Nitration of Indoles. V. Nitration of Electronegatively Substituted Indoles. Synthesis of the Four *bz*,3-Dinitroindoles[1]

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Received July 28, 1965

Nitration of 3-acetylindole (**1**) and indole-3-carbonitrile (**10**) with concentrated nitric acid gives predominantly the 6-nitro derivatives **2** and **11**, with lesser amounts of the 4-nitro derivatives **3** and **12**. Nitration of 1,3-diacetylindole (**6**) in concentrated sulfuric acid gives a mixture containing 3-acetyl-5-nitroindole (**7**) and **2**. The synthesis of the four *bz*,3-dinitroindoles is described: 3,4-dinitroindole (**27**) from nitration of ethyl indole-2-carboxylate (**23**) *via* ethyl 4-nitroindole-2-carboxylate (**24**) and the dinitro ester **25** and acid **26**; 3,5-dinitroindole (**20**) from 5- (**8**) or 3-nitroindole (**19**), or from indole-2-carboxylic acid (**16**) *via* 3-nitroindole-2-carboxylic acid (**17**) and the dinitro acid **21**; 3,6-dinitroindole (**15**) from 6-nitroindole-3-carboxaldehyde (**13**) or **19**; and 3,7-dinitroindole (**31**) from ethyl 7-nitroindole-2-carboxylate (**28**) *via* the dinitro ester **29** and acid **30**.

An electron-withdrawing substituent in the 3-position stabilizes the sensitive indole nucleus toward oxidative destruction[3–7] sufficiently that well-defined mononitro derivatives can be isolated. Thus, nitration in acetic acid occurs at the 6-position with ethyl indole-3-carboxylate,[8] indole-3-carboxylic acid,[9] indole-3-carboxaldehyde,[10,11] 2-methylindole-3-carboxaldehyde,[12] and N,N,2-trimethylindole-3-glyoxylamide[13a]; and at the 6- *and* 4-positions with 1-methyl- and 1,2-dimethylindole-3-carboxaldehyde,[12] 3-acetyl-2-methylindole,[5] ethyl indole-3-glyoxylate,[10] and N,N-dialkylindole-3-glyoxylamides.[13a] Nitration with concentrated nitric acid occurs[5] at the 6-position with 2-methylindole-3-carboxaldehyde, 3-acetyl-2-methyl-4-nitroindole, 3-nitro-2-phenylindole,[1] 3,4-dinitro- and 3,5-dinitro-2-methylindole, and 1,2-dimethyl-3,5-dinitroindole; at the 4-position with 2-methyl- and 1,2-dimethyl-3,6-dinitroindole; and at the 6- *and* 4-positions with 2-methyl-3-nitroindole and 2-methyl-3H-indol-3-one oxime. Deformylation and deacetylation, with replacement at the 3-position by a nitro group, occurs frequently during nitrations in acetic acid or in concentrated nitric acid, forming 3-nitroindoles from 1-methyl-, 2-methyl-, and 1,2-dimethylindole-3-carboxaldehyde[12] and 3-acetyl-2-methylindole[5]; and 3,6-dinitroindoles from 2-methyl-[5,12] and 1,2-dimethylindole-3-carboxaldehyde[12] and 3-acetyl-2-methyl-4-nitroindole.[5] Nitration in concentrated sulfuric acid of indole-3-carboxaldehyde[10,11] and ethyl indole-3-glyoxylate[10] gives mixtures containing more 5- than 6-nitro derivatives,[13b] an observation consistent with the 5-nitration observed with protonated 2-alkyl-[4,5,10,14] and 2-phenylindoles.[1,14]

Nitration of 3-acetylindole (**1**) in acetic acid is reported to have failed, giving unchanged 3-acetylindole in 71% yield.[15] With concentrated nitric acid, however, we have obtained a nitration product (see Chart I) containing more 3-acetyl-6-nitroindole (**2**, 33%) than 3-acetyl-4-nitroindole (**3**, 2%). The structures of **2** and **3** were established by deacetylation with boiling concentrated hydrochloric acid to the known 6-[8,16,17] (**4**) and 4-nitroindole[16] (**5**), using a procedure which had previously been applied to the preparation of 2-methyl-6-nitroindole from 3-acetyl-2-methyl-6-nitroindole.[5] The fact that deacetylation was not observed during the nitration of **1**, whereas considerable deacetylation occurred during the nitration of 3-acetyl-2-methylindole[5] and deacetylation and deformylation have been observed frequently during nitrations of 2-methylindoles[5,12] (see above), indicates that the 2-methyl group promotes deacylation. In fact, the only examples reported to date of deacylation during nitration of 3-acylindoles not containing a 2-methyl group are those of 1-methylindole-3-carboxaldehyde[12] and 6-nitroindole-3-carboxaldehyde (**13**, see below). The effect of the 2-methyl group in promoting nitrative displacement is attributed to its capacity (relative to

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[1] Paper IV: W. E. Noland, K. R. Rush, and L. R. Smith, *J. Org. Chem.*, **31**, 65 (1966).

[2] From the Ph.D. Thesis of K. R. Rush, University of Minnesota, Sept. 1963; *Dissertation Abstr.*, **25**, 2241 (1964); National Science Foundation Graduate Fellow, June 1961–Sept. 1963.

[3] For a summary of the destruction of unstabilized indole nuclei under nitration conditions, see ref. 4 concerning indole, 1-methylindole, skatole, 1,3-dimethylindole, and 2,3-dimethylindole, and ref. 5 concerning 1,2,3-trimethylindole. Although it was hoped that the 5-nitro group would exert a stabilizing influence toward oxidative destruction and permit 6-nitration,[5] attempted nitration of 1,2,3-trimethyl-5-nitroindole[5] with nitric acid (*d* 1.42) produced an exothermic reaction, giving an amorphous, partly acidic, light yellow powder from which could be isolated only a small amount (10 wt. %) of yellow crystals: m.p. 138–153°; $\lambda_{\max}^{95\%\,\mathrm{EtOH}}$, mμ (log ε, based on mol. wt. of **1**), 326 (2.03); ν_{NH} none, $\nu_{\mathrm{C=O}}$ 1742 (s), 1618 (s), $\nu_{\mathrm{NO_2}}$ 1555 (s) or 1522 (ms), 1339 (vs) cm.$^{-1}$ (Nujol). [*Anal.* Found: C, 48.37; H, 4.05; N, 17.03 (R. E. Johnson, unpublished work, University of Minnesota, 1965)]. In contrast, 3-alkylindoles containing an amino substituent which would be positively charged are sufficiently stabilized in nitric acid solutions that nitration can occur. Thus, nitration in acetic acid occurs at the 6-position in tryptophan[6] and 2-methyl- and 1,2-dimethylgramine, and largely at the 6- but also at the 4-position in gramine and 1-methylgramine.[7]

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

[5] Paper III: W. E. Noland, L. R. Smith, and K. R. Rush, *ibid.*, **30**, 3457 (1965).

[6] R. De Fazi, G. Berti, and A. Da Settimo, *Gazz. chim. ital.*, **89**, 2238 (1959).

[7] (a) G. Berti and A. Da Settimo, *ibid.*, **90**, 525 (1960); (b) J. B. Hester, Jr., *J. Org. Chem.*, **29**, 1158 (1964).

[8] R. Majima and M. Kotake, *Chem. Ber.*, **63**, 2237 (1930).

[9] M. S. Melzer, *J. Org. Chem.*, **27**, 496 (1962).

[10] G. Berti and A. Da Settimo, *Gazz. chim. ital.*, **91**, 728 (1961).

[11] Paper I: W. E. Noland and R. D. Rieke, *J. Org. Chem.*, **27**, 2250 (1962).

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

[13] (a) A. Da Settimo, *Gazz. chim. ital.*, **92**, 150 (1962). (b) Similar results have recently been reported for nitration in concentrated sulfuric acid of 1-methylindole-3-carboxaldehyde, 2-methylindole-3-carboxaldehyde, and 1,2-dimethylindole-3-carboxaldehyde, which give in about 92% yield mixtures containing a small excess of the 5- over the 6-nitro derivatives: A. Da Settimo and M. F. Saettone, *Tetrahedron*, **21**, 1923 (1965).

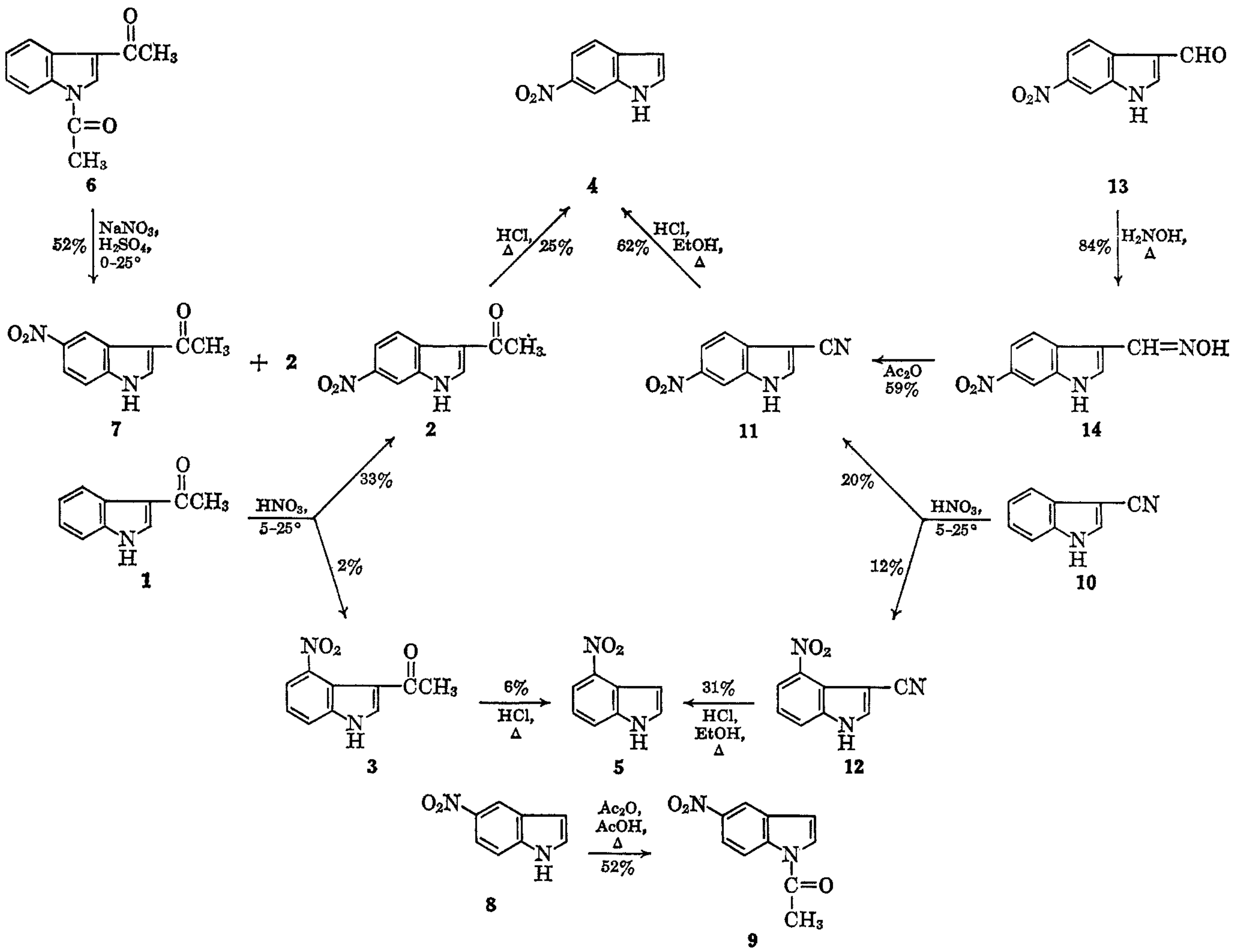
[14] A. Da Settimo and M. F. Saettone, *ibid.*, **21**, 823 (1965).

[15] (a) T. E. Young, *J. Org. Chem.*, **27**, 507 (1962). (b) Similarly, it has been reported that 19 3-arylacetylindoles were recovered unchanged from nitric–acetic acid media at room temperature, although at higher temperatures extensive decomposition occurred; in the only cases tried where nitration was successful, the 3,4-dimethoxy- and 3,4-methylenedioxyphenylacetylindoles, nitration occurred in the phenyl group of the 3-substituent, not in the indole nucleus: T. E. Young and M. F. Mizianty, *ibid.*, **29**, 2030 (1964).

[16] S. M. Parmerter, A. G. Cook, and W. B. Dixon, *J. Am. Chem. Soc.*, **80**, 4621 (1958).

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

CHART I



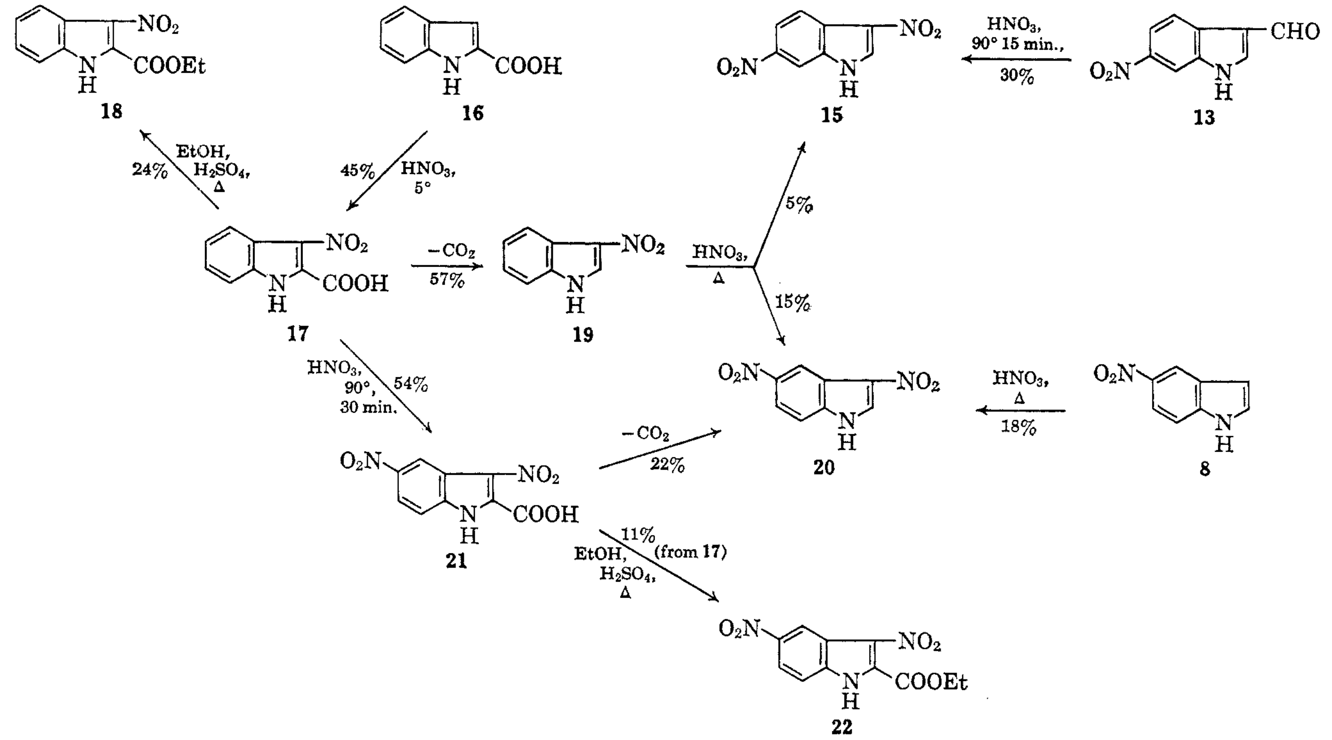
hydrogen) to release electrons and increase the nucleophilicity of the 3-position, and to cause steric compression of the 3-acyl group and decrease the capacity of the acyl group to conjugate with the electrons of the 2,3 double bond. Both effects should increase the rate of nitration (or prior nitrosation[5]) at the 3-position, causing displacement of the acyl cation. Perhaps of significance in support of the steric argument is the fact that 3-acetyl-2-methylindole was nitrated in acetic acid at 0°, while 2-methylindole-3-carboxaldehyde in nitric acid had to be warmed to initiate the reaction.[5]

Nitration of 1,3-diacetylindole (**6**) in concentrated sulfuric acid gave a mixture which appears to consist largely of another new monoacetylnitroindole (**7**), from which some **2** was also isolated. Compound **7**, which is different from **2** and **3**, is assigned the structure 3-acetyl-5-nitroindole because of the similarity of its ultraviolet spectrum[18] in 95% ethanol [λ_{max}, mμ (log ϵ), 258 (infl.) (4.26), 267 (4.31), 278 (infl.) (4.26), 315 (3.93)] to that of 5-nitroindole-3-carboxaldehyde[11] [λ_{max}, mμ (log ϵ), 257 (4.41), 263 (infl.) (4.40), 312 (3.96)], and in accordance with the rule for 5-nitration[1,4,5,10,11,14] in concentrated sulfuric acid. Acetylation of 5-nitroindole[16] (**8**) with acetic anhydride containing a little acetic acid did not give **7** but gave instead 1-acetyl-5-nitroindole (**9**, 52%), the structure of which is indicated by the absence of an NH band and the high frequency (1704 cm.$^{-1}$) of the carbonyl band in the infrared spectrum. Predominant 1-acetylation (64% 1- and 2% 3-), but in the presence of sodium acetate, has also been observed previously, in the acetylation of 2-methyl-5-nitroindole.[4] Another attempted independent synthesis of **7**, by reaction of **8** with methylmagnesium iodide and subsequently with acetyl chloride, gave no well-defined product.

Nitration of indole-3-carbonitrile (**10**) with concentrated nitric acid gave a mixture containing more 6-nitroindole-3-carbonitrile (**11**, 20%) than 4-nitroindole-

[18] The following examples are cited in support of this use in a structural argument of an analogy between the ultraviolet spectrum of an acylindole and the corresponding formylindole [all are $\lambda_{max}^{95\%\ EtOH}$ in mμ (log ϵ)]: 3-acetylindole (**1**) [240 (4.11), 256 (3.96), 296 (4.11)] and indole-3-carboxaldehyde [242 (4.14), 260 (4.07), 296 (4.12)]; 3-acetyl-6-nitroindole (**2**) [279 (4.38), 318 (3.89), 333 (infl.) (3.86)] and 6-nitroindole-3-carboxaldehyde (**13**) [278 (4.23), 316 (infl.) (3.72)]; 3-acetyl-4-nitroindole (**3**) [227 (4.20), 274 (4.02), 303 (infl.) (3.74), 347 (infl.) (3.43)] and 4-nitroindole-3-carboxaldehyde[13a] [227 (4.30), 287 (3.94), 357 (3.63)]; 3-acetyl-2-methylindole [215 (4.47), 243 (4.14), 267 (4.02), 301 (4.05)] and 2-methylindole-3-carboxaldehyde [217 (4.31), 246 (4.14), 268 (4.07), 304 (4.11)]; 3-acetyl-2-methyl-5-nitroindole[4] [239 (infl.) (4.18), 261 (4.43), 320 (4.01)] and 2-methyl-5-nitroindole-3-carboxaldehyde[13b] [259 (4.43), 318 (4.00)]; 3-acetyl-2-methyl-6-nitroindole[5] [260 (infl.) (4.11), 283 (4.33), 351 (4.00)] and 2-methyl-6-nitroindole-3-carboxaldehyde[13] [284 (4.35), 346 (infl.) (3.97)]. As can be seen from the data cited, and the additional data which follow, the agreement of the ultraviolet spectrum of the same acyl derivative in the 2-unsubstituted series with that in the 2-methyl series is not so good, though often still useful: 3-acetyl-5-nitroindole (**7**, see text) and 3-acetyl-2-methyl-5-nitroindole[4] (see above); 1-acetyl-5-nitroindole (**9**) [232 (infl.) (4.06), 255 (4.40), 263 (4.40), 297 (4.00)] and 1-acetyl-2-methyl-5-nitroindole[4] [262 (4.35), 310 (3.86)]; 1-methyl-5-nitroindole-3-carboxaldehyde[13b] [267 (4.46), 318 (3.93)] and 1,2-dimethyl-5-nitroindole-3-carboxaldehyde[13b] [269 (4.45), 320 (3.97)]; 3-acetyl-4-nitroindole (**3**, see above) and 3-acetyl-2-methyl-4-nitroindole[5] [228 (4.27), 250 (infl.) (4.11), 280 (3.87), 366 (3.54)].

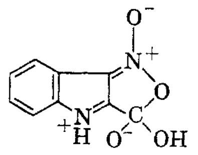
CHART II



3-carbonitrile (12, 12%). The structure of **11** was correlated with that of **2** by decyanation of **11** with boiling ethanolic hydrochloric acid to 6-nitroindole (**4**), identical with the sample prepared by deacetylation of **2**. The structure of **11** was proved by an independent synthesis[19] from 6-nitroindole-3-carboxaldehyde[10,11] (**13**) *via* the oxime **14** to **11**. The structure of **12** was proved, and correlated with that of **3**, by decyanation in the manner used with **11**, to 4-nitroindole (**5**), identical with samples prepared by the Fischer indole synthesis[16] and by deacetylation of **3**. The predominance of 6-nitro over 4-nitro derivatives is consistent with the greater steric hindrance at the 4-position.[6,7a] Similarly, the relatively larger proportion of 4-nitro derivative from the nitration of indole-3-carbonitrile than from that of 3-acetylindole is attributed to the smaller steric bulk and directional orientation of the 3-cyano group relative to the 3-acetyl group.

Nitration of 6-nitroindole-3-carboxaldehyde (**13**) by warming with concentrated nitric acid is accompanied by deformylation, giving 3,6-dinitroindole (**15**). Nitration of indole-2-carboxylic acid (**16**) with nitric acid also occurs at the 3-position (see Chart II), giving[20] 3-nitroindole-2-carboxylic acid (**17**), which can be decarboxylated to 3-nitroindole[21] (**19**). Nitration of **19** by warming with nitric acid gave 3,5-dinitroindole (**20**, 15%), identical with a sample prepared by nitration of 5-nitroindole (**8**), and 3,6-dinitroindole (**15**, 5%), identical with the sample prepared by nitration of **13**. Although nitration of **17** is reported to give only degradation products,[20] warming **17** with nitric acid gave a 54% yield of 3,5-dinitroindole-2-carboxylic acid (**21**), the structure of which was proved by decarboxylation to **20**. The dinitro acid **21** was difficult to purify, possibly accounting for the previous failure to isolate it.

The dominance of 5-nitration (54% after crystallization) and the failure to isolate a 6-nitro product from **17**, in contrast to the modest amount of 6-nitration with **19**, suggests that **17** may exist in a form particularly conducive to 5-nitration. Such a possible form might be the nitronolactol **17a**, in which negative charge is stabilized out on the 3-nitro group and there is an increase in the double-bond character at the 1,2-bond—an electronic environment known[1,4,5,10,14,22] to promote 5-nitration. Isolation of 5-nitro derivatives **20** and **21** as the predominant products from nitration in nitric acid of the nitroindoles **19** and **17** stands in contrast to the formation of 6- and 4-nitro derivatives from 2-methyl-3-nitroindole under similar conditions.[5] This suggests that the 2-methyl group is an important factor in promoting 6- and 4-nitration, just as it is in promoting nitrative displacement at the 3-position, and for the same reasons as discussed above, because the 6- and 4-positions are the *para* and *ortho* positions with respect to the center of enhanced nucleophilicity at the 3-position.



17a

In contrast to the formation from **16** in nitric acid of the 3-nitro (**17**) and then the 3,5-dinitro (**21**) derivative, the corresponding ester, ethyl indole-2-carboxylate (**23**) (Chart III), nitrates in acetic acid at the 4-position, giving ethyl 4-nitroindole-2-carboxylate (**24**), identical with a sample prepared[16] by the Fischer indole synthesis and different from the ethyl ester (**18**)

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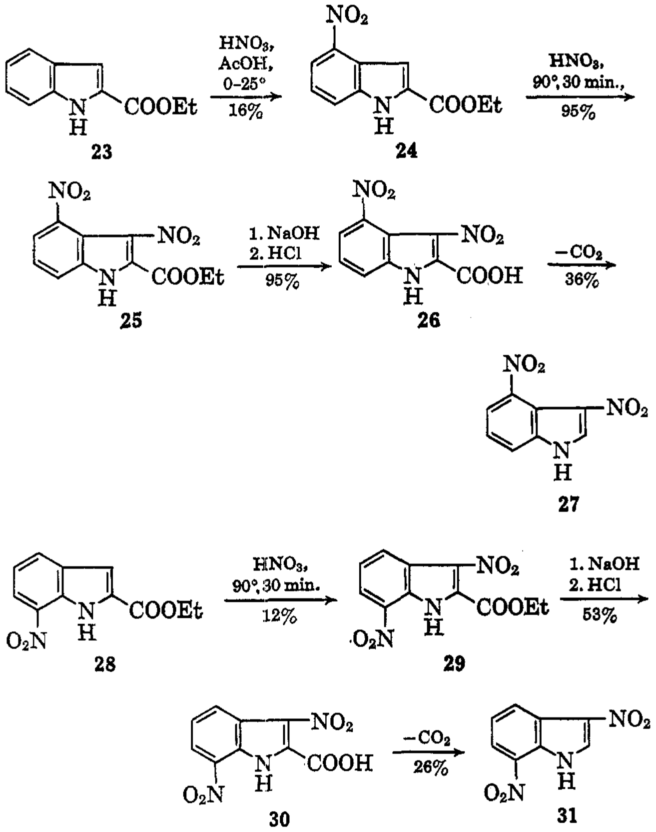
(19) A similar method has recently been used to prepare 5-nitroindole-3-carbonitrile: J. De Graw and L. Goodman, *J. Med. Chem.*, **7**, 213 (1964).

(20) K. N. Menon and R. Robinson, *J. Chem. Soc.*, 780 (1932).

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

(22) K. Brown and A. R. Katritzky, *Tetrahedron Letters*, 803 (1964).

CHART III



of **17**. The preference in **23** for primary nitration at the 4-position, rather than at the normally strongly preferred open 3-position, is attributed to the steric hindrance to attack at the 3-position afforded by the neighboring ethoxycarbonyl group. The orientation of nitration at the 4-position, rather than primarily at the 6-position, also suggests that the 4-position is electronically preferred to the 6-position for electrophilic attack when steric hindrance from a substituent larger than hydrogen in the neighboring 3-position is not the dominant factor—as it has been in all the cases previously encountered.

Further nitration of **24**, by warming with nitric acid, gave a dinitro ester (**25**)[23] different from the ethyl ester (**22**) of **21**. Saponification of **25** gave a dinitro acid (**26**), which was decarboxylated to a dinitroindole (**27**). Compound **27** was resistant to oxidative degradation with chromic acid but is assigned the structure 3,4-dinitroindole because of the great similarity of its ultraviolet spectrum in 95% ethanol [λ_{max}, mμ (log ϵ), 231 (4.06), 291 (3.88), 334 (3.94)] to that of 3,4-dinitro-2-methylindole[5] [λ_{max}, mμ (log ϵ), 233 (4.08), 300 (broad plateau) (3.94), 338 (4.00)]. It follows then that **24** has been nitrated in the 3-position, and that **25** and **26**, the precursors of **27**, are also 3,4-dinitro derivatives.

The low solubility of **25** precluded a detailed examination of its n.m.r. spectrum,[24] but the spectrum of a saturated though very dilute solution in hexadeuterioacetone contains in the aromatic proton region only a complex multiplet around 8 p.p.m. (δ scale, tetramethylsilane = 0, 1 p.p.m. = 60 c.p.s.), with ω (whole band width above noise level) $\cong$ 37 c.p.s. The ethyl ester group appears as the usual methylene quartet, at 4.47 p.p.m. (J = 7 c.p.s.), and methyl triplet, at 1.37 p.p.m. (J = 7 c.p.s.). The n.m.r. spectrum of the precursor **24** in a saturated, but dilute, solution in hexadeuterioacetone also contains complex absorption in the aromatic proton region, in the form of two groups each of three peaks, with the first group (1.9 protons) at 8.08 (ω = 18 c.p.s.), the strongest peak of which (0.8 proton), at 8.09, may be due to the 3-proton, and the second group (2.0 protons) at 7.62 p.p.m. (ω = 18 c.p.s.). The ethyl ester group of **24** appears as a methylene quartet at 4.44 (J = 7 c.p.s.) and a methyl triplet at 1.40 p.p.m. The NH proton is not discernible in either the n.m.r. spectra of **24** or **25**, which were determined down to 13.3 p.p.m. The n.m.r. spectrum of **27**, also in a saturated, but very dilute, solution in hexadeuterioacetone, clearly establishes that the second nitro group is in the 3-position, consistent with structure **27**, since the 2-proton, *ortho* to the nitro group, appears as a singlet (1.1 protons) at 8.65 p.p.m., without the *meta* coupling which would have been present if it were due to a 5-proton with the second nitro group in the 6-position. The remaining aromatic protons (3.0) appear as a complex at 7.70 (ω = 45 c.p.s.) of five major peaks. The NH group (0.9 proton) appears as a diffuse hump at about 12.17 p.p.m. (ω = 60 c.p.s.).

A nitration and decarboxylation sequence similar to that of **24** → **25** → **26** → **27**, but starting with ethyl 7-nitroindole-2-carboxylate[16] (**28**), also gave a dinitro ester (**29**) and acid (**30**), and a dinitroindole (**31**). Compound **31**, like **27** and **32**, was resistant to oxidative degradation with chromic acid and, unlike **27**, no suitable ultraviolet model was available. Analogy with the nitration of **24**, which also contains a preexisting deactivating nitro group in the benzene ring, would predict, however, that nitration of **28** has occurred in the 3-position. Consequently, **29**, **30**, and **31** are assigned the structures of 3,7-dinitroindoles.

The n.m.r. spectra[24] of **28**, **29**, and **31** in hexadeuterioacetone solution are consistent with the 3,7-dinitroindole structures but do not appear consistent with the alternative structures of 4,7-, 5,7-, or 6,7-dinitroindoles, which would have simpler spectra in the aromatic proton region. The spectrum of the 7-nitro ester starting material **28** in 17% (w./v.) solution contains downfield a hyperfinely split triplet (2.1 protons) at 8.15 p.p.m. ($J_{av\ 6,5+4,5}$ = 7 c.p.s.), believed to be the AB portion of an ABX system attributed to the 6- and 4-protons *ortho* and *para* to the 7-nitro group. Further upfield is a four-line multiplet (2.1 protons) believed to consist of a triplet at 7.27 ($J_{av\ 5,6+5,4}$ = 7 c.p.s.) due to the X portion (5-proton) of the ABX system upon which is superimposed a singlet at 7.29 p.p.m. attributed to the 3-proton. The ethyl ester group appears as a methylene quartet (1.9 protons) at 4.42 (J = 7 c.p.s.) and a methyl triplet (2.9 protons) at 1.40 p.p.m. (J = 7 c.p.s.). In the dinitro ester **29** the pattern is similar, except for a general downfield shift and the disappearance of one of the two strong central peaks (attributed to loss of the 3-proton) from the aromatic upfield four-line multiplet of **28**. In the spectrum of a 17% (wt./v.) solution of **29** the downfield

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[23] This experiment was first performed by L. R. Smith, Ph.D. Thesis, University of Minnesota, May 1960; *Dissertation Abstr.*, **21**, 1766 (1961).

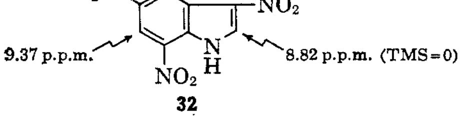
[24] We are indebted to L. L. Landucci and H. A. Kirst for obtaining all the n.m.r. spectra reported in this paper.

hyperfinely split triplet (2.0 protons) is at 8.43 ($J_{\text{av } 6,5 + 4,5}$ = 8 c.p.s.), and what is now an aromatic upfield triplet (1.1 protons), attributed to the 5-proton, is at 7.58 p.p.m. ($J_{\text{av } 5,6 + 5,4}$ = 8 c.p.s.). The ethyl ester group appears as a methylene quartet (1.9 protons) at 4.51 (J = 7 c.p.s.) and a methyl triplet (3.3 protons) at 1.42 p.p.m. (J = 7 c.p.s.). In **28** and **29** the NH group appears as a diffuse hump, in **28** at about 10.46 (0.9 proton, ω = 60 c.p.s.) and shifted downfield in **29** to about 12.26 p.p.m. (0.7 proton, ω = 50 c.p.s.). In the spectrum of a saturated, but very dilute, solution of dinitroindole **31** the aromatic upfield triplet (1.2 protons) attributed to the 5-proton is still present, at 7.61 ($J_{\text{av } 5,6 + 5,4}$ = 8 c.p.s.), but the downfield hyperfinely split triplet has been replaced by a four-peak multiplet (2.8 protons) at 8.48 p.p.m. (ω = 28 c.p.s.), which may consist of a lopsided downfield triplet (2.2 protons) at 8.57 ($J_{\text{av } 6,5 + 4,5}$ = 9 c.p.s.) on the upfield side of which is a singlet (0.6 proton) at 8.25 p.p.m., attributed to the 2-proton *ortho* to the 3-nitro group. The NH proton was not discernible down to 13.3 p.p.m.

With the preparation of 3,7-dinitroindole (**31**), the synthesis of the four *bz*,3-dinitroindoles is complete. Attempted preparation of **20** and **15** in the manner of **27** and **31** by nitration of the ethyl 5- and 6-nitroindole-2-carboxylates,[16] in the same way as with **24** and **28**, gave no well-defined nitration products.

In concentrated nitric acid or in acetic acid, electronegatively substituted indoles such as **1**, **10**, **16**, and **23** are nitrated readily at room temperature or below, while indoles such as 2-methyl- and 1,2-dimethylindole, which would certainly be expected to be much more reactive toward electrophilic attack, require thermal (or nitrite ion catalyzed) initiation to start the reaction promptly. This is in accord with the generalizations we have formulated previously.[5] Thus, with the less basic indoles, a significant proportion of the free indole would be available for electrophilic attack at room temperature or below, and thermal dissociation of the protonated form would not be required to initiate the reaction.

During the determination of the n.m.r. spectra of the dinitroindoles reported in this paper, the n.m.r. spectrum of the related trinitroindole[25] **32** was also examined, in saturated but dilute hexadeuterioacetone solution.[24] The spectrum is a textbook example, confirming the previous tentative assignment[25] of the structure 3,5,7-trinitroindole to **32**. The spectrum consists of a pair of doublets at 9.37 (0.9 proton) and 9.07 (1.0 proton) with a *meta*-coupling constant of 2 c.p.s., and a singlet at 8.82 p.p.m. (1.1 protons). The doublets are attributed to the 6- and 4-protons *ortho,ortho* and *ortho,para*, respectively, to the 5- and 7-nitro groups, and the singlet is attributed to the 2-proton *ortho* to the 3-nitro group. The NH proton was not discernible down to 13.3 p.p.m.



32

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 3-Acetylindole (1).—A solution of 3-acetylindole[26] (2.56 g., 0.0161 mole) in concentrated nitric acid (d 1.42, 40 ml.) was stirred at 5° for 0.5 hr. and then at room temperature for 0.5 hr. The resulting mixture was poured into water, and the precipitate (2.85 g.) was filtered off, washed with water, dried, dissolved in ethanol, and treated with charcoal. Concentration to 200 ml. and cooling gave **3-acetyl-6-nitroindole** (2) (total yield, see below, 1.09 g., 33%) as small bright yellow needles (0.89 g.), m.p. 310–330°. Several recrystallizations from methanol yielded a sample: m.p. 340–342°; $\lambda_{\max}^{95\%\ \text{EtOH}}$, m$\mu$ (log ϵ), 279 (4.38), 318 (3.89), 333 (infl.) (3.86); ν_{NH} 3100 (m), $\nu_{\text{C=O}}$ 1637 (s), ν_{NO_2} 1511 (s), 1337 (s) (stronger) or 1318 (s) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{10}H_8N_2O_3$ (204.18): C, 58.82; H, 3.95; N, 13.72. Found: C, 58.67; H, 4.08; N, 13.72.

Concentration of the mother liquor to 25 ml. and cooling gave more 3-acetyl-6-nitroindole (0.09 g.), m.p. 280–310°. Addition of an excess of water to the filtrate precipitated a mixture (0.34 g.), m.p. 200–220°, which was dissolved in 1:1 benzene–ethyl acetate and placed on a column of neutral alumina (25 g.) which had been packed wet with petroleum ether. Elution with benzene–ethyl acetate (9:1 v./v.) removed first a mixture (0.12 g.), m.p. 170–210°, and then more 3-acetyl-6-nitroindole (0.10 g.), m.p. 310–330°. The mixture (0.12 g.) was dissolved in methanol and allowed to evaporate slowly at room temperature for 14 days. The resulting precipitate was filtered off and recrystallized from methanol, yielding **3-acetyl-4-nitroindole** (3) (total yield, see below, 0.06 g., 2%) as pale yellow needles (0.02 g.): m.p. 228–230°; $\lambda_{\max}^{95\%\ \text{EtOH}}$, m$\mu$ (log ϵ), 227 (4.20), 274 (4.02), 303 (infl.) (3.74), 347 (infl.) (3.43); ν_{NH} 3160 (m), $\nu_{\text{C=O}}$ 1639 (s), ν_{NO_2} 1515 (s), 1333 (ms) or 1314 (ms) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{10}H_8N_2O_3$ (204.18): C, 58.82; H, 3.95; N, 13.72. Found: C, 58.99; H, 4.02; N, 14.87.

Concentration of the filtrate from the 14-day precipitation gave a mixture (0.05 g.), m.p. 185–220°, which was shown by ultraviolet analysis to contain 3-acetyl-4-nitroindole (0.04 g.) and 3-acetyl-6-nitroindole (0.01 g.).

6-Nitroindole (4). A. From 3-Acetyl-6-nitroindole (2).—A mixture of 3-acetyl-6-nitroindole (0.06 g., 0.00029 mole) and concentrated hydrochloric acid (100 ml.) was refluxed for 7 hr. The solution was cooled and extracted with ether. The ether extracts were dried, treated with charcoal, and diluted with petroleum ether, causing precipitation of microscopic dark yellow needles (0.01 g.), m.p. 333–340°, which gave no depression in mixture melting point with starting material. Concentration of the organic mother liquor to a very small volume and cooling yielded **4** as bright yellow needles (0.01 g., 25% based on unrecovered starting material): m.p. 142–144° (lit. m.p. 139–140.5°,[8] 141–142°,[17] 144–145°[16]); ν_{NH} 3300 (m), ν_{NO_2} 1493 (s), 1337 (s), and 1330 (s) (stronger) (doublet) cm.$^{-1}$ (Nujol). There was no depression in mixture melting point, 142–144°, with the sample prepared by hydrolysis of 6-nitroindole-3-carbonitrile, and the infrared spectra in Nujol were identical.

B. From 6-Nitroindole-3-carbonitrile (11).—A solution of 6-nitroindole-3-carbonitrile (0.26 g., 0.00139 mole) in concentrated hydrochloric acid (50 ml.) and ethanol (50 ml.) was refluxed for 7 days, cooled, and partially evaporated under aspirator vacuum. An equal volume of water was added, the solution was extracted with methylene chloride, and the extracts were dried, treated with charcoal, and concentrated to a small volume. Addition of petroleum ether caused separation of bright yellow crystals (0.14 g., 62%): m.p. 141–143°; $\lambda_{\max}^{95\%\ \text{EtOH}}$, m$\mu$ (log ϵ), 250 (4.03), 326 (3.95), 353 (infl.) (3.91). The ultraviolet spectrum is in excellent agreement with that reported.[16]

4-Nitroindole (5). A. From 3-Acetyl-4-nitroindole (3).—By the method used for the preparation of 6-nitroindole from 3-acetyl-6-nitroindole, except that the reflux time of the initially inhomogeneous mixture was 5 hr., 3-acetyl-4-nitroindole was hydrolyzed in 6% yield to yellow crystals (from methylene chloride–petroleum ether), m.p. 200–205°. There was no de-

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

(26) J. E. Saxton, *J. Chem. Soc.*, 3592 (1952).

pression in mixture melting point, 202–206°, with a sample prepared[16] *via* the Fischer indole synthesis, and the infrared spectra in Nujol were identical, except for the presence in the present sample of an impurity band at 1724 (m) cm.$^{-1}$.

B. **From 4-Nitroindole-3-carbonitrile (12).**—By the method used for the preparation of 6-nitroindole from 6-nitroindole-3-carbonitrile, except that the reflux time was 5 days, 4-nitroindole-3-carbonitrile was hydrolyzed and decarboxylated in 31% yield (after recovery of 13% of starting material) to bright yellow crystals (from methylene chloride–petroleum ether): m.p. 206–209° (lit.[16] m.p. 205–206°); ν_{NH} 3260 (ms), $\nu_{\mathrm{NO_2}}$ 1508 (ms), 1316 (vs) cm.$^{-1}$ (Nujol). There was no depression in mixture melting point, 207–209°, with a sample prepared[16] *via* the Fischer indole synthesis, and the infrared spectra in Nujol were identical; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 236 (4.03), 282 (infl.) (3.38), 380 (3.78).

Nitration of 1,3-Diacetylindole (6).[27]—A solution of sodium nitrate (0.85 g., 0.0100 mole) in concentrated sulfuric acid (*d* 1.84, 50 ml.) was added dropwise over a period of 1 hr. to a stirred solution of 1,3-diacetylindole[26] (2.01 g., 0.0100 mole) in concentrated sulfuric acid (50 ml.) and cooled in an ice bath to 0° until the addition was complete. The resulting solution was stirred for 2 hr. more at room temperature and then poured over crushed ice (1 l.). The precipitate, a mixture, was filtered, dried, dissolved in acetone, and decolorized with charcoal. Two recrystallizations from acetone gave a sample, m.p. 289–290° dec. An acetone solution of the sample was passed through a column of alumina (50 g.) which had been packed wet with petroleum ether. Elution with additional acetone (250 ml.) removed what appears to be a mixture, consisting largely of **3-acetyl-5-nitroindole** (7), as a pale yellow powder (1.07 g., 52%): m.p. 295–297° dec.; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 258 (infl.) (4.26), 267 (4.31), 278 (infl.) (4.26), 267 (4.31), 278 (infl.) (4.26), 315 (3.93); ν_{NH} 3080 (ms), $\nu_{\mathrm{C=O}}$ 1633 (s), $\nu_{\mathrm{NO_2}}$ 1509 (s), 1333 (s) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{10}H_8N_2O_3$ (204.18): C, 58.82; H, 3.95; N, 13.72. Found: C, 59.08, 58.47; H, 4.04, 4.03; N, 12.58, 13.82.

A sample (0.32 g.) dissolved in N,N-dimethylformamide (3 ml.) was rechromatographed on alumina (30 g.) which had been packed wet with benzene. The column was eluted with benzene to stop movement of the band. Then elution with 1:3 (v./v.) ethyl acetate–benzene removed a pure sample (0.06 g.), as shown by thin layer chromatography. Two recrystallizations from methanol, once with charcoal, gave **3-acetyl-6-nitroindole** (2), m.p. 338–340°.

Anal. Found: C, 58.75; H, 4.00; N, 13.43.

Further elution with 1:3 ethyl acetate–benzene removed a sample (0.24 g.) resembling the mixture described above and assumed to be largely 3-acetyl-5-nitroindole.

1-Acetyl-5-nitroindole (9).—A solution of 5-nitroindole[16,28] (0.41 g., 0.00253 mole) and acetic acid (0.5 ml.) in acetic anhydride (14 ml., 0.15 mole) was refluxed for 48 hr. The solution was poured into water and stirred until all of the acetic anhydride dissolved. The resulting precipitate was recrystallized from acetone–ethanol, with charcoal, giving pale yellow needles (0.27 g., 52%), m.p. 179.5–181°. Sublimation at 160° (1.5 mm.) yielded the analytical sample: m.p. 179.5–181°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 232 (infl.) (4.06), 255 (4.40), 263 (4.40), 297 (4.00); ν_{NH} none, $\nu_{\mathrm{C=O}}$ 1704 (s), $\nu_{\mathrm{NO_2}}$ 1534 (m) or 1497 (s), 1319 (vs) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{10}H_8N_2O_3$ (204.18): C, 58.82; H, 3.95; N, 13.72. Found: C, 59.19; H, 4.01; N, 13.51.

Nitration of Indole-3-carbonitrile (10).—Indole-3-carbonitrile[29] (1.00 g., 0.00704 mole) was dissolved in concentrated nitric acid (*d* 1.42, 5 ml.) at 5° and then allowed to warm to room temperature and remained there for 0.5 hr. The resulting precipitate (0.84 g.) was washed with water, dried, and dissolved in a minimum of ethyl acetate and placed on a column of neutral alumina (25 g.) which had been packed wet with petroleum ether. Elution with ethyl acetate first yielded **6-nitroindole-3-carbonitrile** (11) (total, see below, 0.26 g., 20%) as pale yellow needles (0.15 g.): m.p. 264–265°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 249 (infl.) (4.23), 258 (4.32), 261 (infl.) (4.31), 309 (3.92), 335 (infl.) (3.83), 354 (infl.) (3.73); ν_{NH} 3280 (s), $\nu_{\mathrm{C\equiv N}}$ 2210 (s), $\nu_{\mathrm{NO_2}}$ 1513 (s), 1346 (vs) or 1332 (s) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_9H_5N_3O_2$ (187.15): C, 57.76; H, 2.69; N, 22.45. Found: C, 58.28, 57.20; H, 2.78, 2.77; N, 23.16, 23.20.

Continued elution with ethyl acetate removed a mixture (0.06 g.), which was shown by ultraviolet analysis to contain 6-nitroindole-3-carbonitrile (0.05 g.) and 4-nitroindole-3-carbonitrile (0.01 g.).

Further elution with ethyl acetate yielded **4-nitroindole-3-carbonitrile** (12) (total, see above, 0.16 g., 12%) as bright yellow granules (0.15 g.): m.p. 314.5–317°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 234 (4.09), 349 (3.75); ν_{NH} 3160 (s), $\nu_{\mathrm{C\equiv N}}$ 2200 (s), $\nu_{\mathrm{NO_2}}$ 1507 (s), 1365 (s) or 1336 (s) or 1297 (vs) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_9H_5N_3O_2$ (187.15): C, 57.76; H, 2.69; N, 22.45. Found: C, 57.96; H, 2.73; N, 22.71.

6-Nitroindole-3-carbonitrile (11). By Dehydration of 14.—A solution of 6-nitroindole-3-carboxaldoxime (0.37 g., 0.00180 mole) in acetic anhydride (10 ml.) was refluxed for 2 hr. and then poured into water and kept until all of the acetic anhydride dissolved. The resulting brown precipitate was recrystallized from ethyl acetate–petroleum ether, with charcoal, yielding pale yellow needles (0.20 g., 59%), m.p. 254–258°. There was no depression in mixture melting point, 258–260°, with the sample prepared from indole-3-carbonitrile, and the infrared spectra in Nujol were identical.

6-Nitroindole-3-carboxaldoxime (14).—A solution of hydroxylamine hydrochloride (0.60 g., 0.0086 mole) and sodium acetate trihydrate (1.25 g., 0.0092 mole) in water (20 ml.) was added to a refluxing solution of 6-nitroindole-3-carboxaldehyde,[10,11] (0.41 g., 0.00216 mole) in ethanol (125 ml.), and refluxing was continued for 3 hr. The solution was cooled and poured into water, and solid carbon dioxide was added. The resulting precipitate was recrystallized from methanol–water, yielding orange (needles (0.37 g., 84%): m.p. 257–258°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 214 (4.25), 251 (infl.) (4.04), 256 (4.06), 283 (4.32), 323 (3.87), 382 (3.74); ν_{NH} 3280 (ms), ν_{OH} 2700 (w), $\nu_{\mathrm{C=N,\ C=C}}$ 1629 (m) and 1616 (m) (doublet), $\nu_{\mathrm{NO_2}}$ 1499 (s), 1335 (vs) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_9H_7N_3O_3$ (205.17): C, 52.68; H, 3.44; N, 20.48. Found: C, 52.46; H, 3.40; N, 20.29.

3,6-Dinitroindole (15).—A solution of 6-nitroindole-3-carboxaldehyde[10,11] (0.12 g., 0.00063 mole) in concentrated nitric acid (*d* 1.42, 5 ml.) was warmed at 90° on a steam bath for 0.25 hr. Water was then added to the solution, and the resulting precipitate was filtered off and recrystallized from methanol, yielding small pale yellow needles (0.04 g., 30%): m.p. 301–302°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 227 (3.99), 295 (4.21), 334 (4.15); ν_{NH} 3270 (ms), 3110 (m), $\nu_{\mathrm{NO_2}}$ 1513 (s), 1381 (vs), 1344 (vs) or 1318 (vs) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_8H_5N_3O_4$ (207.14): C, 46.38; H, 2.43; N, 20.29. Found: C, 49.96, 46.85; H, 2.45, 2.57; N, 20.26.

3-Nitroindole-2-carboxylic Acid (17).—The compound was prepared[20] in 45% yield from indole-2-carboxylic acid[30] by nitration with concentrated nitric acid at 5°. It crystallized from ethanol–water as bright yellow crystals: m.p. 232–233° (lit. m.p. 230° dec.,[21] 232°[20]); $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 256 (4.09), 264 (infl.) (4.05), 354 (3.91); ν_{NH} 3240 (ms), ν_{OH} 2680 (m), $\nu_{\mathrm{C=O}}$ 1724 (s), $\nu_{\mathrm{NO_2}}$ 1520 (ms), 1383 (vs) or 1340 (ms) cm.$^{-1}$ (Nujol).

Ethyl 3-Nitroindole-2-carboxylate (18).—A solution of 3-nitroindole-2-carboxylic acid (1.54 g., 0.00747 mole) in absolute ethanol (50 ml.) containing concentrated sulfuric acid (2.5 ml.) was refluxed for 5 hr. The solvent was evaporated and the yellow solid residue was recrystallized from ethanol, yielding yellow needles (0.42 g., 24%): m.p. 140–141.5°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 220 (infl.) (4.22), 257 (4.08), 346 (3.86); ν_{NH} 3340 (s) (KBr), 3210 (m) (Nujol), $\nu_{\mathrm{C=O}}$ 1738 (s) (KBr), 1745 (s) (Nujol), $\nu_{\mathrm{NO_2}}$ 1482 (s), 1357 (s) or 1329 (s) or 1304 (s) (KBr), 1381 (vs) or 1335 (s) or 1312 (s) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{11}H_{10}N_2O_4$ (234.21): C, 56.41; H, 4.30; N, 11.96. Found: C, 56.45; H, 4.33; N, 12.17.

3-Nitroindole (19).—A mixture of 3-nitroindole-2-carboxylic acid (0.49 g., 0.00238 mole) and copper(II) oxide (0.10 g.) in freshly distilled quinoline (15 ml.) was refluxed for 2 hr. and then poured into ice-cold aqueous 20% hydrochloric acid. The resulting solution and dark precipitate were extracted with ether, and the extracts were washed with sodium bicarbonate solution and evaporated. The yellow solid residue was recrystallized

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(27) K. R. Rush, unpublished work.

(28) Ethyl 5-nitroindole-2-carboxylate,[16] m.p. 221–222°, the precursor of 5-nitroindole, has the following ultraviolet spectrum: $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 276 (4.47), 305 (infl.) (3.89), 327 (3.92).

(29) (a) R. Pschorr and G. Hoppe, *Chem. Ber.*, **43**, 2543 (1910); (b) H. M. Blatter, H. Lukaszewski, and G. de Stevens, *Org. Syn.*, **43**, 58 (1963).

(30) W. E. Noland and F. J. Baude, *ibid.*, **43**, 40 (1963).

from methanol–water, yielding pale yellow crystals (0.22 g., 57%): m.p. 213–214° (lit.[21] m.p. 210°); $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 249 (3.99), 267 (3.87), 273 (3.85), 351 (3.99); ν_{NH} 3220 (s), $\nu_{\mathrm{NO_2}}$ 1506 (s), 1377 (s) or 1328 (s) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_8H_6N_2O_2$ (162.14): C, 59.26; H, 3.73; N, 17.28. Found: C, 59.41; H, 3.87; N, 17.37.

Nitration of 3-Nitroindole (19).—A mixture of 3-nitroindole (0.0792 g., 0.000488 mole) and concentrated nitric acid (*d* 1.42, 2 ml.) was warmed on a steam bath until solution occurred, and then kept at room temperature for 1 hr. Water was added, causing precipitation of a mixture, m.p. 214–253°, which was dissolved in methanol (10 ml.) and allowed to evaporate slowly, precipitates being collected at 24-hr. intervals. The first two precipitates were recrystallized from methanol, giving **3,6-dinitroindole** (15) as small pale yellow needles (0.0055 g., 5%), m.p. 290–296°. There was no depression in mixture melting point, 291–296°, with the sample prepared from 6-nitroindole-3-carboxaldehyde, and the infrared spectra in Nujol were identical.

The next two precipitates were also recrystallized from methanol, giving **3,5-dinitroindole** (20) as pale yellow needles (0.0153 g., 15%), m.p. 271–277°. There was no depression in mixture melting point, 274–280°, with the sample prepared from 5-nitroindole, and the infrared spectra in Nujol and the ultraviolet spectra in 95% ethanol were essentially identical.

3,5-Dinitroindole (20). A. From 5-Nitroindole (8).—A solution of 5-nitroindole[16] (0.35 g., 0.00216 mole) in concentrated nitric acid (*d* 1.42, 3 ml.) was warmed on a steam bath until a vigorous reaction occurred. The solution was cooled and the resulting precipitate was filtered off and dissolved in benzene–ether (3:1 v./v.) and placed on a column of alumina (5 g.) which had been packed wet with petroleum ether. Elution with 3:1 benzene–ether yielded pale yellow needles (0.08 g., 18%): m.p. 284–285°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 248 (4.32), 308 (3.99), 346 (3.99); ν_{NH} 3330 (m), 3100 (w) (KBr), 3300 (m), 3200 (m), 3100 (mw) (Nujol), $\nu_{\mathrm{NO_2}}$ 1535 (s), 1378 (s), 1350 (s) or 1314 (ms) (KBr), 1522 (ms), 1376 (s), 1344 (s) or 1305 (ms) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_8H_5N_3O_4$ (207.14): C, 46.38; H, 2.43; N, 20.29. Found: C, 46.63; H, 2.52; N, 20.09.

B. From 3,5-Dinitroindole-2-carboxylic Acid. (21).—A mixture of 3,5-dinitroindole-2-carboxylic acid (0.22 g., 0.000877 mole) and copper(II) oxide (0.12 g.) in quinoline (15 ml.) was refluxed for 2 hr. and then cooled and poured into cold aqueous 20% hydrochloric acid. The resulting solution and solid residue were extracted with ethyl acetate, and the extracts were dried, concentrated, and diluted with petroleum ether. The gray precipitate which formed was recrystallized from methanol–water, with charcoal, yielding pale yellow crystals (0.04 g., 22%), m.p. 275–278°. There was no depression in mixture melting point, 277–282°, with the sample prepared from 5-nitroindole, and the infrared spectra in Nujol were essentially identical.

3,5-Dinitroindole-2-carboxylic Acid (21).—A solution of 3-nitroindole-2-carboxylic acid (0.75 g., 0.00363 mole) in concentrated nitric acid (*d* 1.42, 15 ml.) was warmed at 90° on a steam bath for 0.5 hr. and then poured into water. The yellow solution was extracted with ether, the ether was evaporated to a small volume, water was added, and the solution was kept at room temperature for 2 hr. The resulting precipitate was recrystallized from methanol–water, with charcoal, yielding yellow microcrystals (0.49 g., 54%): m.p. 252–255° dec. with gas evolution; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 255 (4.40), 321 (4.08), 351 (infl.) (4.01); $\nu_{\mathrm{NH,OH}}$ 3360–2460 (broad), 2700 (w), 2650 (w), $\nu_{\mathrm{C=O}}$ 1712 (s), $\nu_{\mathrm{NO_2}}$ 1536 (s), 1350 (vs) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_9H_5N_3O_6$ (251.15): C, 43.04; H, 2.01. Found: C, 43.18, H, 2.26.

Ethyl 3,5-Dinitroindole-2-carboxylate (22).—A solution of 3-nitroindole-2-carboxylic acid (0.46 g., 0.00223 mole) in concentrated nitric acid (*d* 1.42, 25 ml.) was warmed at 90° on a steam bath for 0.75 hr. and then poured into an excess of water and extracted with ether. The ether was evaporated and the yellow residue was dissolved in ethanol (20 ml.) containing concentrated sulfuric acid (1 ml.). The solution was refluxed for 4.5 hr. and then concentrated and poured into water. The resulting oily suspension was extracted with ether, and the ether was washed with sodium bicarbonate solution and evaporated. The yellow residue was recrystallized from methylene chloride–petroleum ether, yielding pale yellow crystals (0.07 g., 11%): m.p. 156–158°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 252 (4.24), 323 (4.01); ν_{NH} 3240 (s) (KBr), 3210 (ms) (Nujol), $\nu_{\mathrm{C=O}}$ 1742 (s), 1702 (m) (KBr), 1742 (s), 1708 (ms) (Nujol), $\nu_{\mathrm{NO_2}}$ 1533 (s), 1510 (s), 1353 (vs) (KBr), 1532 (s), 1508 (s), 1349 (vs) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{11}H_9N_3O_6$ (279.21): C, 47.32; H, 3.25; N, 15.05; Found: C, 47.03; H, 3.45; N, 14.80.

Ethyl 4-Nitroindole-2-carboxylate (24).—Concentrated nitric acid (*d* 1.42, 3 ml.) was added dropwise, with stirring, to a slurry of ethyl indole-2-carboxylate[30] (4.00 g., 0.0211 mole) in acetic acid (5 ml.) in an ice bath. The slurry was allowed to warm to room temperature and was kept overnight. The resulting precipitate was recrystallized from ethanol, with charcoal, yielding long yellow needles (0.77 g., 16%): m.p. 228–229° (lit.[16] m.p. 228–230°); [$\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ),[31] 219 (4.49), 251 (4.09), 354 (4.02); ν_{NH} 3270 (ms), $\nu_{\mathrm{C=O}}$ 1692 (s), $\nu_{\mathrm{NO_2}}$ 1534 (ms), 1349 (ms) or 1335 (s) cm.$^{-1}$ (Nujol). There was no depression in mixture melting point, 227–229°, with a sample of m.p. 228–230° prepared[16] by the Fischer indole synthesis, and the infrared spectra in Nujol and the ultraviolet spectra in 95% ethanol were identical.

Ethyl 3,4-Dinitroindole-2-carboxylate (25).[28]—A solution of ethyl 4-nitroindole-2-carboxylate (0.15 g., 0.00064 mole) in concentrated nitric acid (*d* 1.42, 75 ml.) was warmed on a steam bath for 30 min. and then cooled in an ice bath. Water (70 ml.) was added, and the resulting precipitate was recrystallized from ethanol–water, with charcoal, yielding small light yellow needles (0.17 g., 95%): m.p. 221–222°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 214 (4.48), 243 (4.02), 324 (3.95), 357 (infl.) (3.87); ν_{NH} 3240 (ms), $\nu_{\mathrm{C=O}}$ 1693 (s), $\nu_{\mathrm{NO_2}}$ 1544 (s), 1349 (s) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{11}H_9N_3O_6$ (279.21): C, 47.32; H, 3.25; N, 15.05. Found: C, 47.32; H, 3.26; N, 15.27.

Increasing the reaction time or the concentration of ester resulted in a decreased yield. Attempted further nitration of the product by heating on a steam bath for 3 hr. in concentrated sulfuric acid with fuming nitric acid (*d* 1.5) gave no crystalline product.

3,4-Dinitroindole-2-carboxylic Acid (26).—A solution of ethyl 3,4-dinitroindole-2-carboxylate (1.00 g., 0.00358 mole) in aqueous 10% sodium hydroxide (30 ml.) was refluxed for 3 hr. and then cooled and acidified with aqueous 10% hydrochloric acid. The resulting precipitate was recrystallized from ethyl acetate–petroleum ether, yielding pale yellow crystals (0.85 g., 95%): m.p. 254° dec. with gas evolution; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 240 (4.09), 333 (broad) (3.93); ν_{NH} 3240 (ms), $\nu_{\mathrm{C=O}}$ 1698 (s), $\nu_{\mathrm{NO_2}}$ 1550 (s), 1524 (ms) (infl.), 1361 (ms), 1339 (s) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_9H_5N_3O_6$ (251.15): C, 43.04; H, 2.01; N, 16.73. Found: C, 42.97; H, 2.09; N, 16.69.

3,4-Dinitroindole (27).—A mixture of 3,4-dinitroindole-2-carboxylic acid (0.58 g., 0.00231 mole) and copper(II) oxide (0.08 g.) in quinoline (15 ml.) was refluxed for 1 hr. and then cooled and poured into ice-cold aqueous 20% hydrochloric acid. The precipitate and the solution were extracted with ethyl acetate, and the extracts were dried, treated with charcoal, and concentrated. Addition of petroleum ether caused separation of pale yellow granular crystals (0.17 g., 36%): m.p. 275.5–277°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 231 (4.06), 291 (3.88), 334 (3.94); ν_{NH} 3220 (m), $\nu_{\mathrm{NO_2}}$ 1513 (s), 1377 (s), 1350 (s) or 1325 (s) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_8H_5N_3O_4$ (207.14): C, 46.38; H, 2.43; N, 20.29. Found: C, 46.64; H, 2.57; N, 20.41.

Ethyl 3,7-Dinitroindole-2-carboxylate (29).—A solution of ethyl 7-nitroindole-2-carboxylate[16] (2.06 g., 0.00879 mole) in concentrated nitric acid (*d* 1.42, 27 ml.) was warmed at 90° on a steam bath for 0.5 hr. and then cooled and poured into ice–water (200 ml.). The resulting emulsion crystallized after standing for 2 hr. The crystals were filtered off and recrystallized from ethanol, with charcoal, yielding long white needles (0.29 g., 12%): m.p. 153.5–155°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 227 (infl.) (4.24), 348 (4.13); ν_{NH} 3280 (ms), $\nu_{\mathrm{C=O}}$ 1713 (s), $\nu_{\mathrm{NO_2}}$ 1554 (m), 1529 (s), 1382 (vs), 1334 (vs) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{11}H_9N_3O_6$ (279.21): C, 47.32; H, 3.25; N, 15.05. Found: C, 47.20; H, 3.29; N, 15.30.

3,7-Dinitroindole-2-carboxylic Acid (30).—A solution of ethyl 3,7-dinitroindole-2-carboxylate (2.58 g., 0.00925 mole) in aqueous 10% sodium hydroxide (70 ml.) was stirred at room temperature for 3 min. The resulting copious yellow precipitate was filtered off and stirred with aqueous 10% hydrochloric acid. Acidification of the filtrate with aqueous 10% hydrochloric

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(31) The hydrolysis product, 4-nitroindole-2-carboxylic acid,[16] m.p. 328–329° dec., has the following ultraviolet spectrum: $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 248 (4.11), 359 (3.94).

acid gave additional precipitate. The precipitates were recrystallized from ethyl acetate–petroleum ether, yielding pale yellow needles (1.22 g., 53%): m.p. 217–217.5°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 229 (4.20), 347 (4.12); ν_{NH} 3300 (m), ν_{OH} 2670 (w), $\nu_{C=O}$ 1742 (s), ν_{NO_2} 1524 (s), 1361 (s), 1344 (s), or 1314 (s) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_9H_5N_3O_6$ (251.15): C, 43.04; H, 2.01; N, 16.73. Found: C, 43.12; H, 2.08; N, 16.99.

3,7-Dinitroindole (31).—A mixture of 3,7-dinitroindole-2-carboxylic acid (0.80 g., 0.00318 mole) and copper(II) oxide (0.15 g.) in quinoline (25 ml.) was refluxed for 1 hr. and then cooled and poured into ice-cold aqueous 20% hydrochloric acid. The precipitate and the solution were extracted with ethyl acetate, and the extracts were dried, treated with charcoal, and concentrated. Addition of petroleum ether caused separation of pale yellow needles (0.17 g., 26%): m.p. 260–261.5°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$, m$\mu$ (log ϵ), 225 (4.20), 347 (4.16); ν_{NH} 3230 (m), ν_{NO_2} 1522 (s), 1383 (vs), 1333 (vs) cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_8H_5N_3O_4$ (207.14): C, 46.38; H, 2.43; N, 20.29. Found: C, 46.64; H, 2.48; N, 20.28.

Reactions of 3,α-Epoxyoxindoles and Their Rearrangement to 2,3-Disubstituted Indoles

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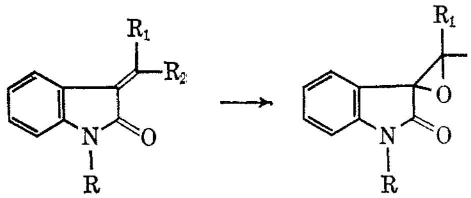
Received March 5, 1965

The reaction of alkylindeneoxindoles and alkaline hydrogen peroxide yields 3,α-epoxyoxindoles. Conversion of these compounds in the presence of alkali to 2,3-disubstituted indoles appears to be a general reaction. Evidence is presented in support of the assigned structures.

In the course of our studies of oxindole chemistry, it became desirable to prepare epoxides of the general structure II. It appeared that this could be accomplished by epoxidation of I with hydrogen peroxide.

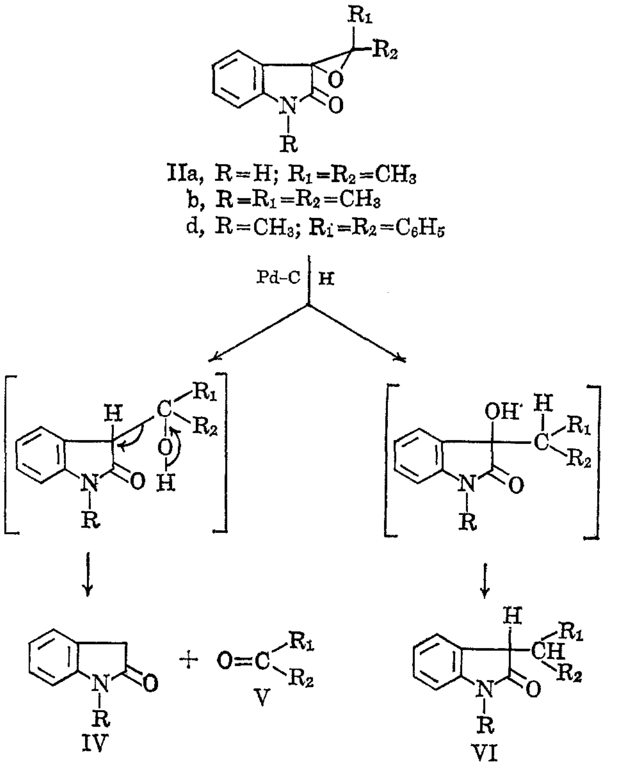


I II

When an alcoholic solution of 3-isopropylideneoxindole (Ia, Table I) was treated with 30% hydrogen peroxide under alkaline conditions, a new compound was obtained in high yield. Evidence in this paper shows that the new compound is the 3,α-epoxyoxindole IIa (Table II). Under the same reaction conditions, all the compounds in Table I (Ia–h) were subsequently converted into the corresponding epoxides IIa–h (Table II).

Support for the structural assignment of compounds II was obtained by catalytic hydrogenation of IIa, IIb, and IId (see Chart I).

CHART I



IIa, R=H; $R_1=R_2=CH_3$
b, $R=R_1=R_2=CH_3$
d, $R=CH_3$; $R_1=R_2=C_6H_5$

IV V VI

Compounds IV, V, and VI have been isolated from the reaction mixtures and identified. The epoxides II apparently yielded the expected two isomeric alcohols, both of which are unstable under the reaction conditions. As shown in the equation, the β-hydroxy carbonyl compound undergoes a dealdolization, similar to the dealdolization of diacetone alcohol studied by Westheimer and Cohen,[1] to give the oxindoles IV and the ketones V. The α-hydroxy carbonyl compound (a dioxindole), however, undergoes hydrogenolysis to yield the 3-substituted oxindoles VI. No attempt was made to isolate acetone (V, $R_1 = R_2 = CH_3$) in these reactions, but its presence was presumed because of the formation of oxindole IV. To verify this presumption, benzophenone (V, $R_1 = R_2 = C_6H_5$) was isolated and identified from the hydrogenation of IId as well as the corresponding oxindoles IV and VI. No attempt was made to isolate VI from the reduction of IIb.

A recent publication[2] describes the synthesis and structure proof of IId. The procedure described was repeated in our laboratories and the product was shown to be identical with IId prepared by the method described in this paper.

Compounds II behave in an interesting manner in the presence of base. When IIa, IIb, and IId were refluxed in dilute methanolic sodium hydroxide for several days, no reaction was observed. On the other hand, pyrrolidine at its boiling point converted IIa to acetone and an unstable material. Except for a small amount of unidentified material, no reaction was

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[1] F. Westheimer and Cohen, *J. Am. Chem. Soc.*, **60**, 90 (1938).

[2] A. Schönberg and K. Junghans, *Ber.*, **96**, 3328 (1963).