia was allowed to evaporate, water was added to the residue, and the resulting mixture was extracted with methylene chloride. The methylene chloride extracts were dried and concentrated, and petroleum ether was added, causing formation of a dark orange precipitate. The precipitate was dissolved in a minimum of benzene and placed on a column of alumina (25 g.) which had been packed wet with petroleum ether. Elution with 1:1 benzene–petroleum ether removed bright yellow needles (0.64 g., 60%): m.p. 140–141.5°[41]; lit.[30a] m.p. 138–139°; $\lambda_{\max}$, mμ (log ϵ), in 95% ethanol 214 (4.30), 264 infl. (4.12), 282 (4.32), 340 (3.92); ν_{NO_2} 1505 (ms), 1326 (s) cm.$^{-1}$ in Nujol.

5-Nitro-2,3,3-trimethyl-3H-indole (43).[2b]—A solution of sodium nitrate (1.70 g., 0.0200 mole) in concentrated sulfuric acid (50 ml.) was added dropwise, with stirring, over a period of 1 hr. to a solution of 2,3,3-trimethyl-3H-indole[61] (3.18 g., 0.0200 mole) in concentrated sulfuric acid (25 ml.) cooled to 5° in an ice bath. The resulting solution was poured into ice–water (1 l.), producing a clear yellow solution. Basification to pH 10 with aqueous sodium hydroxide solution caused separation of a crystalline product, which was recrystallized from methylene chloride–petroleum ether, with charcoal, yielding blunt straw-colored needles (3.32 g., 81%): m.p. 130–131.5°[41]; lit. 88% yield,[31] m.p. 124–125°,[30a] 127°,[31] 128°[30b]; $\lambda_{\max}$, mμ (log ϵ), in 95% ethanol 222 infl. (4.01), 302 (4.08); $\nu_{\text{C=N}}$ 1565 (s), ν_{NO_2} 1517 (s), 1339 (s) cm.$^{-1}$ in Nujol. There was no depression in mixture melting point, 130–131.5°, with a sample[30] prepared by polyphosphoric acid catalyzed[30b] cyclization of 3-methyl-2-butanone *p*-nitrophenylhydrazone.[62]

---

(57) R. Robinson, private communication, April 16, 1959.

(58) M. Nakazaki, *Bull. Chem. Soc. Japan*, **32**, 838 (1959).

(59) H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.*, **65**, 2452 (1943).

(60) K. T. Potts and J. E. Saxton, *Org. Syn.*, **40**, 68 (1960).

(61) (a) G. Plancher, *Chem. Ber.*, **31**, 1496 (1898); (b) W. E. Noland and C. F. Hammer, *J. Org. Chem.*, **25**, 1530 (1960).

(62) H. D. Dakin, *J. Biol. Chem.*, **4**, 235 (1908); *Chem. Zentr.*, **79**, I, 1260 (1908).

The Action of Triphenylphosphine Dibromide on Sterol and Bile Acid Derivatives[1]

DANIEL LEVY AND ROBERT STEVENSON

Department of Chemistry, Brandeis University, Waltham, Massachusetts

Received May 10, 1965

By the action of triphenylphosphine dibromide, cholesterol and cholestanol give 3β-bromocholest-5-ene and 3α-bromocholestane, respectively; cholest-1-en-3-one and 4-bromocholest-4-en-3-one are similarly obtained from cholestanone. The order of reactivity of the hydroxyl groups of cholic acid toward this reagent is 3 > 7 > 12.

The conversion of alcohols to alkyl halides by the use of tertiary phosphine dihalides has been described by Horner and co-workers[2]; furthermore, attention has recently been drawn to the advantages of these reagents over phosphorus pentahalides in effecting substitution without elimination or molecular rearrangement. Other reactions which have been reported[2,3] for these reagents include the conversion of carboxylic acids to acid chlorides, aldehydes and ketones to *gem*-dihalogen products, amides and oximes to nitriles, and phenols to aryl halides. The use of triphenylphosphine dibromide as a reagent for the cleavage of ethers under mild conditions has also been recently described.[4] The mechanism of the formation of alkyl halides from alcohols is under study by Wiley[5] and a preliminary account of the gross features has been given. With regard to the stereochemical consequences of this displacement, an inversion of configuration

---

[1] The award of a research grant (AM-3439) from the National Institute of Arthritis and Metabolic Diseases, U.S. Public Health Service (to R. S.), is gratefully acknowledged.

[2] L. Horner, H. Oediger, and H. Hoffmann, *Ann.*, **626**, 26 (1959).

[3] G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Am. Chem. Soc.*, **86**, 964 (1964).

[4] A. G. Anderson and F. J. Freenor, *ibid.*, **86**, 5037 (1964).

[5] G. A. Wiley, B. M. Rein, and R. L. Hershkowitz, *Tetrahedron Letters*, 2509 (1964).