# The Cycloaddition Reaction of 3-Alkylindoles with *p*-Benzoquinone

WAYLAND E. NOLAND AND FREDERIC J. BAUDE[1]

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

*Received March 22, 1966*

3-Alkylindoles, including skatole, 3-ethylindole, 1,3-dimethylindole, 2,3-dimethylindole, and 1,2,3-trimethylindole, react with *p*-benzoquinone in acetic acid at room temperature, giving 2:1 cycloadducts ($-H_2$) which are shown to be 7b,14b-dialkyl-5a,7b,12a,14b-tetrahydrobisindolo[2,3-*b*:2′,3′-*b*′]benzo[1,2-*d*:4,5-*d*′]difurans (**1a–e**). The cycloadducts derived from indoles unsubstituted in the 2 position (**1a–c**, but not **1d** and **e**) undergo acid-catalyzed or thermal isomerization to 2,5-bis(3-alkylindol-2-yl)hydroquinones (**2a–c**), different (**2a**) from 2,5-bis(2-methylindol-3-yl)hydroquinone (**7**), and which (**2a**) are readily oxidized to the corresponding quinones (as with **2a** → **3**), different (**3**) from the known 2,5-bis(2-methylindol-3-yl)-*p*-benzoquinone (**6**). The structure of **2a** was proved by a double Fischer indole synthesis of its O,O′-dimethyl derivative (**2g**). Cycloadduct **1a** (but not **1d**) underwent facile hydrogenolysis in inert solvents to 2,5-bis(3-methylindolin-3-yl)hydroquinone (**14a**) or, in ethanol solution, to its N,N′-diethyl derivative **14b**, identical with a sample prepared by lithium aluminum hydride reduction and cleavage of the N,N′,O,O′-tetraacetyl derivative **14d** of **14a**. Pyrolysis of **14a** either gave partial breakdown, to 2-(3-methylindolin-3-yl)hydroquinone (**16**) and skatole, or at higher temperatures **14a** and **b** gave complete breakdown to hydroquinone and skatole or 1-ethyl-3-methylindole (**17**). Action of alkali on the methiodide (**18**) of **14b** under attempted Emde conditions gave no reduction but instead dehydroiodination to a double zwitterion **19**. Acetylation of **19** was accompanied by N,N′-didemethylation, giving the O,O′-diacetyl derivative **14c** of **14b**. 2,2′-(2,5-Dimethoxy-*p*-phenylene)dipropionaldehyde (**21**) and its diphenylhydrazone (**22**) were synthesized, but an attempted double Fischer indolenine synthesis to 3,3′-(2,5-dimethoxy-1,4-phenylene)bis(3-methyl-3H-indole) (**23**), which upon hydrogenation should yield the O,O′-dimethyl derivative of **14a**, failed. The probable mechanisms of formation of the cycloadducts **1** and their derivatives are discussed, with particular reference to other reactions of 3-alkylindoles and of indolenines reported in the literature. The synthesis of 2,3,4-trimethylindole is described.

In 1911, Möhlau and Redlich[2] reported that 2-methylindole and its substituted derivatives, 1,2-dimethylindole (which reacted more rapidly than 2-methylindole) and 2,5-dimethylindole, reacted readily with *p*-benzoquinone in 1:2 molar ratio in boiling ethanol to give deeply colored 1:1 adducts ($-H_2$), (2-methylindol-3-yl)-*p*-benzoquinones, in 90–100% yields. The corresponding reactions of 2-methylindole and 2,5-dimethylindole with methyl-*p*-benzoquinone gave 1:1 adducts ($-H_2$) in high yields (80 and 90%). 2-Phenylindole formed a similar 1:1 adduct ($-H_2$) from *p*-benzoquinone, but more slowly and in lower yield (40%) than with 2-methylindole, while only trace amounts of indole reacted. Refluxing of the product from 2-methylindole with aqueous 40% potassium hydroxide regenerated 2-methylindole.

In 1951, in an extensive study of the reactions of indoles with quinones, Bu'Lock and Harley-Mason[3] confirmed the earlier finding[2] with respect to the reaction of 2-methylindole with *p*-benzoquinone in boiling ethanol, and found that the reaction was strongly acid catalyzed, even by a little acetic acid in ethanol. They demonstrated the generality of the reaction of 3-unsubstituted indoles both with *p*-benzoquinones and the more reactive *o*-benzoquinones, and with the corresponding 1,4- and 1,2-naphthoquinones, all of which give deeply colored indol-3-ylquinones. The reaction was found to be inhibited by steric hindrance in cases where the 2-methyl group of the usually more nucelophilic 2-methylindole interacts with substitution on the quinone nucleus. In each reaction, the indol-3-ylhydroquinone, which may be assumed to be the initial, addition product, is oxidized to the resonance-stabilized, corresponding indol-3-ylquinone by a second molecule of the reactant quinone, which is itself reduced to the corresponding hydroquinone. In 1959, Bruce[4] proved by unambiguous syntheses that the 1:1 adducts ($-H_2$) of indole with *p*- and *o*-benzoquinone have the structures (indol-3-yl)-*p*-benzoquinone and 4-(indol-3-yl)-*o*-benzoquinone to which Bu'Lock and Harley-Mason[3] had assigned them.

Bu'Lock and Harley-Mason[3] found that, in favorable cases and under vigorous conditions, the initially formed indol-3-ylquinones may react further, either with another indole molecule or with another quinone molecule. Thus, in boiling acetic acid, 2-methylindole and *p*-benzoquinone gave a brownish violet 2:1 adduct ($-2H_2$), assumed to be the symmetrically substituted 2,5-bis(2-methylindol-3-yl)-*p*-benzoquinone (**6**), along with the intensely violet, previously described 1:1 adduct ($-H_2$). Indoles having both open 2 and 3 positions form red 1:2 adducts ($-2H_2$) with *p*-quinones in boiling acetic acid. Thus, indole and *p*-benzoquinone gave what was assumed to be 2,2′-(indol-2,3-ylene)bis(*p*-benzoquinone), and 1-methylindole-5,6-diol and 1,4-naphthoquinone gave what was assumed to be 2,2′-(5,6-dihydroxy-1-methylindol-2,3-ylene)bis(1,4-naphthoquinone). Similarly, indole and 1,4-naphthoquinone gave a violet 1:1 adduct ($-H_2$), which was converted by further reaction with 1,4-naphthoquinone into a brilliant scarlet 1:2 adduct ($-2H_2$), assumed to be 2,2′-(indol-2,3-ylene)bis(1,4-naphthoquinone).

The 3-substituted indoles, skatole and 2,3-dimethylindole, also reacted, the latter in lower yield, with *p*-benzoquinone in acetic acid, at room temperature, yielding 2:1 adducts ($-H_2$)[3] (**1a** and **d**) which differ strikingly from the deeply colored 2:1 adduct ($-2H_2$, **6**) derived from 2-methylindole in that they are colorless and have lost only one molecule of hydrogen during their formation. The adducts were inert to aqueous alkali, and formed diacetyl derivatives **1aAc** and **1dAc** with boiling acetic anhydride. Consequently, it was suggested that the adducts contain two indoline

(1) From the work of F. J. Baude, University of Minnesota, M.S. thesis, Dec 1962, and Ph.D. thesis, Dec 1964; *Dissertation Abstr.*, **26**, 82 (1965). This investigation was supported by U. S. Public Health Service Research Grant No. CA-04073-03 to -07 from the National Cancer Institute. We are also grateful to the Monsanto Co. for fellowships to F. J. B. during the summers of 1962–1964.

(2) R. Möhlau and A. Redlich, *Chem. Ber.*, **44**, 3605 (1911).

(3) J. D. Bu'Lock and J. Harley-Mason, *J. Chem. Soc.*, 703 (1951).

(4) J. M. Bruce, *ibid.*, 2366 (1959).

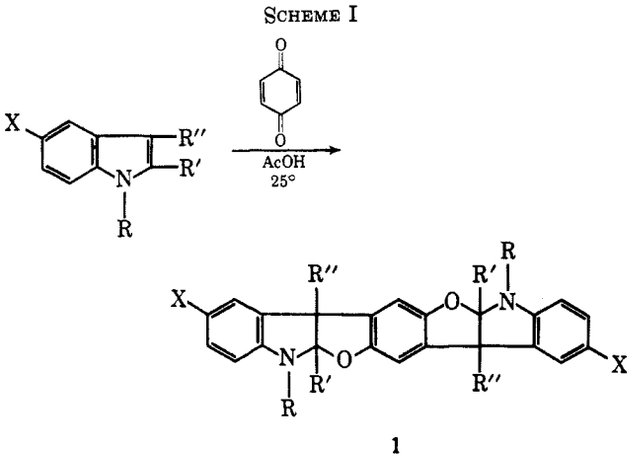
nuclei, but no further proposal was made concerning their structure.

The object of the present work has been to determine the scope of the reaction involving formation of these colorless 2:1 products from 3-alkylindoles and *p*-benzoquinone, and to determine the structure of these products.

## Scope of the Reaction

We have confirmed the formation of **1a** and **d** (Scheme I) from skatole and 2,3-dimethylindole, and of the diacetyl derivative (**1aAc**) of **1a**, and have established the generality of the reaction of 3-alkylindoles with *p*-benzoquinone by formation of the corresponding 2:1 adducts ($-H_2$) from 3-ethylindole (**1b**), 1,3-dimethylindole (**1c**), 1,2,3-trimethylindole (**1e**), and 5-bromoskatole[5] (**1f**). The steric (and possibly also electronic) limits of the reaction are suggested by the facts that 2,3,4-trimethylindole, 2-methyl-3-phenylindole, and 4-(indol-3-yl)-2-butanone[6,7] did not give crystalline products with *p*-benzoquinone under similar conditions. Also, methyl-*p*-benzoquinone did not give a crystalline product with skatole under similar conditions.

SCHEME I




**1**

| | R | R′ | R″ | X | % yield |
|---|---|---|---|---|---|
| **1a** | H | H | $CH_3$ | H | 57 |
| **1b** | H | H | $C_2H_5$ | H | 26 |
| **1c** | $CH_3$ | H | $CH_3$ | H | 9 |
| **1d** | H | $CH_3$ | $CH_3$ | H | 15 |
| **1e** | $CH_3$ | $CH_3$ | $CH_3$ | H | 10 |
| **1f**[5] | H | H | $CH_3$ | Br | 11 |
| **1aAc** | Ac | H | $CH_3$ | H | 95 (from **1a**) |
| **1dAc** | Ac | $CH_3$ | $CH_3$ | H | .. |

## Physical Data on the Cycloaddition Products 1

Preliminary X-ray crystallographic analysis[8] of **1a** showed the crystals to be monoclinic, with $a = 16.4$, $b = 9.2$, $c = 6.2$ A, and $\beta = 94°$. The unit cell volume is, therefore, 933 ± 15 A.[3] If two molecules of $C_{24}H_{20}N_2O_2$, of molecular weight 368, are assumed to be present, the calculated density would be 1.31 ± 0.02 g/cc, a reasonable value. Systematic extinctions showed that the space group is either $P2/n$ or $P2_1/n$. In $P2/n$ either two molecules of symmetry $\bar{1}$ or 2 or four molecules of symmetry 1 would be expected. In $P2_1/n$ either two molecules of symmetry $\bar{1}$ or four of symmetry 1 would be expected. The calculated density shows that no more than two molecules of molecular weight 368 are likely to be present; thus, a dimer or higher polymer is ruled out. It is unfortunate that the space group uncertainty of **1a** was not resolved before the crystal was lost, since the possible stereoisomeric form with *endo* orientation of the indoline rings would be expected to have symmetry 2 and the *exo* form to have symmetry $\bar{1}$; a clear-cut choice of $P2_1/n$ would have demonstrated that this is the *exo* form ($P2/n$, of course, would have left the *endo–exo* question unresolved).

In a similar X-ray crystallographic analysis[9] of **1c** the crystals appeared to be triclinic, with $1/a^* = 7.61 \pm 0.02$, $1/b^* = 8.63 \pm 0.03$, $c = 15.43 \pm 0.05$ A, and $\gamma^* = 101°40'$ (when it was apparent that the symmetry was triclinic, only enough data were collected to determine the unit cell volume). The unit cell volume is, therefore, 1035 ± 6 A$^3$. This, combined with an experimental density of 1.286 ± 0.005 g/cc indicates that the unit cell contains either one molecule of molecular weight 801 ± 6 or two molecules of molecular weight 401 ± 3 (the calculated value for $C_{26}H_{24}N_2O_2$ is 396).

The 2:1 adducts ($-H_2$) **1a–f** all have very similar ultraviolet spectra (Table I), indicating that the same chromophore is present in all cases. The adducts **1a**, **b**, **d**, and **f**) derived from indoles having an NH group also have an NH band in their infrared spectra, which, as shown in the case of **1a**, is replaced by a single amide carbonyl band upon diacetylation to **1aAc**. This suggests that the two nitrogens are chemically equivalent, and secondary (in the cases of **1a**, **b**, **d**, and **f**). None of the adducts **1a–f** has carbonyl bands in their infrared spectra, and the absence of bands in the hydroxyl or NH region of the infrared spectra of **1c** and **e**, as well as of **1aAc**, shows that no oxygens are present as hydroxyl groups. Consequently, the two oxygen atoms of the adducts **1** must be present in ether linkages.

TABLE I

ULTRAVIOLET SPECTRA OF THE 2:1 ADDUCTS ($-H_2$) (**1**) OF 3-ALKYLINDOLES AND *p*-BENZOQUINONE[a]

| Compd | $\lambda_{max}^{95\%\ EtOH}$, mμ (log ε) | | | |
|---|---|---|---|---|
| **1a** | 225[a] (4.32) | 244[a] (4.00) | 299[a] (3.83) | 319 (4.08) |
| **1b** | 227[a] (4.31) | 244[a] (4.00) | 296[a] (3.85) | 320 (4.08) |
| **1c** | 232 (4.24) | 251 (4.03) | 293[a] (3.86) | 320 (4.03) |
| **1d** | 226[a] (4.35) | 247[a] (3.98) | 297[a] (3.81) | 320 (4.03) |
| **1e** | 231[a] (4.17) | 250[a] (3.95) | 297[a] (3.71) | 323 (3.94) |
| **1f**[b] | 234 (4.42) | 258 (4.37) | 303 (4.04) | 328 (4.18) |
| **1aAc** | 234 (4.37) | 251[a] (4.19)[c] | 285 (3.68) | 311 (3.90) |

[a] Inflection. [b] Spectrum run in tetrahydrofuran, mp 265–266° dec; data from ref 5. [c] Also plateau at 275 (3.67).

(5) C. Reich, undergraduate research assistant, unpublished work University of Minnesota, 1962–1963. This portion of the investigation was supported by U. S. Public Health Service Research Grant No. CA-04073-05 from the National Cancer Institute.

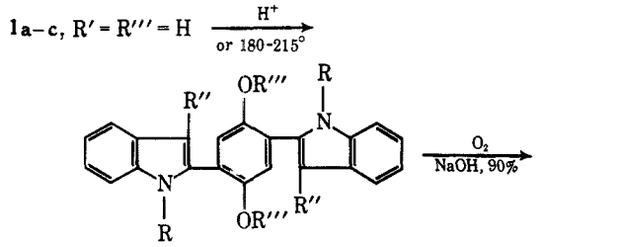
(6) (a) J. Szmuszkovicz, *J. Am. Chem. Soc.*, **79**, 2819 (1957); (b) R. F. Lange, Ph.D. thesis, University of Minnesota, June 1958, pp 77–78; *Dissertation Abstr.*, **20**, 1172 (1959).

(7) We wish to express our appreciation to George B. Bodem, undergraduate research assistant, Oct 1, 1958–Aug 31, 1959, for extensive exploratory studies, including that cited here, which were carried out at the inception of this work. This portion of the investigation was supported by U. S. Public Health Service Research Grant No. CA-04073-01 from the National Cancer Institute.

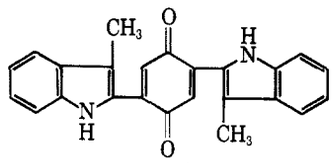
(8) Mary E. Hart, National Science Foundation undergraduate research participant working under the supervision of Professor William N. Lipscomb, University of Minnesota, summer 1959.

(9) We thank Professor Doyle Britton and Mrs. Judy Konnert of the University of Minnesota X-Ray Crystallographic Laboratory for assistance in obtaining and interpreting the X-ray data.

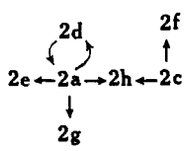
SCHEME II




2, R = R‴ = H; R″ = $CH_3$



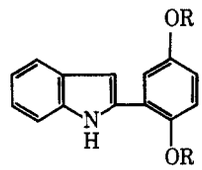

3



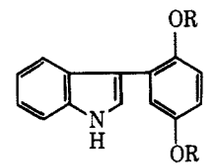

| | R | R″ | R‴ | % yield | From |
|---|---|---|---|---|---|
| 2a | H | $CH_3$ | H | 91 | 1a |
| 2b | H | $C_2H_5$ | H | 80 | 1b |
| 2c | $CH_3$ | $CH_3$ | H | 78 | 1c |
| 2d | Ac | $CH_3$ | Ac | 68 | 2a |
| 2e | H | $CH_3$ | Ts | 100 | 2a |
| 2f | $CH_3$ | $CH_3$ | Ac | 94 | 2c |
| 2g | H | $CH_3$ | $CH_3$ | 100 | 2a |
| 2h | $CH_3$ | $CH_3$ | $CH_3$ | 78 | 2a |
| | | | | 100 | 2c |

## Isomerization Products 2

The 2:1 adducts ($-H_2$) **1a–c** (Scheme II) derived from indoles unsubstituted in the 2 position, but not the adducts **1d** and **e** derived from 2-methyl-substituted indoles, undergo acid-catalyzed or thermal isomerization (to **2a–c**). The isomers and their derivatives (**2e, g,** and **h**) have ultraviolet spectra (Table II) which show more conjugation than is present in their adduct precursors, but the isomer spectra are similar to each other, indicating the probable presence of the same chromophore in each case. The ultraviolet absorption maxima and intensities of the isomers and their derivatives agree more closely with the spectra reported (Table II) for the indole 2-substituted derivatives, 2-(indol-2-yl)hydroquinone[10] (**4a**) and its dimethyl ether, 2-(2,5-dimethoxyphenyl)indole[10] (**4b**), than with those for the indole 3-substituted derivatives, 2-(indol-3-yl)hydroquinone[4] (**5a**) and its dimethyl ether, 3-(2,5-dimethoxyphenyl)indole[4] (**5b**). This suggests that the isomers **2a–c** are 2,5-bis(indol-2-yl)-hydroquinone derivatives.




**4a**, R = H
**b**, R = $CH_3$




**5a**, R = H
**b**, R = $CH_3$

TABLE II
ULTRAVIOLET SPECTRA OF THE ISOMERIZATION PRODUCTS 2, THEIR DERIVATIVES, AND MODELS 4, 5, AND 7

| Compd | $\lambda_{max}^{95\% EtOH}$, mμ (log ε) | | | |
|---|---|---|---|---|
| 2a | 227 (4.74) | 250[a] (4.35) | 309 (4.26) | 353 (4.49) |
| 2b | 228 (4.55) | 247[a] (4.21) | 304 (4.04) | 347 (4.17) |
| 2c | 230 (4.82) | | 298 (4.28) | 323 (4.26) |
| 2d | | 240[a] (4.54) | | 309 (4.43) |
| 2e | 225 (4.75) | 249[a] (4.20) | 330[a] (4.20) | 357 (4.34) |
| 2f | 229 (4.87) | 248[a] (4.37) | | 308 (4.37) |
| 2g | 225 (4.69) | 251[a] (4.27) | 308[a] (4.15) | 349 (4.47) |
| 2h | 230 (4.86) | 252[a] (4.33) | 303[a] (4.27) | 327 (4.39) |
| 4a[b] | 222 (4.55) | 246 (4.25) | 303 (4.12) | 335 (4.31) |
| 4b[b] | 222 (4.56) | 247 (4.24) | 304 (4.16) | 331 (4.33) |
| 5a[c] | 224 (4.54) | 267 (3.99) | 292 (3.89) | 309 (3.96) |
| 5b[c] | 225 (4.56) | 271 (4.01) | 291[a] (3.93) | 306 (3.99) |
| 7a | 228 (4.78) | 281 (4.27) | 289[a] (4.22) | 315 (4.20) |
| 7b | 225 (4.80) | 283 (4.39) | 290 (4.40) | 301[a] (4.30) |
| 7c | 231 (4.45) | 284 (3.87) | | 315 (3.94) |

[a] Inflection. [b] Reference 10. [c] Reference 4.

Isomers **2a** and **b** have bands in the NH region of the infrared spectrum, just as do their adduct precursors **1a** and **b** and the parent 3-alkylindoles from which they were derived. Isomer **2c**, however, which should have no NH band, as it is derived from an adduct (**1c**) and an indole (1,3-dimethylindole) which have no NH band in their infrared spectra, also has a band (at 3420 m $cm^{-1}$) in the hydroxyl[11] or NH region. This suggested the possibility that **2c**, and also **2a** and **b**, may contain hydroxyl groups. Acetylation of **2c** in boiling acetic anhydride gave a diacetyl derivative (**2f**) in which the hydroxyl absorption has disappeared and a high-frequency carbonyl band (at 1757 s $cm^{-1}$), characteristic of a phenolic ester,[12] has appeared. This formation of a diacetyl derivative having a single carbonyl band indicates that **2c** must be a dihydric phenol. That **2a** is also a dihydric phenol was shown by formation of a tetraacetyl derivative (**2d**) in which the hydroxyl and NH absorption has disappeared, but which has two carbonyl bands, one in the phenolic ester region (at 1759 ms $cm^{-1}$) and the other (at 1696 s $cm^{-1}$) in the high frequency amide region characteristic of 1-acylindoles.[13] These changes in the infrared spectrum upon tetraacetylation also suggest that the two nitrogens of **2a** are chemically equivalent and secondary, in keeping with their formulation as indole nitrogens. Acidic hydrolysis of the tetraacetyl derivative **2d** regenerated **2a** in 92% yield, showing that no structural rearrangement had occurred during the acetylation. Isomer **2a** formed a ditosyl derivative (**2e**) which, apparently because of the steric (and possibly electronic) effects of the two tosyl groups already present, could not be diacetylated under the conditions under which **2a** was tetraacetylated. That **2e** is an O,O′-ditosyl derivative, rather than an N,N′-ditosyl derivative, is shown by the fact that it (like **2d, f, g,** and **h**) gives no color change with Soloway and Wilen's modification[14] of the ferric chloride test, under conditions where its precursor **2a**, as well as **2b** and **c**, give a positive test (brown color). Attempted didehydroxyla-

(10) J. M. Bruce, *J. Chem. Soc.*, 360 (1960).

(11) In hydroquinone, the strong hydroxyl band occurs at 3240 $cm^{-1}$ in Nujol.

(12) In hydroquinone diacetate, for example, the carbonyl band occurs at 1760 s $cm^{-1}$ in Nujol.

(13) For example, the carbonyl band occurs in 1-acetylskatole at 1695 $cm^{-1}$ [(a) T. A. Geissman and A. Armen, *J. Am. Chem. Soc.*, **74**, 3916 (1952)]; in 1,1′-oxalylbis(3-methylindole) at 1689 $cm^{-1}$ in KBr [(b) F. Millich and E. I. Becker, *J. Org. Chem.*, **23**, 1096 (1958)]; and in 9-acetyl-2-(1-acetyl-indol-3-yl)-4,4-dimethyl-3,4-dihydrocarbazole at 1686 in chloroform, and at 1710, 1691, and 1677 $cm^{-1}$ in Nujol [(c) W. E. Noland, C. G. Richards, H. S. Desai, and M. R. Venkiteswaran, *ibid.*, **26**, 4254 (1961)].

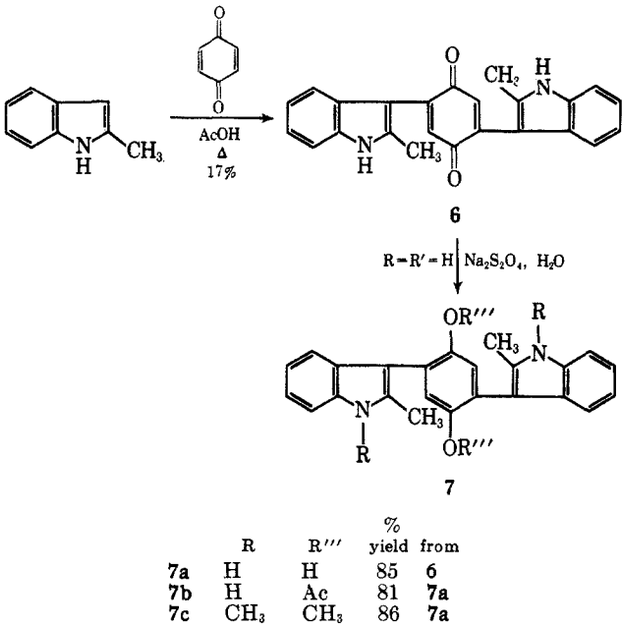
(14) S. Soloway and S. H. Wilen, *Anal. Chem.*, **24**, 979 (1952).

tion of **2a** by hydrogenolytic removal[15] of the O-tosylate groups of **2e** with Raney nickel gave unchanged **2e** in 60% recovery. Dihydric phenols, and especially hydroquinone, are known to be quite resistant to reduction to the corresponding aromatic hydrocarbons.[16]

Isomer **2a** was dimethylated with methyl iodide and potassium carbonate to what must be an O,O′-dimethyl derivative (**2g**) because it is different from **2c**, the N,N′-dimethyl derivative of **2a**, and still has an NH band (at 3400 mw $cm^{-1}$), and because it gives a negative ferric chloride test (no color change with Soloway and Wilen's modification[14]). Tetramethylation of **2a** with dimethyl sulfate and sodium hydride in N,N-dimethylformamide gave a derivative (**2h**), having no hydroxyl or NH absorption, which was identical with the O,O′-dimethyl derivative obtained by methylation of **2c** with methyl iodide and potassium carbonate.

Oxidation of **2a** with air in alkaline medium gave a deep violet quinone (**3**), establishing that the two phenolic hydroxyl groups of **2a** are in a *p*- (or *o*-) relationship to each other. The quinone **3** is different from the known[8] quinone, 2,5-bis(2-methylindol-3-yl)-*p*-benzoquinone (**6**, Scheme III) prepared from the reaction of

SCHEME III

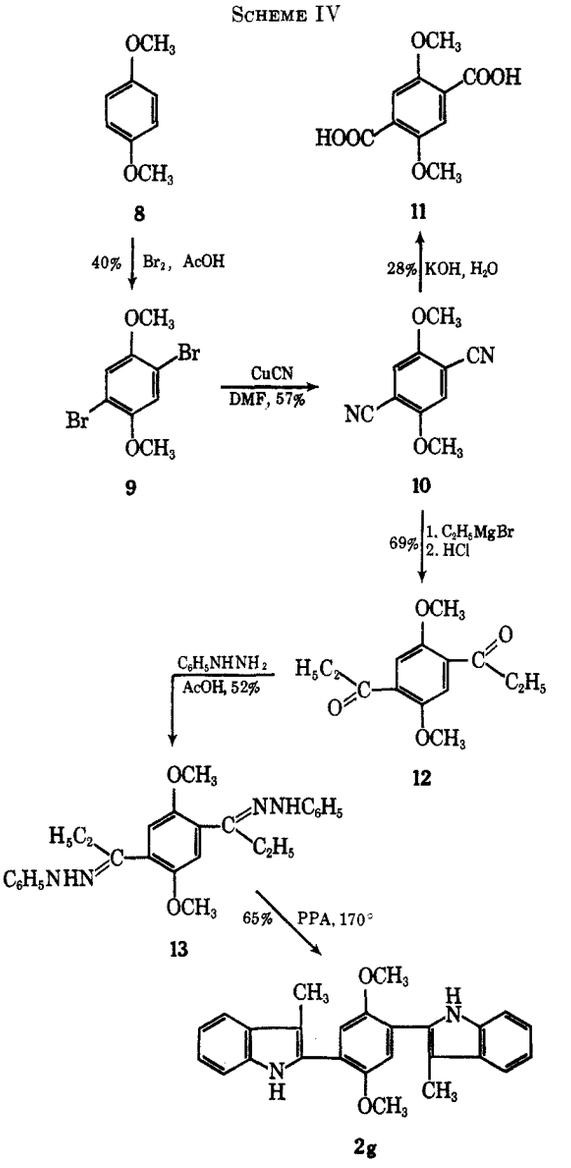



| | R | R‴ | % yield | from |
|---|---|---|---|---|
| **7a** | H | H | 85 | **6** |
| **7b** | H | Ac | 81 | **7a** |
| **7c** | $CH_3$ | $CH_3$ | 86 | **7a** |

2-methylindole with *p*-benzoquinone. Similarly, **2a** is different from the hydroquinone **7a** prepared by reduction of **6** with sodium hydrosulfite. Furthermore, the tetramethyl derivative **2h** of **2a** is different from the tetramethyl derivative **7c** of **7a**, and **7a** formed only an O,O′-diacetyl derivative (**7b**, carbonyl band at 1742 s $cm^{-1}$) under the conditions (boiling acetic anhydride) under which **2a** formed a tetraacetyl derivative (**2d**). Consequently, and in agreement with the ultraviolet evidence cited previously, it appeared likely that **2a** was 2,5-bis(3-methylindol-2-yl)hydroquinone. This fact was subsequently proved by an unambiguous, double Fischer indole synthesis of the O,O′-dimethyl derivative **2g** of **2a**.

For the synthesis of **2g**, 1,4-dimethoxybenzene (**8**, Scheme IV) was brominated in glacial acetic acid to

SCHEME IV




the known 1,4-dibromo-2,5-dimethoxybenzene[17] (**9**). Using a modified Rosenmund–von Braun synthesis,[18a] the action of cuprous cyanide in N,N-dimethylformamide gave 2,5-dimethoxyterephthalonitrile[18b] (**10**), the structure of which was confirmed by alkaline hydrolysis to 2,5-dimethoxyterephthalic acid[19] (**11**). Reaction of **10** with ethylmagnesium bromide gave, after hydrolysis of the water-soluble diketimine hydrochloride, 2,5-dimethoxy-1,4-dipropionylbenzene (**12**). The bisphenylhydrazone (**13**) of **12** was heated with poly-

(15) G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, S178 (1949).

(16) (a) W. H. Pirkle and J. L. Zabriskie, *J. Org. Chem.*, **29**, 3124 (1964); (b) S. W. Pelletier and D. M. Locke, *ibid.*, **23**, 131 (1958); (c) G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 522 (1955); (d) G. C. Weber and F. J. Sowa, *J. Am. Chem. Soc.*, **60**, 94 (1938); (e) A. L. Kranzfelder, J. J. Berbanc, and F. J. Sowa, *ibid.*, **59**, 1488 (1937); (f) P. A. Sartoretto and F. J. Sowa, *ibid.*, **59**, 603 (1937).

(17) J. Habermann, *Chem. Ber.*, **11**, 1034 (1878).

(18) (a) L. Friedman and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961). (b) The preparation of 2,5-dimethoxyterephthalonitrile (**10**) by another method (dehydration of the diamide) has recently been described: K. Wallenfels, G. Bachmann, D. Hofmann, and R. Kern, *Tetrahedron*, **21**, 2239 (1965).

(19) (a) J. U. Nef, *Ann. Chem.*, **258**, 298 (1890); (b) J. C. Westfahl and T. L. Gresham, *J. Am. Chem. Soc.*, **76**, 1076 (1954).

phosphoric acid in a double Fischer indole synthesis,[20] giving 2,5-bis(3-methylindol-2-yl)-1,4-dimethoxybenzene, identical with the sample prepared by dimethylation of **2a**. Consequently, **2a** has the structure 2,5-bis(3-methylindol-2-yl)hydroquinone. Since **2c** has been structurally related to **2a** through the fully methylated derivative **2h**, **2c** is 2,5-bis(1,3-dimethylindol-2-yl)hydroquinone. By analogy, **2b** is assigned the structure 2,5-bis(3-ethylindol-2-yl)hydroquinone. Thus, the cycloaddition reaction of 3-alkylindoles with *p*-benzoquinone, followed by acid-catalyzed or thermal isomerization of the products, offers a short and simple route to the previously unknown 2,5-bis(3-alkylindol-2-yl)-hydroquinones, which are, in turn, readily oxidized to the corresponding quinones.

### Hydrogenolysis Products 14a and 14b

The 2:1 adduct ($-H_2$) **1a** underwent hydrogenolysis and diethylation with Raney nickel in ethanol at 70°, giving an N,N′-diethyl tetrahydro derivative (**14b**). In **14b** the prominent NH band in the infrared spectrum of **1a** has disappeared, and phenolic hydroxyl bands have appeared at 2680 m and 2590 mw $cm^{-1}$. Acetylation of **14b** in boiling acetic anhydride gave an O,O′-diacetyl derivative (**14c**), having no NH bands in the hydroxyl and NH region, but having a single strong carbonyl band at 1760 $cm^{-1}$ in the phenolic ester[12] region.

To aid in the determination of structure of **14b**, an attempt was made to prepare the N,N′-diethyl derivative of **1a**, which could serve as a precursor of **14b**. Ethylation of **1a** with ethyl bromide and potassium carbonate in a refluxing mixture containing N,N-dimethylformamide and ether, however, gave a compound (**15**) having the apparent composition $C_{30}H_{28}N_2O_6$, which corresponds to a diethyl derivative of **1a** which has incorporated two molecules of carbon dioxide, but the structure has not been determined.

Hydrogenolysis of **1a** with Raney nickel in solvents that cannot alkylate, such as N,N-dimethylformamide and dioxane, gave the tetrahydro derivative **14a**, which melts variably around 250°, accompanied by dissociation. Probably because of its extensively hydrogen-bonded, saltlike character, it is too insoluble to be crystallized from the common low-boiling organic solvents. The necessary use of higher boiling solvents causes difficulties, as the compound tends to dissociate at the temperatures required for solution during crystallization and at the temperatures required for effective vacuum drying to remove the solvents, which are tenaciously held by the compound. Consequently, no entirely satisfactory elemental analyses were obtained. The compound is readily characterized, however, through its thermally stable N,N′,O,O′-tetraacetyl derivative **14d**. Reduction of **14d** with lithium aluminum hydride cleaved the two phenolic ester groups (infrared band at 1765 s) and reduced the two N-acetyl groups (band at 1665 s $cm^{-1}$) to N-ethyl groups, giving **14b**, and proving that **14b** is the N,N′-diethyl derivative of **14a**. In agreement with their chemical properties, the ultraviolet spectra of **14a–c** (Table III) are somewhat similar to what would be expected from a superposition of the spectra of two molecules of indoline and one molecule of hydroquinone. Attempted hydrogenolysis of **1d**, the 2:1 adduct ($-H_2$) derived from 2,3-dimethylindole, with Raney nickel in N,N-dimethylformamide gave only unchanged **1d** in 75% recovery, indicating that the 2-methyl group inhibits hydrogenolysis, just as it prevents isomerization.

TABLE III

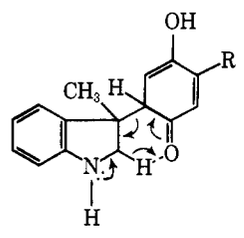
ULTRAVIOLET SPECTRA OF THE HYDROGENOLYSIS PRODUCTS **14**, THEIR DERIVATIVES, AND MODEL COMPOUNDS

| Compd | $\lambda_{max}^{95\%\ EtOH}$, mμ (log ε) | | |
|---|---|---|---|
| **14a**[a] | 243 (4.27) | | 297 (3.88) |
| **14b** | 254 (4.15) | | 301 (3.96) |
| **14c** | 257 (4.24) | | 308 (3.78) |
| **14d** | 254 (4.47) | 279 (4.00) | 289 (3.92) |
| **16**[b] | 228[c] (3.95) | | 295 (3.78) |
| Indoline[d] | 240 (3.83) | | 292 (3.35) |
| Hydroquinone[e] | 225 (3.71) | | 293 (3.43) |
| **17** | 227 (4.52) | 286[c] (3.75) | 290 (3.76) |

[a] Difficult to purify; $c = 2.23 \times 10^{-5}$ *M*; sample does not wholly obey Beer's law; see Experimental Section for further data. [b] $c = 5.62 \times 10^{-5}$ *M*; sample does not wholly obey Beer's law; see Experimental Section for further data. [c] Inflection. [d] W. E. Noland and C. F. Hammer, *J. Org. Chem.*, **25**, 1525 (1960). [e] R. Adams and J. L. Anderson, *J. Am. Chem. Soc.*, **72**, 5154 (1950); A. Kiss, J. Molnar, and C. Sandorfy [*Bull. Soc. Chim. France*, 275 (1949)] report 299 (3.35).

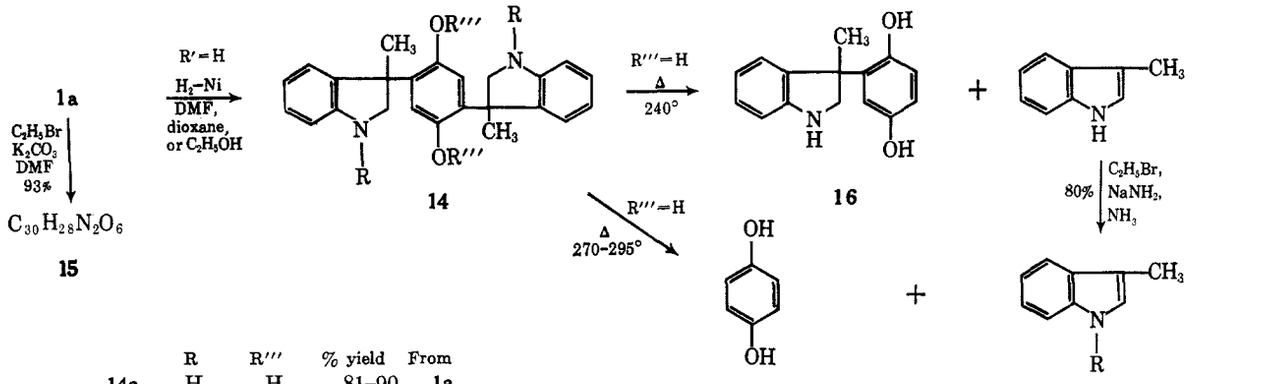
Vacuum sublimation of **14a** at 240°, slightly below its melting point, gave two bands of sublimate, containing skatole and a less volatile component, 2-(3-methylindolin-3-yl)hydroquinone (**16**). Removal of one of the indoline nuclei from **14a** causes the lower of the two ultraviolet bands characteristic of the indoline nuclei, the band at 243 mμ nearest to the hydroquinone band, to lose sufficient intensity to be overcome by an inflection at 228 mμ characteristic of the hydroquinone nucleus (see Table III). More vigorous pyrolysis of **14a** at 260–280°, slightly above its melting point, and subsequent vacuum sublimation of the brown solid residue, produced complete dissociation, giving skatole (85% of two molecules) and hydroquinone (76%). Similarly, pyrolysis of **14b** at 270–295°, about 50° above its melting point, and extraction of the residue gave hydroquinone (62%) and the previously unknown 1-ethyl-3-methylindole (**17**, 81% of two molecules), which was synthesized independently by ethylation of skatole. The thermal dissociation of **14a** and **b** may proceed through consecutive intramolecular abstractions of the indoline proton by neighboring oxygen of the hydroquinone moiety acting as a base in a six-membered ring transition state. Alternatively, the

(20) For other examples of double Fischer indole syntheses involving diketones, see (a) B. Robinson, *Can. J. Chem.*, **42**, 2900 (1964); (b) B. Robinson, *J. Chem. Soc.*, 3097 (1963); (c) F. G. Mann and T. J. Willcox, *ibid.*, 1525 (1958); (d) G. V. Bhide, N. L. Tikotkar, and B. D. Tilak, *Chem. Ind.* (London), 363 (1957). (e) Referee II has suggested another possible mechanism, where a phenolic hydroxyl group ketonizes and the resulting carbonyl oxygen acts as a hydride acceptor in attacking the oxidizable 2 position of a neighboring indoline nucleus. This mechanism, while not ruled




out, appears relatively unattractive to us because it requires that the carbonyl *oxygen* act as an electrophile.

SCHEME V

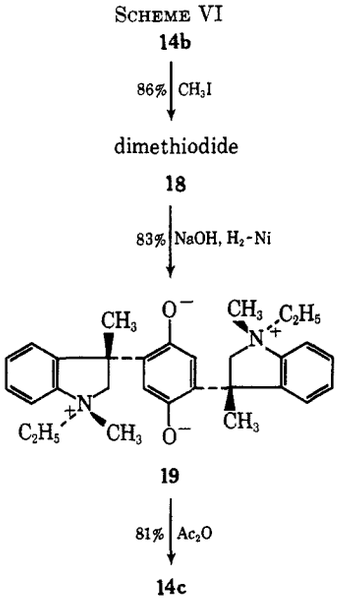



| | R | R''' | % yield | From |
|---|---|---|---|---|
| 14a | H | H | 81–90 | 1a |
| 14b | $C_2H_5$ | H | 74 | 1a |
| | | | 30 | 14d |
| 14c | $C_2H_5$ | Ac | 97 | 14b |
| 14d | Ac | Ac | 91 | 14a |

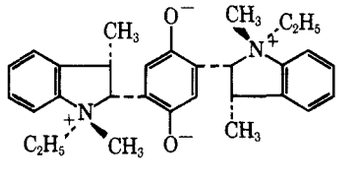
indoline nitrogen of another molecule may act as the base.[20e]

We hoped to cleave the indoline nuclei of **14b** by an Emde reduction of its dimethiodide, by analogy with the reduction of 1,1,3-trimethylindolinium iodide with sodium amalgam, which is reported to give, besides the demethylation product, 1,3-dimethylindoline (76%), an appreciable quantity of the cleavage product, dimethyl(2-phenylpropyl)amine (24%), and a trace of N,N-dimethyl-2-isopropylaniline.[21] Consequently, the dimethiodide **18** of **14b** was prepared by methylation with methyl iodide in refluxing benzene solution. Under modified Emde reduction conditions, by hydrogenation with Raney nickel[22] in aqueous ethanolic alkali, however, **18** (Scheme VI) gave what appears to

SCHEME VI




be a double zwitterion (**19**), corresponding in composition to the loss of two molecules of hydrogen iodide from **18**, with no reduction. The nmr spectrum of an 8% solution (w/v) of **19** in deuteriochloroform shows the two methyls of the N-ethyl groups as a triplet centered at $\delta$ 1.04 ($J$ = 7.2 cps, 6.1 protons), the two 3-methyl groups as a sharp singlet at 1.81 (6.4 protons), the two N-methyl groups as another sharp singlet at 2.49 (5.8 protons), which probably overlaps the upfield peak of an apparent quartet centered at 2.73 ($J$ = 7.2 cps, 4.1 protons) and is attributed to the two methylenes of the N-ethyl groups, the two indolinium ring methylene groups as a quartet centered at 4.79 ($J$ = 8.4 cps, 3.9 protons), the two aromatic protons in the 3 and 6 positions of the hydroquinone nucleus as a sharp singlet at 6.68 (1.9 protons), and the eight aromatic protons of the two indolinium nuclei as a complex, with the major peak at 7.40 (7.8 protons). Of greatest significance is the appearance of the two 3-methyl groups in the nmr spectrum as a sharp singlet, unsplit by any proton in the 3 position of the indoline nucleus. The nmr spectrum clearly supports structure **19** for the double zwitterion, as well as the corresponding structures for the related compounds **14a–d**, **16**, and **18**. The spectrum rules out the alternative structures **19x** in which the hydroquinone nucleus




**19x**

would be attached at the 2 positions of the indolinium nuclei (in which the 3-methyl peak would appear in the nmr spectrum as a doublet, split by the 3 proton), and the unsymmetrical combination of structures **19** and **19x** in which the hydroquinone nucleus would be attached to the 3 position of one indolinium nucleus and to the 2 position of the other, which would give a much more complex nmr spectrum, in which the first 3-methyl peak would appear as a singlet and the second 3-methyl peak would appear as a doublet.

The ultraviolet absorption maximum of hydroquinone dianion in water undergoes a hypsochromic and hypochromic shift as the hydroquinone passes to the monoanion and finally to the neutral state[23] (as shown in Table IV). Similarly, with the double zwitterion **19**,

(21) J. von Braun, K. Heider, and L. Neumann, *Chem. Ber.*, **49**, 2613 (1916).

(22) S. Sugasawa and H. Matsuo, *Pharm. Bull.* (Tokyo), **4**, 142 (1956); *Chem. Pharm. Bull.* (Tokyo), **6**, 601 (1958).

(23) J. H. Baxendale and H. R. Hardey, *Trans. Faraday Soc.*, **49**, 1140 (1953).

TABLE IV

EFFECT OF INCREASING ACIDITY ON THE ULTRAVIOLET SPECTRUM OF THE DOUBLE ZWITTERION 19

| Compd | Solvent[a] | $\lambda_{max}$, mμ (log ε) | | | |
|---|---|---|---|---|---|
| 19 | 95% EtOH | | | | 319 (3.95) |
| 19 | 95% EtOH (0.012 *M* HCl) | | | | 318 (3.92) |
| 19 | 95% EtOH (0.051 *M* HCl) | 252[b] (3.1) | | 269[b] (3.0) | 316 (3.89) |
| 19 | 63% EtOH[c] (4 *M* HCl) | 252[b] (2.8) | | 269[b] (2.8) | 310 (3.72) |
| 18 | 95% EtOH | 254[b] (3.56) | 259[b] (3.53) | 267 (3.42) | 301 (3.84) |
| Hydroquinone dianion[d] | Water | | | | 319 (3.50) |
| Hydroquinone monoanion[d] | Water | | | | 307 (3.44) |
| Hydroquinone[d] | Water | | | | 288 (3.36) |

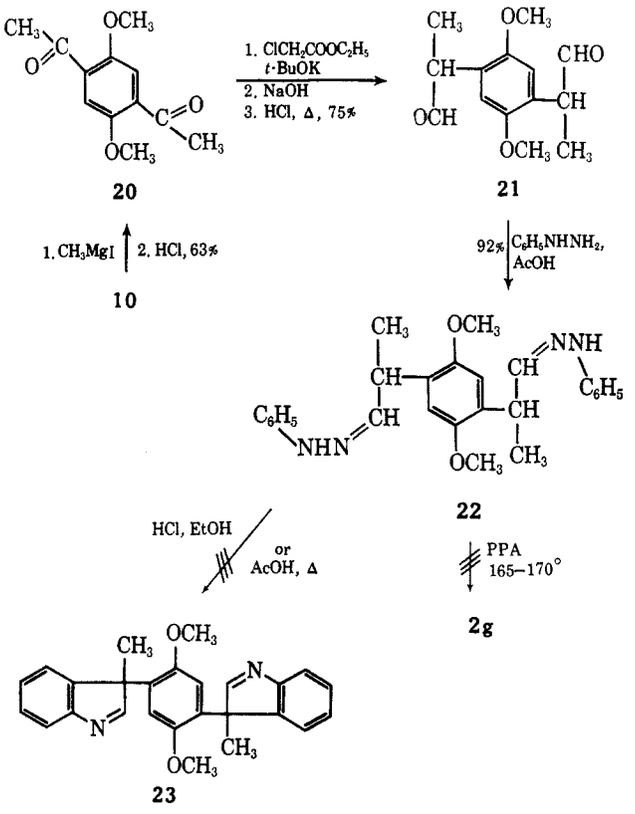
[a] Referenced against 95% ethanol or water, asappropriate, unless otherwise specified. [b] Inflection. [c] Referenced against 63% ethanol, 4 *M* in HCl. [d] Reference 23.

as the acidity of the medium is increased, that part of its absorption attributable to the hydroquinone portion should also pass from that of a dianion to a monoanion, and finally to the neutral state, at which point it should correspond to that of the dimethiodide **18** from which it was originally derived. That this trend is qualitatively true in 95% ethanol is illustrated by the data in Table IV, although no correction was made for changes in medium or chloride ion concentration (except for use of the proper reference solution in the case of 4 *M* HCl in 63% ethanol), or in the relative absorption of iodide ion (with **18**) *vs.* chloride ion (with **19**). It is also noteworthy that, as the intensity of the hydroquinone peak of **19** decreases with increasing acidity, the benzenoid absorption, apparent in the spectrum of the dimethiodide **18** and attributed to the benzene chromophore in the indolinium nuclei, also becomes apparent in the spectra of **19**. The change in ultraviolet spectrum of indolines, upon acidification, to the benzenoid absorption of anilinium ions has been noted previously.[24]

Action of boiling acetic anhydride on **19** gave **14c** in 81% yield. It is assumed that the acetate ions formed by acetylation of the hydroquinone dianion portion of **19** have carried out a double SN2 displacement on the N-methyl groups of the quaternary nitrogens. This would cause N,N′-didemethylation to **14c**, with concomitant formation of methyl acetate, which would have escaped by volatilization from the boiling solution. It is plausibly assumed that, during formation of the dimethiodide **18**, the methyl groups have approached and become attached to the nitrogens on the least hindered side of the indoline ring, *trans* to the large hydroquinonyl substituent in the 3 position. It is logical, then, that nucleophilic attack by acetate ion should also occur on the less hindered side on the methyl group, rather than on the N-ethyl group *cis* to the large hydroquinonyl group. Selective attack by nucleophilic reagents on a methyl group attached to a quaternary nitrogen also containing other alkyl groups has been reported previously, with reagents such as hydride,[25] thiophenoxide,[26] and, to some extent, acetate ion.[27]

An attempt was made to prepare 3,3′-(2,5-dimethoxy-1,4-phenylene)bis(3-methyl-3H-indole) (**23**), which upon hydrogenation should yield the O,O′-dimethyl derivative of **14a**. This would constitute a proof of structure of **14a** by synthesis. Reaction of 2,5-dimethoxyterephthalonitrile (**10**, Scheme VII) with methylmagnesium iodide gave 1,4-diacetyl-2,5-dimethoxybenzene (**20**). Compound **20** was converted *via* the Darzens reaction,[28] using ethyl chloroacetate and potassium *t*-butoxide, to 2,2′-(2,5-dimethoxy-*p*-phenylene)-dipropionaldehyde (**21**), which was converted to the corresponding diphenylhydrazone (**22**). A double Fischer indolenine synthesis from **22** with refluxing ethanolic hydrogen chloride[29] or refluxing glacial acetic acid[30] would be expected to give the desired **23**. However, only poorly defined yellow or tan solids melting over a wide range were obtained. A more vigorous reaction of **22** with polyphosphoric acid at elevated temperature would be expected to give **2g** by a Plancher-

SCHEME VII




(24) H. F. Hodson and G. F. Smith, *J. Chem. Soc.*, 1877 (1957).

(25) A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. A. P. Meisinger, *J. Am. Chem. Soc.*, **82**, 4651 (1960).

(26) (a) E. R. Trumbull, J. Häberli, and H. Ammon, Paper 127 presented before the Organic Division at the 134th National Meeting of the American Chemical Society, Chicago, Ill., Sept 11, 1958, Abstracts p 76P; (b) M. Shamma, N. C. Deno, and J. F. Remar, *Tetrahedron Letters*, 1375 (1966).

(27) H. R. Snyder and J. H. Brewster, *J. Am. Chem. Soc.*, **71**, 291 (1949).

(28) W. S. Johnson, J. S. Belew, L. J. Chinn, and R. H. Hunt, *ibid.*, **75**, 4995 (1953).

(29) F. E. King and R. Robinson, *J. Chem. Soc.*, 270 (1933).

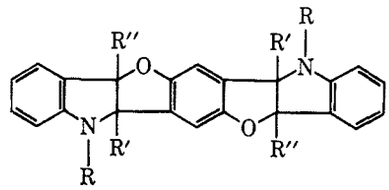
(30) F. J. Evans, G. G. Lyle, J. Watkins, and R. E. Lyle, *J. Org. Chem.*, **27**, 1553 (1962).

type rearrangement,[31] if **23** were formed as an intermediate. However, only an intractable solid, which begins to char above 330°, was obtained.

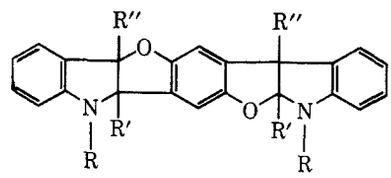
### Structure of the Cycloaddition Products 1

The structures established for the isomerization products **2** and for the hydrogenolysis products **14** indicate that the 2:1 adducts ($-H_2$) have either the symmetrical structures **1** or **24**, or an unsymmetrical combination of the two (**25**). Differentiation between the possible structures is based (1) on considerations of the probable mechanism of reaction of 3-alkylindoles with *p*-benzoquinone, (2) on the relative probability of rearrangement during formation of the two key types of derivatives (**2** *vs.* **14**), (3) on the ease of hydrogenolysis of **1a** to **14a** and **b**, and (4) on the chemical shifts of the indoline 3-methyl peaks in the nmr spectra of **1a** and its N,N′-diacetyl derivative **1aAc**.

(1) Structure **1**, which would result from electrophilic attack of the quinone at the 3 position of the 3-alkylindole nucleus, has analogy in the acid-catalyzed cycloaddition of 1,3-dimethylindole to mesityl oxide. The product from the latter reaction[32] has been shown[33] to have the structure in which the more sterically hindered 3 position, rather than the unsubstituted 2 position,[34] has added to the $\beta$ carbon of the $\alpha,\beta$-unsaturated ketone. Structure **1** probably also has analogy in the similar acid-catalyzed cycloadditions of 1,3-dimethylindole to 3-methyl-2-cyclohexen-1-one[33,35] and 2,5-hexanedione,[35] the structures of the products of which have not been proved. Structure **24**, which would result from electrophilic attack of the quinone at the unsubstituted 2 position of the indole nucleus, has analogy, but only in the site of initial electrophilic attack, in the formation of 2,2′-benzylidenebis(3-methylindoles)[34] by acid-catalyzed condensation of benzaldehyde with skatole and 1,3-dimethylindole, and in the formation of the 3-alkylindole dimers, diskatole,[36,37a] 1,3-dimethylindole dimer,[37] 3-ethylindole dimer,[38] and 3-*n*-propylindole dimer,[36b] by electrophilic substitution of a protonated 3-alkylindole at the 2 position of another 3-alkylindole molecule. Formation of structure **24** seems improbable, however, since there seems to be no reason why, if electrophilic attack occurs at the 2 position of the 3-alkylindole, the attack should not be followed rapidly by loss of the 2 proton (as in the examples[36–38] cited above), producing *substitution* by a hydroquinonyl group, which would subsequently be oxidized by more *p*-benzoquinone to a deeply colored, conjugated (indol-2-yl)-*p*-benzoquinone.[10] The same argument can be applied against formation of the unsymmetrical structure **25**, one side of which would result from initial electrophilic attack at the 2 position of the 3-alkylindole.



**24**



**25**

(2) The points of attachment of the hydroquinonyl group to the indole-derived nuclei differ, being at the 2 position of the indole nuclei in the isomerization products **2**, and at the 3 position of the indoline nuclei in the hydrogenolysis products **14**. This indicates that, during formation of one or the other type of derivatives, migration of the hydroquinonyl group must have occurred, either from the 3 to the 2 position, or in the reverse direction. Since the vigorous acidic or thermal conditions of the isomerization of **1a–c** to **2a–c** are conducive to skeletal rearrangement, while such rearrangement is very improbable under the mild, neutral conditions of the hydrogenolysis of **1a** to **14a** and **b**, migration of the hydroquinonyl group must have occurred in the former case, from the 3 position of **1a–c** to the 2 position of **2a–c**.

(3) The facile hydrogenolysis of **1a** to **14a** and **b**, with Raney nickel under mild conditions, with adsorbed hydrogen or hydrogen at 2 atm of pressure, is entirely consistent with cleavage of the N–C–O system of structures **1**. While the argument is not rigorous, the hydrogenolysis would hve been expected to proceed somewhat less readily were it to involve the benzyl system, Ar–C–O, of structure **24** or one-half of structure **25**.

(4) The extreme insolubility of **1a** (mp 255–256°) precluded a satisfactory determination of its nmr spectrum, but a single peak at $\delta$ 1.56, assumed to be the 3-methyl peak, was located[7] above the background from a saturated (but still very dilute) solution in N,N-dimethylformamide. Similarly, the extreme insolubility of the N,N′-diacetyl derivative **1aAc** (mp 414–416°, uncorr) in deuteriochloroform, acetone, tetrahydrofuran, dimethyl sulfoxide, trifluoroacetic acid, and N,N-dimethylformamide, precluded a complete determination of its nmr spectrum, but in pyridine, in which the compound is very slightly soluble, two peaks stand out, the 3-methyl peak at $\delta$ 1.67 and the N-acetyl methyl peak at $\delta$ 2.55.[39] Occurrence of the 3-methyl peak in **1a** and **1aAc** near to and slightly upfield from the 3-methyl peak in **19** (at $\delta$ 1.81) favors structure **1a**, and shows that the C-3 is not bonded to oxygen as in structure **24** or in one-half of structure **25**, since the latter environments would be expected to shift the 3-methyl peak downfield from the position observed in **19**.

Assuming *cis*-ring junctions at the 2 and 3 positions of the indoline rings, two (*meso*) stereoisomers of

(31) R. Robinson and H. Suginome, *J. Chem. Soc.*, 298 (1932).
(32) D. A. Cockerill, R. Robinson, and J. E. Saxton, *ibid.*, 4369 (1955).
(33) B. Robinson and G. F. Smith, *ibid.*, 4574 (1960).
(34) W. E. Noland and D. N. Robinson, *Tetrahedron*, **3**, 68 (1958).
(35) R. Robinson and J. E. Saxton, *J. Chem. Soc.*, 2596 (1953).
(36) (a) G. Berti, A. Da Settimo, and D. Segnini, *Tetrahedron Letters*, **No. 26**, 13 (1960); *Ann. Chim.* (Rome), **52**, 535 (1962); (b) G. F. Smith and A. E. Walters, *J. Chem. Soc.*, 940 (1961); (c) R. L. Hinman and E. R. Shull, *J. Org. Chem.*, **26**, 2339 (1961).
(37) (a) See footnote *d* of Table III; (b) William C. Kuryla, Ph.D. Thesis, University of Minnesota, Sept 1960, pp 27, 64; *Dissertation Abstr.*, **21**, 3272 (1961).
(38) G. C. Licke, unpublished work as a National Science Foundation undergraduate research participant, University of Minnesota, summer 1961.
(39) L. F. Johnson, Varian Associates, Palo Alto, Calif., letters to W. E. N. of March 31 and July 21, 1960.

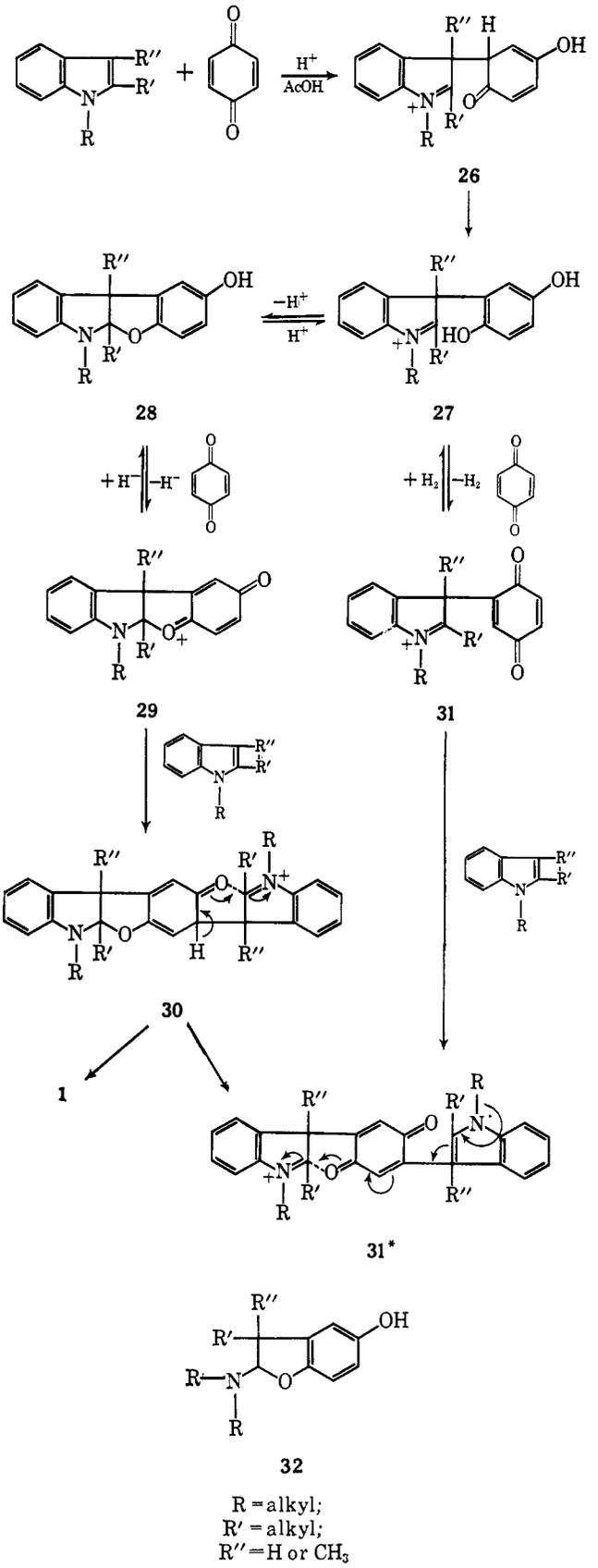
structure **1** are possible, one in which the indoline rings are bent toward each other (*endo*) with respect to the central plane of the benzodifuran nucleus, and one in which the indoline rings are bent away from each other (*exo*). As already noted above in the summary of the X-ray crystallographic data, the stereochemistry is unknown, but we tend to favor the *exo* configuration as the one offering the least steric hindrance to addition of the second 3-alkylindole molecule during its formation.

## Mechanism

In the formation of **1**, the initial electrophilic attack of *p*-benzoquinone at the 3 position of the 3-alkylindole must produce an indolenium cation (**26**), which in the case of the NH indoles may exist in equilibrium with the conjugate base, the indolenine. The indolenium cation **26** may enolize to the hydroquinone **27**, which can then cyclize by nucleophilic addition of the *o*-hydroxyl of the 3-hydroquinonyl substituent to the indolenine double bond, giving an intermediate cycloadduct (**28**). This cycloaddition process has a close analogy in the exothermic reaction of enamines derived from aliphatic aldehydes with *p*-benzoquinone, which has recently been reported to give 3-alkyl-2-dialkylamino-5-benzofuranols (**32**).[40] The ring-closure step involving intramoelcular nucleophilic addition to an indolenine also has analogy in the alkaloid series, in the probable biogenesis of physostigmine (eserine)[41] and its N-oxide, geneserine, and the related synthesis of *dl*-noreserethole,[42] and in the synthesis of *dl*- and *meso*-chimonanthine from N-methyltryptamine,[43] where the ring-closure steps involve addition of the secondary amino group of the 3-(2-methylaminoethyl) side chain to an indolenine.

Oxidation of the cycloadduct **28** (Scheme VIII), with *p*-benzoquinone would give a quinoid cation intermediate (**29**), which could add the second 3-alkylindole molecule at the least hindered site of the quinone moiety, giving the indolenium cation **30**. Enolization of **30** and cyclization by nucleophilic addition of the enolate oxygen to the indolenine double bond would give **1**. Alternatively, the hydroquinone **27** may be oxidized by *p*-benzoquinone to a quinone (**31**) before cyclization occurs. Addition of the second 3-alkylindole molecule to **31** must occur symmetrically, *para* to the indolenine nucleus already present, at the most electrophilic and least hindered site of the quinone moiety, if **1** is to be the final product. This addition can be concerted with cyclization of the components of **31**, giving **30** in one step *via* transition state **31***.

SCHEME VIII




R = alkyl;
R′ = alkyl;
R″ = H or $CH_3$

If addition of the second 3-alkylindole molecule to the $\alpha,\beta$-unsaturated ketone system of **26** occurs more rapidly than enolization of the ketone, then another pathway to **1** can be visualized (Scheme IX), *via* **26*** → **33** → **34** → **1**. In this sequence, oxidation by

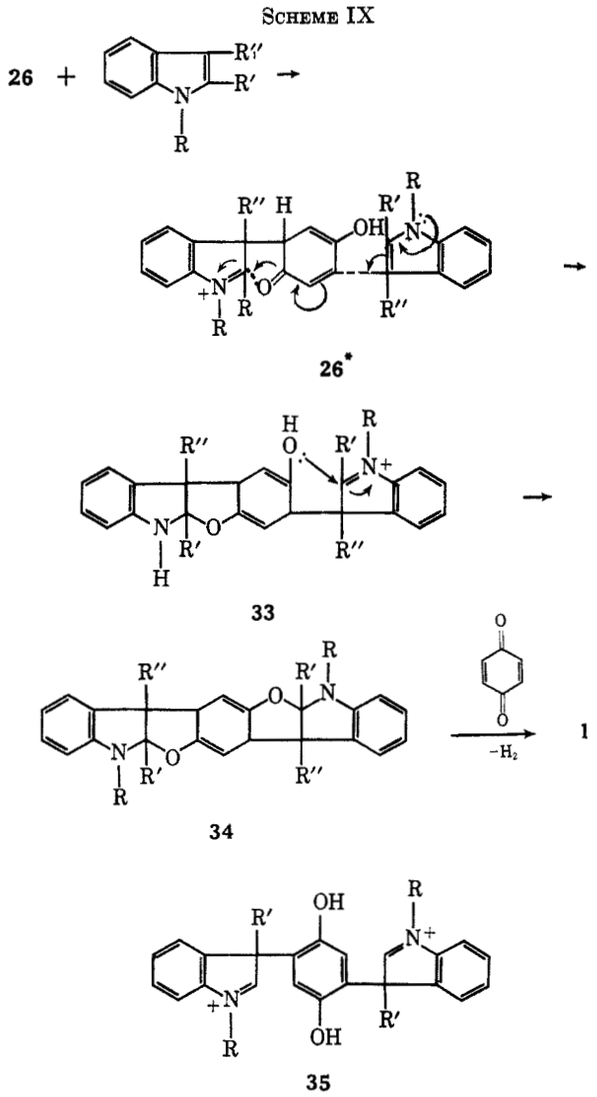
(40) (a) K. C. Brannock, R. D. Burpitt, H. E. Davis, H. S. Pridgen, and J. G. Thweatt, *J. Org. Chem.*, **29**, 2579 (1964). (b) Note added: G. Domschke [*Chem. Ber.*, **99**, 930 (1966)] has just described the preparation, in a reaction analogous to the formation of **1**, of 2,6-bis(4-morpholino)-2,6-diphenyl-2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b*′]difuran in 9% yield from the reaction of the enamine, 4-(1-phenylvinyl)morpholine, with *p*-benzoquinone in methylene chloride or benzene. Warming of the product with hydrochloric acid or by itself caused elimination of 2 moles of morpholine and formation of the corresponding 2,6-diphenylbenzo[1,2-*b*:4,5-*b*′]difuran in quantitative yield. Similar difurans were obtained from reactions of 4-(1,2-diphenylvinyl)morpholine and 4-(1-cyclohexen-1-yl)morpholine with *p*-benzoquinone.

(41) E. Leete, in P. Bernfeld, "Biogenesis of Natural Compounds," Pergamon Press Ltd., The Macmillan Co., New York, N. Y., 1963, pp 779–780.

(42) (a) R. Robinson and H. Suginome, *J. Chem. Soc.*, 304 (1932); (b) F. E. King, M. Liguori, and R. Robinson, *ibid.*, 1475 (1933).

(43) A. I. Scott, F. McCapra, and E. S. Hall, *J. Am. Chem. Soc.*, **86**, 302 (1964).

SCHEME IX



*p*-benzoquinone (of the dihydrobenzene **34**) is the last step on the route to **1**.

The isomerization of the cycloaddition products **1a–c** to **2a–c** must involve a sequence of two acid-catalyzed or thermal reversals of the cyclization steps back to an indolenine or indolenium cation (illustrated by the double structure **35**), analogous to the dehydration of a carbinolamine or the cleavage of an acetal. The resulting indolenines must then readily undergo a sequence of two acid-catalyzed or thermal Plancher rearrangements[31,44] in which the hydroquinonyl group migrates from the 3 position of each indolenine nucleus to the 2 position of the resulting indole nucleus.[45] The apparently exclusive migration of the hydroquinonyl group rather than the methyl groups is readily understandable in a kinetic sense, since the electron-rich hydroquinonyl group should have a very high migratory aptitude. Preference for migration of the hydroquinonyl group to the 2 position is also understandable in a thermodynamic sense. Under the strongly acidic conditions of the Fischer rearrangement,[46] with zinc chloride[47] and aluminum chloride,[48] both phenyl[47] and alkyl[48] substituents of 3-substituted indoles migrate preferentially to the 2 position, but with 2,3-disubstituted indoles there is a strong preference for the 2 position by a phenyl group over a competing alkyl group.[46] Thus, with aluminum chloride, 2-methyl-3-phenylindole isomerizes to 3-methyl-2-phenylindole, and 5,6-dihydro-7H-benzo[*c*]carbazole isomerizes to 11H-benzo[*a*]carbazole, apparently *via* dehydrogenation of the intermediate 5,6-dihydro-11H-benzo[*a*]-carbazole.[46] Formation in the present work of structures **2**, rather than the alternative 2,5-bis(2-alkylindol-3-yl)hydroquinones, from the isomerization of **1a–c** is consistent with these observations.

The failure of the 2-methyl-substituted cycloaddition products **1d** and **1e** to isomerize in boiling ethanolic hydrochloric acid may be attributed to the fact that indolization involving proton loss cannot occur, and expulsion of a methyl group would be required. There is no apparent reason, however, why the first step in the process, acid-catalyzed reversal of the cyclization step, should not occur, just as it must in the isomerization of **1a–c**. Thus, there should be an opportunity in the reversibly formed, open indolenine form (illustrated by structure **35**) for exchange of the hydroquinonyl and methyl groups between the 3 and 2 positions. Such equilibration has been observed in indolenines, though only under much more vigorous conditions, in the case in which a phenyl group is present instead of the hydroquinonyl group. Thus, with polyphosphoric acid (on which the detailed studies were carried out), or in tetralin with boron trifluoride, aluminum chloride, ferric chloride, or zinc chloride, all at temperatures of about 150°, or with 48% hydrobromic acid at reflux temperature, both 2,3-dimethyl-3-phenyl-3H-indole and 3,3-dimethyl-2-phenyl-3H-indole form an equilibrium mixture containing about 70% of the former and 30% of the latter.[44a] Since in **1d** and **e** there appears to be no net migration of the hydroquinonyl group from the 3 to the 2 position under conditions under which **1a** and **b** isomerized, it is concluded that in the open form (indolenine **35**) and/or in the closed form (indolenines **1d** and **e**) the 3 position is the preferred position for the phenyl ring of the hydroquinonyl group.

2,3,4-Trimethylindole, a new compound employed in one of the test reactions with *p*-benzoquinone, was

(44) (a) F. J. Evans, G. G. Lyle, J. Watkins, and R. E. Lyle, *J. Org. Chem.*, **27**, 1553 (1962); (b) F. J. Evans and R. E. Lyle, *Chem. Ind.* (London), 986 (1963); (c) M. Nakazaki, K. Yamamoto, and K. Yamagami, *Bull. Chem. Soc. Japan*, **33**, 466 (1960); (d) M. Nakazaki, *ibid.*, **33**, 472 (1960); (e) F. J. Baude, "The Plancher Rearrangement," University of Minnesota Organic Chemistry Seminars, **30**, pp 29–34, Nov 18, 1964; (f) P. L. Julian, E. W. Meyer, and H. C. Printy, in "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, pp 79–80, 88–89, and 102–108; (g) W. C. Sumpter and F. M. Miller, in "Heterocyclic Compounds," Vol. 8, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1954, pp 33–34.

(45) Electrophilic substitution by carbon at the 2 position of 3-alkylindoles[34] can also be interpreted, in an alternative manner to the suggestion advanced previously,[34] as proceeding by initial electrophilic attack at the 3 position,[33] giving an indolenine which then undergoes a Plancher rearrangement of the attacking group (which must, necessarily, in order to migrate, have a higher migratory aptitude and/or stability in the 2 position than the 3-alkyl substituent originally present). Thus, the formation of 2,2′-benzylidenebis(3-methylindoles) by the acid-catalyzed condensation of benzaldehyde with skatole or 1,3-dimethylindole[34] could be visualized as proceeding through an indolenine (structure II in ref 34) somewhat resembling **35**, which would then undergo a sequence of two Plancher rearrangements involving migration of the benzylidene group from the 3 to the 2 positions of the indole nuclei. The acid-catalyzed formation of 3-alkylindole dimers[35–38] could also be interpreted in similar terms by assuming an initial electrophilic attack by a protonated 3-alkylindole on the 3 position of another 3-alkylindole molecule, followed by a Plancher rearrangement of the 3-alkylindolin-2-yl substituent to the 2 position of the 3-alkylindolenine nucleus. The validity of this "indirect" mechanism relative to the "direct" attack previously suggested[34] to account for electrophilic 2 substitution of 3-alkylindoles remains to be determined.

(46) M. Nakazaki, *Bull. Chem. Soc. Japan*, **33**, 461 (1960).

(47) E. Fischer and T. Schmidt, *Chem. Ber.*, **21**, 1811 (1888).

(48) G. R. Clemo and J. C. Seaton, *J. Chem. Soc.*, 2582 (1954).

prepared by Vilsmeier formylation[49] of 2,4-dimethylindole, giving 2,4-dimethylindole-3-carboxaldehyde, which was subsequently reduced[50] with lithium aluminum hydride to 2,3,4-trimethylindole.

## Experimental Section

Melting points were determined on calibrated Fisher–Johns or Kofler micro hot stages, unless otherwise specified. Melting points above 300° reported as having been determined in a sealed capillary were determined in a Mel-Temp capillary melting point apparatus. Ultraviolet spectra were determined on Bausch and Lomb Spectronic 505 or Cary Model 11 recording spectrophotometers. Infrared spectra were determined on Perkin-Elmer 21 or 421, Beckman IR5, or Unicam SP-200 spectrophotometers. Nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer by Lawrence L. Landucci, to whom we express our thanks. Microanalyses were performed at the University of Minnesota by Mrs. Olga Hamerston and Dr. T. S. Prokopov and their assistants.

**Reaction Products 1 of 3-Alkylindoles with *p*-Benzoquinone. 7b,14b-Dimethyl-5a,7b,12a,14b-tetrahydrobisindolo[2,3-*b*:2′,3′-*b*′]benzo[1,2-*d*:4,5-*d*′]difuran (1a).**—A solution of skatole (50.0 g, 0.381 mole) and *p*-benzoquinone (50.0 g, 0.463 mole) in glacal acetic acid (600 ml) was stirred for 72 hr. The resulting precipitate was filtered and washed with ethanol, giving a light red solid (40.1 g, 57%), mp 231–233°. Seven crystallizations from *o*-dichlorobenzene (1,2,4-trichlorobenzene is also suitable) gave microscopic white crystals, mp 255–256°,[7] lit.[3] mp 250–252°, $\nu_{NH}^{Nujol}$ 3390 m cm$^{-1}$ and $\nu_{C=C}^{Nujol}$ 1609 ms cm$^{-1}$.

*Anal.* Calcd for $C_{24}H_{20}N_2O_2$ (368.42): C, 78.24; H, 5.47; N, 7.60. Found: C, 78.39; H, 5.55; N, 7.40.

**N,N′-Diacetyl Derivative 1aAc of 1a.**—A mixture of **1a** (2.50 g, 0.0679 mole) and acetic anhyride (100 ml, 1.06 moles) was refluxed, with stirring, for 8.5 hr. The mixture was cooled and filtered, and the precipitate was washed with aqueous 50% ethanol, giving a white solid (2.92 g, 95%), mp > 350° uncor. One crystallization from nitrobenzene gave white needles: mp 414–416° uncor (determined on a high-temperature block over a Meker burner);[7] lit.[3] mp 360°; $\nu_{NH}^{Nujol}$ none, $\nu_{C=O}^{Nujol}$ 1674 s, and $\nu_{C=C}^{Nujol}$ 1597 m cm$^{-1}$.[7]

*Anal.* Calcd for $C_{28}H_{24}N_2O_4$ (452.49): C, 74.32; H, 5.35; N, 6.19. Found:[7] C, 74.09; H, 5.35; N, 6.01.

**7b,14b-Diethyl-5a,7b,12a,14b-tetrahydrobisindolo[2,3-*b*:2′,3′-*b*′]benzo[1,2-*d*:4,5-*d*′]difuran (1b).**—A solution of 3-ethylindole[50] (35.8 g, 0.247 mole) and *p*-benzoquinone (26.7 g, 0.247 mole) was kept for 42.5 hr. The resulting precipitate was filtered and washed with ethanol, giving a dark red solid (12.3 g), mp 240–252°. Evaporation of the acetic acid mother liquor and ethanol wash at aspirator pressure gave a red tar, from which addition of absolute ethanol caused separation of more product (0.6 g), mp 240–252°, giving a total of 12.9 g (26%). Eight crystallizations from 1,2,4-trichlorobenzene gave white crystals, mp 257–259°, $\nu_{NH}^{Nujol}$ 3400 ms cm$^{-1}$ and $\nu_{C=C}^{Nujol}$ 1608 ms cm$^{-1}$.

*Anal.* Calcd for $C_{26}H_{24}N_2O_2$ (396.47): C, 78.76; H, 6.10; N, 7.07. Found: C, 78.58; H, 6.13; N, 7.32.

**1,3-Dimethylindole** (C. G. Richards, 1959) was prepared from skatole in 90% yield by methylation[51] with methyl iodide and sodamide in liquid ammonia, bp 72° (1.2 mm), $n^{25}$D 1.5900.

**5,7b,12,14b-Tetramethyl-5a,7b,12a,14b-tetrahydrobisindolo-[2,3-*b*:2′,3′-*b*′]benzo[1,2-d:4,5-d′]difuran (1c).**—A solution of 1,3-dimethylindole (50.0 g, 0.344 mole) and *p*-benzoquinone (38.9 g, 0.360 mole) in glacial acetic acid (150 ml) was stirred for 24 hr. The resulting precipitate was filtered and washed with ethanol, giving a light blue solid (6.2 g, 9%), mp 200–203°. Four crystallizations from acetone–water gave purple-coated, white rhombic crystals, mp 233–235°, $\nu_{NH}^{Nujol}$ none and $\nu_{C=C}^{Nujol}$ 1605 ms cm$^{-1}$.

*Anal.* Calcd for $C_{26}H_{24}N_2O_2$ (396.47): C, 78.76; H, 6.10; N, 7.07. Found: C, 78.80; H, 6.28; N, 7.18.

Recrystallization from benzene–petroleum ether (bp 60–68°) gave a dimorphic form, mp 224–225°, having an infrared spectrum in Nujol markedly different in the fingerprint region from 1050 to 700 cm$^{-1}$ from that of the sample crystallized from acetone–water; $\nu_{NH}$ none, $\nu_{C=C}$ 1607 ms cm$^{-1}$ in halocarbon oil[7] and in Nujol.

*Anal.* Found:[7] C, 78.99; H, 6.24; N, 6.84.

**5a,7b,12a,14b-Tetramethyl-5a,7b,12a,14b-tetrahydrobisindolo-[2,3-*b*:2′,3′-*b*′]benzo[1,2-*d*:4,5-*d*′]difuran (1d).**—A solution of 2,3-dimethylindole[52] (25.8 g, 0.178 mole) and *p*-benzoquinone (19.2 g, 0.178 mole) in glacial acetic acid (300 ml) was kept for 30 hr. The resulting precipitate was filtered and washed with absolute ethanol (50 ml), giving very light green crystals (5.4 g, 15%), mp about 350° uncor. Two recrystallizations from 1,2,4-trichlorobenzene or *o*-dichlorobenzene[7] gave white platelets: mp 349–350°;[7] lit.[3] 345–348°; $\nu_{NH}^{Nujol}$ 3470 w infl, 3320 mw infl, 3250 m, and $\nu_{C=C}^{Nujol}$ 1608 ms cm$^{-1}$.

*Anal.* Calcd for $C_{26}H_{24}N_2O_2$ (396.47): C, 78.76; H, 6.10; N, 7.07. Found: C, 78.89; H, 6.12; N, 6.88.

**5,5a,7b,12,12a,14b-Hexamethyl-5a,7b,12a,14b-tetrahydrobisindolo[2,3-*b*:2′,3′-*b*′]benzo[1,2-*d*:4,5-*d*′]difuran (1e).**—1,2,3-Trimethylindole[53] (16.3 g, 0.102 mole) and *p*-benzoquinone (13.0 g, 0.120 mole) were dissolved in glacial acetic acid (80 ml), producing an exothermic reaction. The solution was kept for 24 hr. The resulting precipitate was filtered and washed with ethanol, giving a light blue solid (2.16 g, 10%), mp 322–333° uncor. Eight crystallizations from 1,2,4-trichlorobenzene and one sublimation at 280–300° (about 0.05 mm) gave white crystals, mp 345–350° uncor, $\nu_{NH}^{Nujol}$ none, and $\nu_{C=C}^{Nujol}$ 1608 ms cm$^{-1}$.

*Anal.* Calcd for $C_{28}H_{28}N_2O_2$ (424.52): C, 79.21; H, 6.65; N, 6.60. Found: C, 79.45; H, 6.65; N, 6.95.

**Reaction of 2,3,4-Trimethylindole with *p*-Benzoquinone.**—A solution of 2,3,4-trimethylindole (for preparation, see the end of the Experimental Section; 5.00 g, 0.0314 mole) and *p*-benzoquinone (3.68 g, 0.0340 mole) in glacial acetic acid (40 ml) was kept for 1 month, but no precipitate separated from the dark brown solution.

**2-Methyl-3-phenylindole.**[54]—The procedure was essentially that of Ockenden and Schofield,[55] except that the concentration of the reactants in acetic acid was increased. A solution of phenylacetone phenylhydrazone[56] (obtained in 97% yield, mp 75–83°, 8.97 g, 0.040 mole) and boron fluoride etherate (47% solution, 12 g, 0.040 mole) in glacial acetic acid (50 ml) was refluxed for 1 hr. The colorless salt which precipitated was filtered off and the filtrate was diluted with water, neutralized with sodium bicarbonate, and extracted with ether. Evaporation of the ether and distillation of the residual dark brown oil gave a very viscous, pale yellow oil (5.85 g, 71%), bp 148–152° (0.25 mm), which solidified after 3 months in a refrigerator to nearly colorless plates: mp 56–59°; lit. mp 59–60°;[55] 65%, mp 58–60°;[55] 57%, mp 78–79°;[46] $\lambda_{max}^{95\%\ EtOH}$ [57] 226 mμ (log ε 4.58), 279 (4.19), and 288 infl (4.13); lit.[46] $\lambda_{max}^{MeOH}$ 225.5 mμ (log ε 4.55) and 278 mμ (log ε 4.21).

**Reaction of 2-Methyl-3-phenylindole with *p*-Benzoquinone.**—A solution of 2-methyl-3-phenylindole (5.43 g, 0.0276 mole) and *p*-benzoquinone (2.98 g, 0.0276 mole) in glacial acetic acid (50 ml) was kept for 72 hr. The resulting black crystals of quinhydrone (0.43 g, 14%), mp 166–171°, were filtered and washed with glacial acetic acid (60 ml). Evaporation of the acetic acid mother liquor and wash at aspirator pressure gave a black tar. Addition of absolute ethanol to the tar produced no solid material.

**Reaction of Skatole with Methyl-*p*-benzoquinone.**—A solution of skatole (2.50 g, 0.0191 mole) and methyl-*p*-benzoquinone (2.33 g, 0.0191 mole) in glacial acetic acid (30 ml) was kept for 79 hr, but no precipitate formed. Evaporation of the acetic acid with a rotary evaporator at aspirator pressure left a red tar from which no solid was obtained.

**Isomerization Products 2. Isomerization of 1a to 2,5-Bis(3-methylindol-2-yl)hydroquinone (2a). A. In Refluxing Ethanolic Hydrochloric Acid.**—A solution of **1a** (2.00 g, 0.00543 mole) in absolute ethanol (100 ml) containing concentrated hydrochloric acid (10 ml) was refluxed for 3 hr. The resulting intensely blue fluorescent, red solution was cooled, diluted with water (250 ml),

(49) P. N. James and H. R. Snyder, "Organic Syntheses," Coll. Vol. 4, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 539; *Org. Syn.*, **39**, 30 (1959).

(50) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).

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

(52) (a) H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.*, **65**, 2452 (1943); (b) C. M. Atkinson, J. C. E. Simpson, and A. Taylor, *J. Chem. Soc.*, 165 (1954).

(53) W. E. Noland, L. R. Smith, and K. R. Rush, *J. Org. Chem.*, **30**, 3457 (1965).

(54) With D. N. Robinson, Ph.D. Thesis, University of Minnesota, March 1959, pp 173–176; *Dissertation Abstr.*, **21**, 60 (1960).

(55) D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 612 (1953).

(56) B. Trenkler, *Ann. Chem.*, **248**, 106 (1888).

(57) Spectrum obtained by Robert J. Bose, University of Minnesota, 1959.

and neutralized with solid sodium bicarbonate, giving a brown solid (1.82 g, 91%), mp 270–275° dec. Five crystallizations from acetone gave light green needles, mp 281–285° dec, $\nu_{OH,NH}^{Nujol}$ 3430 ms cm$^{-1}$ and $\nu_{C=C}^{Nujol}$ 1564 w cm$^{-1}$.

*Anal.* Calcd for $C_{24}H_{20}N_2O_2$ (368.42): C, 78.24; H, 5.47; N, 7.60. Found: C, 77.46, 78.19; H, 5.74, 5.75; N, 7.57.

**B. In Concentrated Sulfuric Acid.**—Compound **1a** (1.00 g, 0.00271 mole) was dissolved in concentrated sulfuric acid (10 ml). The resulting green fluorescent solution was poured into water (100 ml), causing separation of the product as a red salt, **2,2′-(2,5-dihydroxy-1,4-phenylene)bis(3-methyl-3H-indolium) sulfate** (1.16 g, 0.00249 mole, 92% based on a mol wt of 466.51). The red salt (1.16 g) was dissolved in ethanol (50 ml), and neutralized by the addition of solid sodium bicarbonate and water (300 ml), with stirring, giving a precipitate, which was initially very light green but became dark green (0.80 g, 80% from **1a**). Two crystallizations from acetone gave dark green needles, mp 260–265° dec, having an infrared spectrum in Nujol identical with that of the sample prepared in refluxing ethanolic hydrochloric acid.

**C. In Refluxing 1,2,4-Trichlorobenzene.**—Compound **1a** (10.0 g, 0.0253 mole) was refluxed in 1,2,4-trichlorobenzene (80 ml, bp 213°) for 1.5 hr, during which time complete solution occurred, with formation of an intensely blue fluorescent, dark green solution. After cooling, the resulting precipitate was filtered and washed with absolute ethanol (50 ml), giving a green solid (7.70 g), mp 270–280° dec. Evaporation of the 1,2,4-trichlorobenzene mother liquor under vacuum gave more green solid (1.44 g), mp 271–280° dec, making a total of 9.14 g (91%).

**Isomerization of 1b to 2,5-Bis(3-ethylindol-2-yl)hydroquinone (2b) in Refluxing Ethanolic Hydrochloric Acid.**—A solution of **1b** (1.00 g, 0.00252 mole) in absolute ethanol (50 ml) containing concentrated hydrochloric acid (5 ml) was refluxed for 0.5 hr. The resulting intensely blue fluorescent, red solution was cooled, diluted with water (100 ml), and neutralized with solid sodium bicarbonate, giving a dark green precipitate (0.80 g, 80%), mp 213–234° dec. Six crystallizations from acetone gave a light green solid, mp 239–241° dec, $\nu_{OH}^{Nujol}$ 3440 m cm$^{-1}$ and $\nu_{NH}^{Nujol}$ 3350 m (stronger) cm$^{-1}$.

*Anal.* Calcd for $C_{28}H_{24}N_2O_2$ (396.47): C, 78.76; H, 6.10; N, 7.07. Found: C, 78.69; H, 6.32; N, 6.87.

**Isomerization of 1c to 2,5-Bis(1,3-dimethylindol-2-yl)hydroquinone (2c). A. By Sublimation.**—Compound **1c** (0.50 g, 0.00126 mole) was sublimed at 180–188° (0.05 mm). The sublimate was crystallized once from acetone–water, giving a gray solid (0.39 g, 78%), mp 265–267°. Resublimation at 180–190° (0.05 mm) and one recrystallization from acetone–water again gave a gray solid, mp 272–274°, $\nu_{OH}^{Nujol}$ 3420 m cm$^{-1}$.

*Anal.* Calcd for $C_{26}H_{24}N_2O_2$ (396.47): C, 78.76; H, 6.10; N, 7.07. Found: C, 78.96; H, 6.26; N, 6.98.

**B. In Concentrated Sulfuric Acid.**—Compound **1c** (0.50 g, 0.00126 mole) was dissolved in concentrated sulfuric acid (20 ml), and then poured into water (200 ml) and neutralized with solid sodium bicarbonate, giving a yellow precipitate (0.49 g, 98%), mp 243–260°. Sublimation at 210° (1 mm), one crystallization from acetone, and resublimation at about 210° (1 mm) gave a white solid, mp 271–273°, which gave no significant depression in mmp 268–272°, with the sample prepared solely by sublimation.

**Attempted Isomerization of 1d in Refluxing Ethanolic Hydrochloric Acid.**—A solution of **1d** (1.00 g) in absolute ethanol (50 ml) containing concentrated hydrochloric acid (5 ml) was refluxed for 2 hr. The solution was concentrated to 0.5 volume, water (200 ml) was added, and the resulting mixture was neutralized with solid sodium bicarbonate. The resulting precipitate (0.95 g, 95% recovery), mp > 350° uncor, had an ultraviolet spectrum in 95% ethanol identical with that of the starting material.

**Attempted Isomerization of 1e in Refluxing Ethanolic Hydrochloric Acid.**—A solution of **1e** (0.10 g) in absolute ethanol (20 ml) containing concentrated hydrochloric acid (2 ml) was refluxed for 1.5 hr. The light yellow solution was cooled, diluted with water (150 ml), and neutralized with solid sodium bicarbonate, giving a precipitate (0.08 g, 80% recovery), mp 337–339° uncor. Sublimation at about 280–300° (0.05 mm) gave a white solid, mp 332–341° uncor, having an infrared spectrum in Nujol identical with that of the starting material.

**Derivatives of the Isomerization Products 2 and Related Compounds. N,N′,O,O′-Tetraacetyl Derivative 2d of 2a.**—Compound **2a** (3.00 g, 0.00814 mole) was refluxed in acetic anhydride (50 ml, 0.53 mole) for 4 hr. Solution occurred after 0.5 hr, but a precipitate re-formed at the end of 3 hr. The cooled mixture was poured into water (350 ml) and the acetic anhydride was hydrolyzed, giving a tan precipitate (2.99 g, 68%), mp 269–286°. One crystallization from dioxane–water gave a white solid: mp 279–282°; $\nu_{NH}^{Nujo}$ none, $\nu_{C=O}^{Nujol}$ 1759 ms, 1696 s, $\nu_{C=C}^{Nujol}$ 1608 w cm$^{-1}$.

*Anal.* Calcd for $C_{32}H_{26}N_2O_6$ (536.56); C, 71.63; H, 5.26; N, 5.22. Found: C, 71.82; H, 5.40; N, 5.05.

**Acidic Hydrolysis of 2d to 2a.**—A solution of **2d** (1.13 g, 0.00211 mole) in absolute ethanol (150 ml) containing concentrated hydrochloric acid (10 ml) was refluxed for 6 hr. The resulting intensely blue fluorescent, red solution was cooled, diluted with water (300 ml), and neutralized with solid sodium bicarbonate, giving a tan precipitate (0.72 g, 92%), mp 265–275° dec, having an infrared spectrum in Nujol identical with that of **2a** prepared in refluxing ethanolic hydrochloric acid. Sublimation at about 240° (0.05 mm) gave a green solid, mp 277–282° dec, which gave no depression in mixture melting point with the sample of **2a**.

**O,O′-Ditosyl Derivative 2e of 2a.**—A solution of **2a** (2.00 g, 0.00543 mole) and *p*-toluenesulfonyl chloride (5.17 g, 0.0271 mole) in pyridine (30 ml) was refluxed for 0.5 hr. The solution was cooled and diluted with water (100 ml), giving a yellow precipitate. The precipitate was filtered and then stirred with aqueous 3% sodium hydroxide (100 ml) for 15 min, giving a precipitate (3.88 g, 106%), mp about 240° dec. Two crystallizations from acetone gave very light yellow crystals: mp 287–289° dec; $\nu_{NH}^{Nujol}$ 3400 ms, $\nu_{SO_2}^{Nujol}$ 1380 s, and 1193 s or 1179 s or 1153 s cm$^{-1}$.

*Anal.* Calcd for $C_{38}H_{32}N_2O_6S_2$ (676.78): C, 67.43; H, 4.77; N, 4.14; S, 9.48. Found: C, 67.66; H, 4.91; N, 4.10; S, 9.75.

**Attempted Acetylation of 2e.**—A suspension of **2e** (0.10 g, 0.0015 mole) in acetic anhydride (10 ml, 0.11 mole) was refluxed for 3 hr, during which time solution occurred. The yellow solution was cooled, and poured into water to hydrolyze the excess acetic anhydride, giving a yellow precipitate (0.08 g, 80% recovery), mp 189–217° dec, having an infrared spectrum in Nujol identical with that of the starting material. One crystallization from methanol–acetone gave very light yellow crystals, mp 281–283° dec, also having an infrared spectrum in Nujol identical with that of the starting material.

**Attempted Hydrogenolytic Deoxygenation of 2e.**—The procedure of Kenner and Murray[15] was used. Compound **2e** was dissolved in dioxane (30 ml) and hydrogenated at 2 atm over Raney nickel (1 teaspoonful) for 3.5 hr. The catalyst was filtered and washed with dioxane (50 ml). The hydrogenation process was then repeated by adding fresh Raney nickel (1 teaspoonful) to the filtrate and washings, and hydrogenating at 2 atm for 24 hr. The catalyst was filtered and washed with dioxane, and the filtrate and washings were evaporated in a rotary evaporator, leaving a yellow oil. The oil was triturated with absolute methanol, leaving a light yellow, crystalline precipitate (0.12 g, 60% recovery), mp 279–283° dec, having an infrared spectrum in Nujol identical with that of the starting material.

**O,O′-Diacetyl Derivative 2f of 2c.**—A solution of **2c** (0.14 g, 0.0035 mole) in acetic anhydride (15 ml, 0.16 mole) was refluxed for 2 hr. The solution was cooled and water (100 ml) was added to hydrolyze the excess acetic anhydride, giving a white crystalline precipitate (0.16 g, 94%), mp 270–273°. One crystallization from acetone gave a white crystalline solid: mp 273–274°; $\nu_{OH}^{Nujol}$ none, $\nu_{C=O}^{Nujol}$ 1757 s, and $\nu_{C=C}^{Nujol}$ 1583 vw cm$^{-1}$.

*Anal.* Calcd for $C_{30}H_{28}N_2O_4$ (480.45): C, 74.98; H, 5.87; N, 5.83. Found: C, 74.69; H, 5.99; N, 5.52.

**O,O′-Dimethyl Derivative 2g of 2a.**—A mixture of **2a** (0.68 g, 0.00185 mole), methyl iodide (8.00 g, 0.0564 mole), and anhydrous potassium carbonate (10 g) in acetone (100 ml, dried over anhydrous potassium carbonate) was refluxed for 24 hr. The excess methyl iodide and acetone were evaporated on a steam bath, and water (100 ml) was added to the residue, giving a tan solid (0.84 g, 115%, probably still wet). Sublimation at about 220° (0.05 mm) and two crystallizations from acetone–water gave a yellow solid, mp 243–244°, $\nu_{NH}^{Nujol}$ 3400 mw and $\nu_{C=C}^{Nujol}$ 1557 w cm$^{-1}$.

*Anal.* Calcd for $C_{26}H_{24}N_2O_2$ (396.47): C, 78.76; H, 6.10; N, 7.07. Found: C, 78.96; H, 6.28; N, 7.17.

**N,N′,O,O′-Tetramethyl Derivative 2h of 2a. A. From 2a.**—A solution (blue fluorescent) of **2a** (1.00 g, 0.00271 mole) in dry N,N-dimethylformamide (35 ml) was added dropwise with stirring to a slurry of excess sodium hydride in dry N,N-dimethyl-

formamide (40 ml), giving a bright orange mixture. Dimethyl sulfate (40 ml, 0.45 mole) was added dropwise, while the mixture was refluxed. After one-fourth of the dimethyl sulfate had been added, the slurry was white, but, when addition was complete, the slurry was brown. The mixture was cooled, and ethanol (50 ml) and then water (300 ml) were added, giving a cream precipitate. Sublimation at 220–230° (0.05 mm) gave a sample (0.89 g, 78%), mp 233–235°. Resublimation at 210–230° (0.07 mm) gave a white solid: mp 236–238°; $\nu_{OH,NH}^{Nujol}$ none, $\nu_{C=C}^{Nujol}$ 1607 vw, and 1565 vw cm$^{-1}$.

*Anal.* Calcd for $C_{28}H_{28}N_2O_2$ (424.52): C, 79.21; H, 6.65; N, 6.60. Found: C, 78.84; H, 6.64; N, 6.95.

**B. From 2c.**—A mixture of **2c** (0.23 g, 0.00058 mole), methyl iodide (3.00 g, 0.00211 mole), and anhydrous potassium carbonate (5.0 g) in acetone (75 ml, dried over anhydrous potassium carbonate) was refluxed for 24 hr. The excess methyl iodide and acetone were evaporated on a steam bath, and water (100 ml) was added to the residue, giving a cream solid (0.26 g, 106%, probably still wet). Sublimation at 225° (0.2 mm) gave a white solid, mp 230–231°. There was no depression in mmp 229–233° with the sample prepared by tetramethylation of **2a**, and the infrared spectra in Nujol were identical.

*Anal.* Found: C, 78.57; H, 6.61; N, 6.74.

**Ferric Chloride Test on 2,5-Bis(indol-2-yl)hydroquinones and Derivatives.**—A variation of the ferric chloride test, developed by Soloway and Wilen,[14] was used. Ferric chloride hexahydrate (1.75 g) was dissolved in a solution of pyridine and bis(2-methoxyethyl) ether (diglyme, 75 ml), and the mixture was filtered, forming an orange solution. Each of the following compounds (5–10 mg) was dissolved in an aliquot (5 ml) of the orange solution, and the immediately observed color change was noted: **2a–c**, brown; **2d–h**, no change.

**2,5-Bis(3-methylindol-2-yl)-*p*-benzoquinone (3).**—Compound **2a** (0.50 g, 0.00136 mole) was stirred with aqueous 6% sodium hydroxide (50 ml) in the presence of air for 16 hr. The now black precipitate (0.45 g, 90%), mp 230–240° dec, was filtered, washed with water, dried, and recrystallized twice from nitrobenzene, giving very deep violet plates: mp 238–243° dec; $\lambda_{max}$ in tetrahydrofuran 251 mμ (log ε 4.60), 324 (4.37), and 449 (4.04); $\nu_{NH}^{Nujol}$ 3360 mw, $\nu_{C=O}^{Nujol}$ 1607 s, $\nu_{C=C}^{Nujol}$ 1614 m, and 1557 s cm$^{-1}$.

*Anal.* Calcd for $C_{24}H_{18}N_2O_2$ (366.40): C, 78.67; H, 4.95; N, 7.65. Found: C, 78.14; H, 5.25; N, 7.28.

The ultraviolet and visible maxima reported above were determined within 1 hr of preparation of the solution. The spectrum of the tetrahydrofuran solution changed at room temperature with time, more rapidly in the presence of light. One sample of the solution was kept in a dark cupboard for 2 days, giving $\lambda_{max}$ 251 mμ (log ε 4.50), 324 (4.32), and 450 (4.03). Another sample of the solution was kept in laboratory daylight for 2 days, giving $\lambda_{max}$ 251 mμ (log ε 4.42), 306 (4.23), 324 (4.24), and 450 (3.99).

**2,5-Bis(2-methylindol-3-yl)-*p*-benzoquinone (6).**—In our hands, the procedure of Bu'lock and Harley-Mason,[3] involving refluxing for 5 hr, gave no precipitate upon cooling. Consequently, in the present work the reaction was carried out at room temperature.

When 2-methylindole[58] (22.5 g, 0.171 mole) and *p*-benzoquinone (15.0 g, 0.139 mole) were dissolved in glacial acetic acid (450 ml), a violet mixture formed almost instantly. After 16 hr, the violet precipitate was filtered and washed with ethanol until the washings were almost colorless. [The violet filtrate is assumed to contain (2-methylindol-3-yl)-*p*-benzoquinone,[2,3] probably the major product of the reaction.] The precipitate was then extracted with boiling nitrobenzene (200 ml) and washed with ethanol, leaving a brown powder (2.83 g, 17%), mp 338–341°. Two crystallizations from a large amount of nitrobenzene gave a brown powder: mp 308–312°; lit.[3] mp 294–296°; $\lambda_{max}$ in tetrahydrofuran 230 mμ (log ε 4.82), 281 (4.57), 289 infl (4.53), and 500 (3.99); lit.[3] $\lambda_{max}$ in acetone 498 mμ (log ε 3.82); $\nu_{NH}^{Nujol}$ 3310 s, $\nu_{C=O}^{Nujol}$ 1629 s, $\nu_{C=C}^{Nujol}$ 1616 mw, and 1565 vs cm$^{-1}$.

*Anal.* Calcd for $C_{24}H_{18}N_2O_2$ (366.40): C, 78.67; H, 4.95; N, 7.65. Found: C, 78.15; H, 5.18; N, 7.71.

The ultraviolet and visible maxima reported above were determined within 1 hr of preparation of the solution. The spectrum of the tetrahydrofuran solution changed at room temperature with time, more rapidly in the presence of light. One sample of the solution was kept in a dark cupboard for 2 days, giving $\lambda_{max}$ 230 mμ (log ε 4.70), 280 (4.56), 289 infl (4.52), and 500 (3.96). Another sample of the solution was kept in laboratory daylight for days, giving $\lambda_{max}$ 230 mμ (log ε 4.63), 280 (4.50), 289 infl (4.46), and 487 (3.82).

**2,5-Bis(2-methylindol-3-yl)hydroquinone (7a).**—A mixture of 2,5-bis(2-methylindol-3-yl)-*p*-benzoquinone (**6**, 1.00 g, 0.00273 mole) and sodium hydrosulfite dihydrate (5.00 g, 0.0238 mole) in aqueous 30% ethanol (80 ml) was warmed on a steam bath for 15 min, with occasional shaking. The mixture was cooled and water (350 ml) was added, giving a gray precipitate (0.86 g, 85%), mp 276–281° dec. Two sublimations, at 290–300 (0.03 mm) and 308° (0.08 mm), gave a white solid: mp 285–290° dec; $\nu_{OH}^{Nujol}$ 3460 m, $\nu_{NH}^{Nujol}$ 3330 ms, $\nu_{C=C}^{Nujol}$ 1618 mw, and 1568 m cm$^{-1}$.

*Anal.* Calcd for $C_{24}H_{20}N_2O_2$ (368.42): C, 78.24; H, 5.47; N, 7.60. Found: C, 78.03; H, 5.68; N, 7.73.

**O,O′-Diacetyl Derivative 7b of 7a.**—A solution of 2,5-bis(2-methylindol-3-yl)hydroquinone (**7a**, 0.21 g, 0.00057 mole) in acetic anhydride (10 ml, 0.11 mole) was refluxed for 1 hr. The solution was cooled and water (40 ml) was added to hydrolyze the excess acetic anhydride, giving a light blue precipitate (0.21 g, 81%), mp 287–299°. Sublimation at 285° (0.04 mm), crystallization from acetone–water, and resublimation at 300° (0.05 mm) gave a white solid: mp 306–309°; $\nu_{NH}^{Nujol}$ 3310 ms, $\nu_{C=O}^{Nujol}$ 1742 s, $\nu_{C=C}^{Nujol}$ 1621 mw, and 1566 m cm$^{-1}$.

*Anal.* Calcd for $C_{28}H_{24}N_2O_4$ (452.49): C, 74.32; H, 5.35; N, 6.19. Found: C, 74.21; H, 5.58; N, 6.38.

**N,N′,O,O′-Tetramethyl Derivative 7c of 7a.**—Methyl iodide (5.0 ml, 0.080 mole) and then potassium hydroxide (2.00 g, 0.356 mole) were added to a solution of 2,5-bis(2-methylindol-3-yl)hydroquinone (**7a**, 0.95 g, 0.00258 mole) in acetone (about 200 ml; dried over anhydrous potassium carbonate) under 1 atm of dry nitrogen. The mixture was refluxed under nitrogen for 3 hr, and then the excess methyl iodide and acetone were evaporated on a steam bath in a stream of air. The residue was washed well with water, giving a tan solid (0.94 g, 86%), mp 281–293°. Two sublimations, at 240–260° (0.35 mm) and 270° (0.35 mm), gave a white solid: mp 294–300°; $\nu_{NH}^{Nujol}$ none, $\nu_{C=C}^{Nujol}$ 1607 m, and 1563 m cm$^{-1}$.

*Anal.* Calcd for $C_{28}H_{28}N_2O_2$ (424.52): C, 79.21; H, 6.65; N, 6.60. Found: C, 79.28; H, 6.49; N, 6.30.

**Attempted Preparation of the Dimethiodide of 7c.**—Compound **7c** (0.50 g, 0.0012 mole) was dissolved in warm N,N-dimethylformamide (135 ml), methyl iodide (10 ml, 0.16 mole) was added, and the solution was refluxed for 24 hr. The excess methyl iodide was evaporated on a steam bath and water was added to the residual solution. The resulting yellow precipitate (0.47 g, 94% recovery), mp 273–299°, was washed with water and sublimed at 260° (0.25 mm), giving a white solid, mp 296–301°, having an infrared spectrum in Nujol identical with that of the starting material.

**Total Synthesis of the O,O′-Dimethyl Derivative 2g of 2a. 2,5-Dimethoxyterephthalonitrile (10).**—The preparation was carried out essentially according to the procedure of Friedman and Schechter[18] for the conversion of 1-bromonaphthalene to 1-naphthonitrile. 1,4-Dibromo-2,5-dimethoxybenzene[17] (**9**, 75.4 g, 0.255 mole; prepared in 40% yield, mp 143–145°; lit.[17] mp 142°) was dissolved in warm N,N-dimethylformamide (200 ml), cuprous cyanide [47.5 g, 0.265 mole as $Cu_2(CN)_2$] was added, and the mixture was refluxed for 4.5 hr. The green mixture was cooled, poured into a solution of ferric chloride hexahydrate (120 g) in 1.6 *N* hydrochloric acid (230 ml), and warmed at 60–65° on a steam bath for 15 min. The mixture was cooled and the tan precipitate was filtered, washed with 20% (by volume) ammonium hydroxide solution (500 ml) and then with water, and crystallized from dioxane, giving light tan crystals (27.5 g, 57%), mp 298–305°. Two more crystallizations from dioxane gave white crystals: mp 299–304°; lit.[18a] yellow crystals, mp 296–299° dec; $\lambda_{max}^{95\%\ EtOH}$ 222 mμ (log ε 4.54), 240 infl (4.04), 245 (4.10), 252 (4.20), and 355 (3.85); $\nu_{C\equiv N}^{Nujol}$ 2220 m cm$^{-1}$; lit.[18a] $\nu_{C\equiv N}^{Nujol}$ 2235 cm$^{-1}$.

*Anal.* Calcd for $C_{10}H_8N_2O_2$ (188.18): C, 63.82; H, 4.29; N, 14.89. Found: C, 63.61; H, 4.50; N, 14.96.

**Hydrolysis of 10 to 2,5-Dimethoxyterephthalic Acid (11).**—A mixture of 2,5-dimethoxyterephthalonitrile (**10**, 0.12 g, 0.00064 mole) in aqueous 50% ethanol (20 ml) containing potassium hydroxide (2.00 g, 0.0356 mole) was refluxed for 24 hr. Solution occurred after 1.5 hr. The solution was cooled (and one-half was accidentally lost at this point) and the ethanol was evaporated in a rotary evaporator. The residual solution was acidified to congo red with concentrated hydrochloric acid, giving a tan

(58) C. F. H. Allen and J. A. Van Allan, "Organic Syntheses," Coll. Vol. 3, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p 597; *Org. Syn.*, **22**, 94 (1942).

precipitate (0.04 g, 28%), mp 255–258°. Sublimation at 235° (0.25 mm) gave a very light yellow solid, which became white upon heating on the hot stage, mp 262–265°, lit. mp 265[19a] and 263–265°,[19b] $\nu_{OH}^{Nujol}$ 3210 ms, and $\nu_{C=O}^{Nujol}$ 1724 s cm$^{-1}$.

**2,5-Dimethoxy-1,4-dipropionylbenzene (12).**—A slurry of 2,5-dimethoxyterephthalonitrile (**10**, 3.00 g, 0.0159 mole) in anhydrous benzene (200 ml) was added all at once to a solution of ethylmagnesium bromide (0.092 mole, from ethyl bromide, 1.00 g, 0.092 mole, and magnesium turnings, 2.90 g, 0.119 g-atom) in anhydrous ether (100 ml). The ether was removed by distillation and the mixture was refluxed for 18 hr. The brown mixture was then poured onto a mixture of ice (200 g) and concentrated hydrochloric acid (100 ml). The water layer, containing the ketimine hydrochloride, was refluxed for 6 hr to hydrolyze the ketimine. The resulting yellow mixture was then cooled, filtered, and washed with water, giving a solid (2.75 g, 69%), mp 128–131°. Sublimation at 110–120° (0.2 mm) gave a yellow solid: mp 136–138°; $\lambda_{max}^{95\%\ EtOH}$ 224 mμ (log ε 4.05), 260 (3.99), and 355 (3.60); $\nu_{C=O}^{Nujol}$ 1670 s cm$^{-1}$.

*Anal.* Calcd for $C_{14}H_{18}O_4$ (250.28): C, 67.18; H, 7.25. Found: C, 67.51; H, 7.29.

**Diphenylhydrazone of 12. 2,5-Dimethoxy-1,4-dipropionylbenzene Bisphenylhydrazone (13).**—A solution of phenylhydrazine (1.00 g, 0.00925 mole) in ethanol (15 ml) and glacial acetic acid (5 ml) were added to a solution of 2,5-dimethoxy-1,4-dipropionylbenzene (**12**, 1.00 g, 0.00400 mole) in boiling ethanol (25 ml). The solution was refluxed for 20 min and then cooled. Water was added to the point of cloudiness, and the solution was heated to boiling and cooled, giving yellow crystals (0.75 g), mp 147–152°. Concentration of the mother liquor gave a second crop as a pale orange-brown solid (0.48 g, 48% recovery), mp 68–79°, shown by its infrared spectrum in Nujol to be largely the ketone starting material, and a third crop as a pale orange-brown solid (0.15 g), mp 81–90°, shown by its infrared spectrum to be mostly the diphenylhydrazone product (total 0.90 g, 52%). Three recrystallizations of the first crop from methanol gave light yellow crystals, mp 153–154°, $\lambda_{max}^{95\%\ EtOH}$ 267 mμ (log ε 4.83) and 297 mμ (log ε 4.52), $\nu_{NH}^{Nujol}$ 3300 mw cm$^{-1}$ and $\nu_{C=C}^{Nujol}$ 1602 s cm$^{-1}$.

*Anal.* Calcd for $C_{26}H_{30}N_4O_2$ (430.53): C, 72.53; H, 7.02; N, 13.01. Found: C, 72.36; H, 6.93; N, 13.23.

**2,5-Bis(3-methylindol-2-yl)-1,4-dimethoxybenzene (2g). The O,O′-Dimethyl Derivative of 2a.**—A solution of 2,5-dimethoxy-1,4-dipropionylbenzene bisphenylhydrazone (**13**, 0.35 g, 0.00081 mole) in polyphosphoric acid (15.0 g) was heated with stirring at an oil bath temperature of 170° for 20 min. The red solution was poured into water (100 ml) and the mixture was stirred to dissolve the polyphosphoric acid. The resulting red precipitate was dissolved in hot ethanol (40 ml), small amounts of sodium bicarbonate were added until a yellow mixture resulted, and water (100 ml) was added. The resulting yellow precipitate (0.21 g, 65%), mp 217–230°, was sublimed at 235–240° (0.20 mm), giving a light yellow solid, mp 247–249°, $\nu_{NH}^{Nujol}$ 3420 mw cm$^{-1}$ and $\nu_{C=O}^{Nujol}$ 1568 mw cm$^{-1}$. There was no depression in mmp 247–249°, with a sample of mp 247–249° prepared by dimethylation of **2a**, but the infrared spectra in Nujol contained differences in the fingerprint region, particularly from 900 to 700 cm$^{-1}$, attributed to dimorphism. Crystallization of the sublimed sample from acetone–water, the solvent medium used for crystallization of the dimethylation product, gave a sample, mp 244–246°, having an infrared spectrum in Nujol identical with that of the dimethylation product of **2a**.

**Hydrogenolysis Products 14a, 14b of 1a and Their Derivatives. Hydrogenolysis of 1a to 2,5-Bis(3-methylindolin-3-yl)hydroquinone (14a). A. In N,N-Dimethylformamide.**—Compound **1a** (5.00 g, 0.0136 mole) was dissolved in warm N,N-dimethylformamide (250 ml). The solution was cooled, Raney nickel (1 teaspoonful) which had been washed free of ethanol with N,N-dimethylformamide was added, and the mixture was hydrogenated at 30 psi for 2 days. The catalyst was removed by filtration and the filtrate was diluted with water (1 l.), giving a white precipitate, which was washed with hot water (4.13 g, 81%): mp 234–237° (dissociates); $\nu_{NH}^{Nujol}$ 3390 m, $\nu_{OH}^{Nujol}$ br, $\nu_{C=O}^{Nujol}$ 1668 s (N,N-dimethylformamide), $\nu_{C=C}^{Nujol}$ 1611 ms cm$^{-1}$. A portion of this crude white precipitate was crystallized six times from pyridine–water, giving white crystals, mp 249.5–251° (dissociates). The sample was dried under vacuum at room temperature (to avoid dissociation) for 24 hr, but the odor of pyridine was still apparent.

*Anal.* Calcd for $C_{24}H_{24}N_2O_2$ (372.45): C, 77.39; H, 6.50; N, 7.52. Found: C, 77.14; H, 6.60; N, 8.26, 8.75, 9.58.

Another portion of the crude white precipitate was crystallized three times from pyridine–water, giving white crystals, mp 257–259° (dissociates). The sample was dried under vacuum at room temperature for 24 hr, but again the odor of pyridine was still apparent.

*Anal.* Found: C, 77.92; H, 6.88; N, 9.70, 9.74.

The following additional attempts were made to obtain a pure sample. In each case, the sample was dried under vacuum at room temperature (to avoid dissociation) for 24 hr before analysis. (1) Another portion of the crude white precipitate was crystallized four times from acetonitrile, giving white crystals, mp 259–261° (dissociates).

*Anal.* C, 74.30; H, 6.41; N, 10.64.

(2) The white precipitate from another run (89% yield) was crystallized four times from chlorobenzene, giving white crystals: mp 243.5–246° (dissociates); $\lambda_{max}^{95\%\ EtOH}$ (sample does not wholly obey Beer's Law) $c = 3.28 \times 10^{-5}$ *M*, 238 mμ (log ε 4.13) and 297 mμ (log ε 3.92); $c = 1.31 \times 10^{-5}$ *M*, 227 mμ infl (log ε 4.07), 237 infl (4.03), and 297 (3.80); $\nu_{NH}^{Nujol}$ 3350 ms, $\nu_{OH}^{Nujol}$ ~2620 m, and $\nu_{C=C}^{Nujol}$ 1599 ms cm$^{-1}$.

*Anal.* Found: C, 78.41; H, 6.38; N, 6.70.

(3) The white precipitate from another run was crystallized twice from *o*-dichlorobenzene, giving white crystals, mp 229–232° (dissociates).

*Anal.* Found: C, 76.35; H, 6.53; N, 6.87.

(4) The white precipitate from another run (87% yield) was crystallized five times from 1,2,4-trichlorobenzene, giving white crystals: mp 248–250° (dissociates); $\lambda_{max}^{95\%\ EtOH}$ (sample does not wholly obey Beer's Law) $c = 2.64 \times 10^{-5}$ *M*, 232 mμ (log ε 4.15), 242 infl (4.09), 296 (3.95); $c = 1.32 \times 10^{-5}$ *M*, 238 mμ (log ε 4.13) and 296 mμ (log ε 3.91); $\nu_{NH}^{Nujol}$ 3350 m, $\nu_{OH}^{Nujol}$ 2680 m, and $\nu_{C=C}^{Nujol}$ 1599 ms cm$^{-1}$.

*Anal.* Found: C, 75.49; H, 6.73; N, 6.90.

**B. In Dioxane.**—Compound **1a** (3.00 g, 0.00814 mole) was suspended in anhydrous dioxane (200 ml). Raney nickel (1 teaspoonful) which had been washed free of ethanol with dioxane was added, and the mixture was hydrogenated at 56° and 30 psi for 24 hr. The catalyst was removed by filtration and the volume of the solution was reduced to about 30 ml in a rotary evaporator under aspirator pressure. The resulting yellow solution was diluted with water (100 ml), giving a pink precipitate (2.74 g, 90%): mp 239–243° (dissociates); $\nu_{OH}^{Nujol}$ 3350 m, $\nu_{NH}^{Nujol}$ 3400 m and 3240 m, and $\nu_{C=C}^{Nujol}$ 1606 ms cm$^{-1}$. Four crystallizations from 1,2,4-trichlorobenzene gave white crystals: mp 253–254° (dissociates); $\lambda_{max}^{95\%\ EtOH}$ $c = 5.58 \times 10^{-5}$ *M*, 296 mμ (log ε 3.88); $c = 2.23 \times 10^{-5}$ *M*, 243 mμ (log ε 4.27) and 297 mμ (log ε 3.88).

*Anal.* Calcd for $C_{24}H_{24}N_2O_2$ (372.45): C, 77.39; H, 6.50; N, 7.52. Found: C, 76.70; H, 6.37; N, 6.29.

**The N,N′-Diethyl Derivative of 14a. 2,5-Bis(1-ethyl-3-methylindolin-3-yl)hydroquinone (14b). A. From Hydrogenolysis of 1a with Raney Nickel in Ethanol.**—A mixture of **1a** (1.00 g, 0.00271 mole) in absolute ethanol (100 ml) was stirred with Raney nickel (3 teaspoonfuls) at 70° for 6 hr. The Raney nickel was removed by filtration and washed with absolute ethanol. The filtrate and washings were diluted with water (300 ml), giving a white precipitate (0.86 g, 74%), mp 219–223°. Six crystallizations from ethanol gave a white solid: mp 230–231°; $\nu_{NH}$ 3400 vw, $\nu_{OH}$ 2680 m and 2590 mw, and $\nu_{C=C}$ 1601 ms cm$^{-1}$ in halocarbon oil–Nujol.

*Anal.* Calcd for $C_{28}H_{32}N_2O_2$ (428.55): C, 78.47; H, 7.53; N, 6.54. Found: C, 78.74; H, 7.72; N, 6.60.

**B. From Reduction of the N,N′,O,O′-Tetraacetyl Derivative 14d of 14a with Lithium Aluminum Hydride.**—A mixture of 2,5-bis(1-acetyl-3-methylindolin-3-yl)hydroquinone diacetate (**14d**, 1.50 g, 0.00277 mole) and lithium aluminum hydride (3.00 g, 0.079 mole) in anhydrous dioxane was refluxed for 2.5 days. The excess lithium aluminum hydride was decomposed by addition of small amounts of acetone and water, the precipitated aluminum salts were filtered, and the filtrate was evaporated to dryness in a rotary evaporator. The solid residue was crystallized from ethanol containing a little sodium hydrosulfite dihydrate, giving white crystals (0.35 g, 30%), mp 224–228°. Three recrystallizations from ethanol gave white crystals, mp 231–233°. There was no depression in mmp 232–233° with a sample of mp 232–233° prepared by hydrogenolysis of **1a** with Raney nickel in ethanol, and the infrared spectra in Nujol were identical.

**O,O′-Diacetyl Derivative of 14b. 2,5-Bis(1-ethyl-3-methylindolin-3-yl)hydroquinone Diacetate (14c). A. From Acetylation of 14b.**—A solution of 2,5-bis (1-ethyl-3-methylindolin-3-yl)-hydroquinone (**14b**, 2.00 g, 0.00467 mole) in acetic anhydride

(50 ml, 0.53 mole) was refluxed for 1.5 hr. The solution was evaporated in a rotary evaporator at aspirator pressure, leaving a yellow solid (2.33 g, 97%), mp 162–197°. Sublimation at about 180° (about 0.05 mm) and two crystallizations from acetone gave a white solid: mp 202–204°; $\nu_{OH,NH}^{Nujol}$ none, $\nu_{C=O}^{Nujol}$ 1760 s, and $\nu_{C=C}^{Nujol}$ 1607 ms cm$^{-1}$.

*Anal.* Calcd for $C_{32}H_{36}N_2O_4$ (512.62): C, 74.97; H, 7.08; N, 5.46. Found: C, 75.33; H, 7.09; N, 5.51.

**B. From Acetylation (with Concurrent Demethylation) of 19.**—A solution of 2,5-bis(1-ethyl-1,3-dimethylindolinio-3-yl)-hydroquinone inner double salt (**19**, 0.45 g, 0.000986 mole) in acetic anhyride (10 ml, 0.11 mole) was refluxed for 2 hr. The brown solution was poured into water to hydrolyze the excess acetic anhydride. The resulting tan precipitate (0.41 g, 81%), mp 193–196°, was sublimed under vacuum and then crystallized from acetone–water, giving white crystals, mp 198–202°. There was no depression in mmp 202.5–205° with a sample of mp 205.5–206.5° prepared by acetylation of **14b**, and the infrared spectra in Nujol were identical.

*Anal.* Found: C, 74.94; H, 7.17; N, 5.44.

**N,N′,O,O′-Tetraacetyl Derivative of 14a. 2,5-Bis(1-acetyl-3-methylindolin-3-yl)hydroquinone Diacetate (14d). A. From 14a Prepared in N,N-Dimethylformamide.**—A solution of 2,5-bis(3-methylindolin-3-yl)hydroquinone (**14a**, prepared in N,N-dimethylformamide, 1.50 g, 0.00403 mole) in acetic anhydride (50 ml, 0.53 mole) and pyridine (50 ml) was refluxed for 3 hr. The hot solution was poured into water, with stirring, and after a few minutes the cream precipitate was filtered (1.99 g, 91%), mp 309–320°. Sublimation under vacuum gave a white solid: mp 314–317°; $\nu_{OH,NH}^{Nujol}$ none, $\nu_{C=O}^{Nujol}$ 1765 s and 1665 s, and $\nu_{C=C}^{Nujol}$ 1604 m cm$^{-1}$.

*Anal.* Calcd for $C_{32}H_{32}N_2O_6$ (540.59); C, 71.09; H, 5.97; N, 5.18. Found: C, 71.66; H, 6.07; N, 5.24.

**B. From 14a Prepared in Dioxane.**—A solution of 2,5-bis(3-methylindolin-3-yl)hydroquinone (**14a**, prepared in dioxane, 0.90 g, 0.0042 mole) in acetic anhydride (50 ml, 0.53 mole) and pyridine (50 ml) was refluxed for 3 hr. The solution was cooled and water (250 ml) was added to hydrolyze the excess acetic anhydride, giving a tan precipitate (0.77 g, 59%), mp 314–321° uncor. Sublimation at 300° (0.02 mm) and crystallization from chlorobenzene gave white crystals: mp 318–322°; $\nu_{OH,NH}^{Nujol}$ none, $\nu_{C=O}^{Nujol}$ 1770 s and 1672 s, and $\nu_{C=C}^{Nujol}$ 1607 mw cm$^{-1}$. There was no depression in mmp 315–317° with the sample obtained by acetylation of **14a** prepared in N,N-dimethylformamide, and the infrared spectra in Nujol were identical.

*Anal.* Found: C, 70.88; H, 5.96; N, 5.41, 5.35.

**Attempted Hydrogenolysis of 1d in N,N-Dimethylformamide.**—Compound **1d** (1.00 g) was dissolved in warm N,N-dimethylformamide (30 ml). The solution was cooled, Raney nickel (1 teaspoonful) which had been washed free of ethanol with N,N-dimethylformamide was added, and the mixture was hydrogenated at 30 psi for 3 days. The catalyst (which was still pyrophoric) was removed by filtration and washed with ethanol. The filtrate and washes were diluted with water, giving a white precipitate (0.75 g, 75% recovery), mp 342–345° dec (sealed capillary), having an infrared spectrum in Nujol essentially identical with that of the starting material.

**Ethylation of 1a to $C_{30}H_{28}N_2O_2$? (15).**—A mixture of **1a** (3.00 g, 0.00814 mole), ethyl bromide (3.49 g, 0.0320 mole), and potassium carbonate (10 g, 0.072 mole) in N,N-dimethylformamide (50 ml) and ether (30 ml) was refluxed for 3 hr. The mixture was diluted with water (400 ml), giving a tan precipitate (3.87 g, 93%), mp 324–330° uncor. Five crystallizations from methylene chloride–petroleum ether (bp 60–68°) gave white crystals: mp 335–337° uncor; $\nu_{OH,NH}^{Nujol}$ none, $\nu_{C=O}^{Nujol}$ 1712 s, and $\nu_{C=C}^{Nujol}$ 1605 m cm$^{-1}$.

*Anal.* Calcd for $C_{30}H_{28}N_2O_6$ (512.34): C, 70.30; H, 5.51; N, 5.47. Found: C, 69.61; H, 5.46; N, 45.8.

**Thermal Dissociation of 2,5-Bis(3-methylindolin-3-yl)hydroquinone (14a). A. To Skatole and (3-Methylindolin-3-yl)hydroquinone (16).**—Attempted sublimation of 2,5-bis(3-methylindolin-3-yl)hydroquinone (**14a**) below its melting point, at about 240° (0.03 mm) gave two bands of sublimate: an upper, more volatile component as a white solid (**skatole**), mp 93–94° (lit.[59] mp 95°); and a lower, less volatile component, also a white solid, which appears to be (**3-methylindolin-3-yl)hydroquinone (16)**: mp 225–226°; $\lambda_{max}^{95\% EtOH}$ (sample does not wholly obey Beer's Law) $c = 5.62 \times 10^{-5}$ *M*, 228 mμ infl (log ε 3.95) and 295 mμ (log ε 3.78); $c = 2.25 \times 10^{-5}$ *M*, 228 mμ infl (log ε 3.91), 235 infl (3.89), and 295 (3.71); $\nu_{NH}^{Nujol}$ 3300 s, $\nu_{OH}^{Nujol}$ 2690 mw and 2630 mw, and $\nu_{C=C}^{Nujol}$ 1600 m cm$^{-1}$.

*Anal.* Calcd for $C_{15}H_{15}NO_2$ (241.28): C, 74.66; H, 6.27; N, 5.81. Found: C, 75.22; H, 6.28; N, 5.82.

**B. To Skatole and Hydroquinone.**—2,5-Bis(3-methylindolin-3-yl)hydroquinone (**14a**, 2.00 g, 0.00537 mole) was heated under dry nitrogen in a dry flask immersed in a Wood's metal bath at 260–280° for 45 min. The cooled brown solid residue was sublimed at 70–80° (0.2 mm), giving **skatole** (1.20 g, 85%), mp 94.5–95.5°, mmp 95.5–96.5° with an authentic sample (Eastman Kodak Co.) of mp 95.5–96.5°. Further sublimation of the residue at 160° (0.2 mm) gave a white solid (0.20 g), mp 170–172°, and a darker band (0.25 g), mp 168–171° (total 0.45 g, 76%). Resublimation of the combined bands at 140° (0.2 mm) gave *hydroquinone* as a white solid, mp 170–172° (lit.,[60] from sublimation, γ form, mp 169°), mmp 170–174° with an authentic sample (Eastman Kodak Co., presumably the α form recrystallized from water, lit. mp 170°,[61] 172.3°[62]) of mp 173–175°.

**Thermal Dissociation of 2,5-Bis(1-ethyl-3-methylindolin-3-yl)-hydroquinone (14b). A. To 1-Ethyl-3-methylindole (17) and Hydroquinone.**—2,5-Bis(1-ethyl-3-methylindolin-3-yl)hydroquinone (**14b**, 2.00 g, 0.00467 mole) was heated above its melting point in a dry flask immersed in a Wood's metal bath at 270–295° for 1.25 hr. The cooled glassy solid was dissolved in ether and extracted with an aqueous solution (2 × 50 ml) containing sodium hydroxide (1.9% by weight) and sodium hydrosulfite dihydrate (1.9% by weight). Evaporation of the ether layer in a rotary evaporator left **1-ethyl-3-methylindole** as a light yellow oil (1.21 g, 81%). Distillation gave a colorless oil, bp 70° (0.2 mm), $n^{41}$D 1.5718, $\nu_{NH}$ none. The infrared spectrum of the oil was identical with that of the sample prepared by ethylation of skatole, except for the NH band in the spectrum of the latter, and the ultraviolet spectra in 95% ethanol were identical.

The alkaline aqueous layer was made acidic to congo red with dilute hydrochloric acid and extracted with ether. Evaporation of the ether left a brown solid (0.32 g, 62%), mp 84–155°. Two sublimations at 120° (0.2 mm) gave **hydroquinone** as a white solid, mp 172–174°, mmp 173–175° with an authentic sample (Eastman Kodak Co.) of mp 173–175°.

**Synthesis of 1-Ethyl-3-methylindole (17) by Ethylation of Skatole.**—The procedure is essentially that of Potts and Saxton[51] for methylation of indole to 1-methylindole. Sodium (5.00 g, 0.217 g-atom) and a few crystals of ferric nitrate nonahydrate were dissolved, with stirring, in anhydrous liquid ammonia (500 ml). A solution of skatole (25.0 g, 0.191 mole) in anhydrous ether (100 ml) was added, followed by a solution of ethyl bromide (24.0 g, 0.220 mole) in anhydrous ether (50 ml). The ammonia was allowed to evaporate overnight, and the solid residue was treated with water (100 ml) and ether (100 ml). Evaporation of the ether layer in a rotary evaporator and distillation of the residual yellow oil gave a yellow oil (24.3 g, 80%), bp 63–65° (0.13–0.16 mm), $n^{27}$D 1.5821, $\nu_{NH}$ 3380 ms cm$^{-1}$ (attributed to unreacted skatole). A portion of the unreacted skatole shown to be present by the infrared spectrum was removed by a procedure similar to that of Noland, Kuryla, and Lange[63] for purification of 1-methylindole. The yellow oil was heated with sodium at 110–120° for 8 hr and the resulting brown semisolid was distilled directly, giving a colorless oil, bp 67–70° (0.20–0.25 mm), $n^{33}$D 1.5762, $\nu_{NH}$ 3380 m cm$^{-1}$ (32% reduction in intensity), having an infrared spectrum identical with that of the colorless oil obtained by redistillation: bp 60.5–62.5° (0.17–0.20 mm), $n^{27.5}$D 1.5802, $\nu_{NH}$ 3420 m and $\nu_{C=C}$ 1617 m cm$^{-1}$. A red picrate formed in methanol solution, but decomposed during attempted vacuum drying at room temperature.

*Anal.* Calcd for $C_{11}H_{13}N$ (159.22): C, 82.97; H, 8.23; N, 8.80. Found: C, 82.77; H, 8.50; N, 9.01.

**Dimethiodide of 14b. 3,3′-(2,5-Dihydroxy-*p*-phenylene)bis(1,3-dimethyl-1-ethylindolinium) Diiodide (18).**—2,5-Bis(1-ethyl-3-methylindolin-3-yl)hydroquinone (**14b**, 2.35 g, 0.00548 mole) was dissolved in warm anhydrous benzene (200 ml) and methyl iodide (15 ml, 0.24 mole) was added. The solution, which became a mixture after about 2 hr, was refluxed for 24 hr and then cooled. The resulting light yellow precipitate (3.37 g, 86%), mp 182–185° dec, was crystallized twice from methanol, giving

(59) E. Fischer, *Ann. Chem.*, **236**, 116 (1886).

(60) W. A. Caspari, *J. Chem. Soc.*, 1093 (1927).

(61) P. Senden, *Bull. Soc. Chim. Belges*, **32**, 97 (1923).

(62) D. H. Andrews, G. Lynn, and J. Johnston, *J. Am. Chem. Soc.*, **48**, 1274 (1926).

(63) W. E. Noland, W. C. Kuryla, and R. F. Lange, *ibid.*, **81**, 6015 (1959).

white crystals: mp 187–189° dec; $\nu_{OH}^{Nujol}$ 3370 m infl, 3130 s, and 2690 w, and $\nu_{C=C}^{Nujol}$ 1602 m cm$^{-1}$.

*Anal.* Calcd for $C_{30}H_{38}N_2O_2I_2$ (712.46): C, 50.57; H, 5.38; N, 3.93. Found: C, 51.13, 50.95; H, 5.50, 5.77; N, 3.91, 4.08.

**Attempted Emde Reduction of 18. 2,5-Bis(1-ethyl-1,3-dimethylindolinio-3-yl)hydroquinone Inner Double Salt (19).**—This reaction was carried out essentially under the conditions used by Sugasawa and Matsuo[22] for the Emde reduction of benzyltrimethylammonium iodide. The dimethiodide of **14b** (**18**, 1.00 g, 0.00140 mole) was dissolved in ethanol (50 ml) and aqueous 10% sodium hydroxide (50 ml) was added, giving a yellow-orange solution. Raney nickel (1 teaspoonful) was added and the mixture was hydrogenated at 32 psi for 28 hr. The white precipitate and most of the solution were decanted, the residue was extracted with hot ethanol, and the Raney nickel was removed by filtration. The decantate and filtrate were combined, water (250 ml) was added, and the ethanol was evaporated in a rotary evaporator. The resulting white precipitate (0.53 g, 83%), mp 156–161°, was crystallized twice from ethanol, giving white crystals: mp 180–181°; $\nu_{OH}^{Nujol}$ none, $\nu_{CH}^{Nujol}$ 2760 m, and $\nu_{C=C}^{Nujol}$ 1595 mw and 1574 mw cm$^{-1}$.

*Anal.* Calcd for $C_{30}H_{36}N_2O_2$ (456.60): C, 78.91; H, 7.95; N, 6.14. Found: C, 79.41; H, 7.82; N, 5.86.

**Attempted Total Synthesis of the O,O'-Dimethyl Derivative of the Hydrogenolysis Product 14a of 1a. 1,4-Diacetyl-2,5-dimethoxybenzene (20).**—A slurry of 2,5-dimethoxyterephthalonitrile (for preparation, see earlier in the Experimental Section; 20.0 g, 0.106 mole) in anhydrous benzene (600 ml) was added all at once to a solution of methylmagnesium iodide [prepared from methyl iodide (60.2 g, 0.424 mole) and magnesium turnings (11.0 g, 0.452 g-atom)] in anhydrous ether (200 ml). The resulting red slurry was hydrolyzed with water (1 l.) and the aqueous layer, containing the water-soluble ketimine hydrochloride, was separated. The benzene layer was extracted with water (500 ml) and the combined aqueous layers were heated just to boiling for 30 min to hydrolyze the ketimine hydrochloride. The resulting mixture was cooled, giving a yellow precipitate (14.7 g, 63%), mp 114–117°. Two crystallizations from ethanol–water gave light yellow needles, which changed to yellow crystals on the hot stage at about 120°: mp 136–137°; $\lambda_{max}^{95\% EtOH}$ 225 mμ (log ε 4.25), 261 (4.00), and 363 (3.59); $\nu_{C=O}^{Nujol}$ 1666 s cm$^{-1}$.

*Anal.* Calcd for $C_{12}H_{14}O_4$ (222.23): C, 64.85; H, 6.35. Found: C, 64.70; H, 6.49.

**2,2'-(2,5-Dimethoxy-*p*-phenylene)dipropionaldehyde (21). By the Darzens Reaction.**—The general procedure of Johnson, Belew, Chinn, and Hunt[23] for the Darzens reaction was used. 1,4-Diacetyl-2,5-dimethoxybenzene (**20**, 6.00 g, 0.0270 mole) and freshly distilled ethyl chloroacetate (Eastman Kodak Co., 7.62 g, 0.0622 mole) were dissolved in anhydrous benzene (80 ml), and the solution was cooled to ice-bath temperature. A solution of potassium *t*-butoxide (from potassium, 1.58 g, 0.404 g-atom) in anhydrous *t*-butyl alcohol (35 ml) was added slowly, with stirring, over a period of 0.5 hr. The resulting solution was stirred at ice-bath temperature for 1 hr and then at room temperature overnight. The brown solution was then recooled to ice-bath temperature, water (100 ml) was added, and the solution was made just acid to litmus with glacial acetic acid (about 5 ml). The benzene layer was separated and the aqueous layer was extracted with benzene (50 ml). The combined benzene layer and extract were washed with aqueous 5% sodium bicarbonate (50-ml, twice), and dried ($Na_2SO_4$). The benzene was evaporated in a rotary evaporator, leaving the crude bisglycidic ester as a red-brown oil: $\nu_{OH}$ 3350 w and 3470 w (impurity), $\nu_{C\equiv N}$ 2220 mw (contamination from the nitrile precursor of the starting material), $\nu_{C=O}$ 1743 vs, 1725 s, $\nu_{C=C}$ 1617 w, and $\nu_{epoxide}$ 1300 s, 926 mw, and 762 m cm$^{-1}$. A solution of the oil and sodium hydroxide (3.00 g, 0.075 mole) in 95% ethanol (50 ml) was refluxed for 1 hr. The ethanol was then removed in a rotary evaporator, the residual brown solid was dissolved in 2.4 *N* hydrochloric acid (100 ml), and the solution was heated slowly to 85°. Carbon dioxide began to evolve at 40°. After 1.5 hr at 85°, the resulting mixture was cooled and the brown, partially crystalline solid was filtered, washed with water, and dried (5.10 g, 75%). Two sublimations at 70° (0.3 mm) gave a white solid: softens at 71°, mp 78–81°; $\nu_{max}^{95\% EtOH}$ 217 mμ (log ε 4.15), 243 infl (3.59), 253 infl (3.32), 297 (3.51), 321 infl (3.26), and 344 infl (2.93); $\nu_{OH}^{Nujol}$ 3420 mw (slight impurity, probably due to autoxidation), $\nu_{C-CH}^{Nujol}$ 2830 m and 2720 mw, $\nu_{C\equiv N}^{Nujol}$ 2220 mw (contamination from the nitrile precursor of the starting material), $\nu_{C=O}^{Nujol}$ 1717 vs, $\nu_{C=C}^{Nujol}$ 1612 w cm$^{-1}$ on a thin film deposited from chloroform; $\nu_{OH}$ 3400 w (impurity), $\nu_{C-CH}^{Nujol}$ 2830 s (largely obscured by Nujol), 2700 mw, $\nu_{C\equiv N}^{Nujol}$ 2200 mw (impurity), $\nu_{C=O}^{Nujol}$ 1718 s, 1701 s, and $\nu_{C=C}^{Nujol}$ 1602 mw cm$^{-1}$. The nmr spectrum of a 12% (w/v) solution in deuteriochloroform shows (in δ, with areas relative to 16 protons, the two low-field aldehyde protons were missed; 1 ppm = 60.00 cps) the two propionaldehyde methyl groups as a doublet centered at δ 1.40 ($J$ = 6.6 cps, 5.4 protons), an impurity peak at 2.62 (0.7 proton), the two methoxyl groups as a strong singlet at 3.78 (5.1 protons), the two benzyl hydrogens and impurities as a complex peak at 3.91 (2.4 protons), and a peak at 4.08 (0.4 proton), and the two aromatic protons as a sharp peak at 6.70 (1.2 protons) and three very weak peaks (0.8 proton) at 6.76 (0.4), 7.07 (0.2), and 7.36 (0.2). A peak at δ 7.30 (0.3 proton, area not included in the 16) was attributed to $CHCl_3$ in the solvent.

*Anal.* Calcd for $C_{14}H_{18}O_4$ (250.28): C, 67.18; H, 7.25. Found: C, 66.91; H, 7.45.

**Bisphenylhydrazone of 21. 2,2'-(2,5-Dimethoxy-*p*-phenylene)dipropionaldehyde Bisphenylhydrazone (22).**—2,2'-(2,5-Dimethoxy-*p*-phenylene)dipropionaldehyde (**21**, 1.23 g, 0.00490 mole) and phenylhydrazine (1.62 g, 0.0150 mole) were dissolved in anhydrous benzene (100 ml), and glacial acetic acid (4 drops) was added. The solution was refluxed and the water formed as a product was collected in a Barrett receiver. The benzene was removed in a rotary evaporator and the red, semiamorphous residue was triturated with methanol. The residual light red precipitate was filtered, washed with methanol–water, and dried (1.94 g, 92%), mp 87–91°. Three crystallizations from absolute methanol gave white needles: mp 114–116°; $\lambda_{max}^{95\% EtOH}$ 240 mμ (log ε 4.17), 280 (4.53), and 302 infl (4.36); $\nu_{NH}^{Nujol}$ 3330 mw and $\nu_{C=C}^{Nujol}$ 1603 s cm$^{-1}$. The three unsuccessful double Fischer indolenine syntheses[64] attempted with the product are summarized in the Discussion.

*Anal.* Calcd for $C_{26}H_{30}N_4O_2$ (430.53): C, 72.53; H, 7.02; N, 13.01. Found: C, 71.73; H, 6.82; N, 12.89.

**Synthesis of 2,3,4-Trimethylindole. 3-Nitro-*o*-xylene** (with D. G. Weetman, 1963).—Nitration of *o*-xylene at −8 to 0° according to the procedure of Emerson and Smith[65] gave 3-nitro-*o*-xylene (76%): bp 84–89° (0.35 mm), $n^{25}D$ 1.5448, $\nu_{NO_2}$ 1520 s, and 1350 s cm$^{-1}$ neat; lit.[65] 86%, bp 127–130° (18 mm),[65] $n^{25}D$ 1.5416.[66]

**3-Amino-*o*-xylene** (with D. G. Weetman, 1963).—Catalytic hydrogenation of 3-nitro-*o*-xylene at 1200 psi and 125° over Raney nickel according to the procedure of Smith and Opie[67] gave 3-amino-*o*-xylene (88%): bp 74–75° (0.35 mm); $n^{25}D$ 1.5652; $\nu_{NH}$ 3400 ms, 3340 s, and 3200 m cm$^{-1}$ neat; lit.[67] 100%; bp 114 (<19 mm),[67] 106° (15 mm);[68] $n^{25}D$ 1.5655[68] and 1.5658.[69]

**2',3'-Acetoxylidide** (With R. J. Sperley, 1962).—Acetylation of 3-amino-*o*-xylene with acetic anhydride in aqueous suspension by the method of Joffe[70] gave 2',3'-acetoxylidide (49%): mp 134–135°; lit. mp 134,[71] 135.5°.[72]

**2,4-Dimethylindole** (with R. J. Sperley, 1962).—2,4-Dimethylindole has previously been prepared by Marion and Oldfield[72] by the Madelung synthesis, but with potassium *t*-butoxide as the catalyst. The present procedure, with sodamide as the catalyst, is that of Allen and Van Allan[58] for 2-methylindole. 2',3'-Acetoxylidide (71 g, 0.435 mole) and sodamide (45 g, 1.15 mole) were mixed thoroughly under dry nitrogen, anhydrous ether (35 ml) was added, and the mixture was warmed slowly in a Wood's metal bath under a stream of dry nitrogen. When the temperature (temperatures are bath temperatures) reached 160–165°, the mixture melted, becoming a highly viscous brown melt. At 193–195° the mixture solidified to a light tan solid and then remelted at 200° and started to froth. The frothing continued while the temperature was raised slowly to 220°, at which point the frothing reached a maximum. After the frothing subsided, the temperature was raised to 230° without further

(64) Described in detail in ref 1.
(65) O. H. Emerson and L. I. Smith, *J. Am. Chem Soc.*, **62**, 141 (1940).
(66) K. A. Kobe and P. W. Pritchett, *Ind. Eng. Chem.*, **44**, 1398 (1952).
(67) L. I. Smith and J. W. Opie, *J. Org. Chem.*, **6**, 427 (1941).
(68) R. van Helden, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.*, **73**, 39 (1954).
(69) I. Heilbron, J. R. A. Pollock, and R. Stevens, "Dictionary of Organic Compounds," Vol. 2, 4th ed., Oxford University Press, New York, N. Y., 1965, p 1143.
(70) I. S. Joffe, *Zh. Obshch. Khim.*, **14**, 812 (1944); *Chem. Abstr.*, **39**, 3786 (1945).
(71) E. Nölting and S. Forel, *Chem. Ber.*, **18**, 2668 (1885).
(72) L. Marion and C. W. Oldfield. *Can. J. Res.*, **25B**, 1 (1947).

evidence of reaction. After the mixture had cooled to room temperature, ethanol (50 ml) and water (50 ml) were added, and the mixture was boiled gently. It was then cooled and extracted with ether (three 75-ml portions). The ether extracts were concentrated to about 75 ml and vacuum distilled. The distillate (51.2 g, 81% crude), which was collected at 60–110° (1 mm), came over mostly light yellow and finally light red. Fractional distillation gave four fractions (all boiling points are at 1 mm): (1) 6.10 g, bp 60–64°, $n^{21.8}$D 1.5838 (which did not yield a crystalline picrate); (2) 6.19 g, bp 64–90°, $n^{21.5}$D 1.5942; (3) 13.70 g, 22%, bp 91–96°, $n^{20.8}$D 1.6012; and (4) 17.69 g, 28%, bp 96–101°, $n^{20.4}$D 1.6002. Fractions 3 and 4, which gave picrates as brick red needles, mp 158–161° dec uncor and 162–163° dec uncor, respectively, were combined and redistilled (at 1 mm), giving four more fractions: (5) 0.68 g, 1%, bp 80–90°, $n^{23.5}$D 1.5963; (6) 2.55 g, 4%, bp 90–94°, $n^{23.5}$D 1.5998; (7) 0.94 g, 1%, bp 94–96°, $n^{23.5}$D 1.6019; (8) 20.09 g, 32%, bp 97–100°, $n^{23.5}$D 1.6023; total of fractions 6–8 was 5.58 g, 37%; lit. 36%,[72] bp 94–96° (1 mm),[72] 180° (20 mm),[73] 275° (atm).[74] Fraction 8 gave a picrate as brick red needles: mp 164–165° dec; lit. mp 155–156° dec,[75] 158–159°,[71,76] and 164.5°.[72] Fraction 7 was analyzed: $\lambda_{max}^{95\%\ EtOH}$ 223 mμ (log ε 4.56), 273 (3.97), 278 infl (3.95), and 289 infl (3.76); $\nu_{NH}$ 3330 s cm$^{-1}$ neat. Elemental analyses have not previously been reported.

*Anal.* Calcd for $C_{10}H_{11}N$ (145.20): C, 82.72; H, 7.64; N, 9.65. Found: C, 82.39; H, 7.63; N, 10.27.

**2,4-Dimethylindole-3-carboxaldehyde** (with R. J. Sperley, 1962).—The procedure is that of James and Snyder[49] for formylation of indole to indole-3-carboxaldehyde. Phosphorus oxychloride (49.1 g, 0.320 mole) was added dropwise with vigorous stirring over a period of 35 min to N,N-dimethylformamide (32.4 g, 0.438 mole) cooled to 0° in an ice–salt bath. After about one-half the phosphorus oxychloride had been added, the solution began to turn faintly pink. After the addition was complete, a solution of 2,4-dimethylindole (46.0 g, 0.317 mole) in N,N-dimethylformamide (32.4 g, 0.438 mole) was added dropwise with stirring over a period of 65 min while the reaction temperature was kept below 5°. After about one-fourth of the solution had been added, the reaction solution turned a milky pink. After the addition was complete, the ice–salt bath was removed and the reaction was kept at 35–38° in a water bath for 1 hr, during which the solution turned light yellow. The reaction solution was then recooled in the ice–salt bath for 10 min, and then snow (110 g) was added, causing the resulting mixture to turn light tan and thicken to a slurry. The mixture was then washed with water (50 ml) onto ice (64 g), giving a red-brown solution. A solution of sodium hydroxide (128 g, 3.20 moles) in water (341 ml) was then added dropwise with stirring until about one-half the alkaline solution had been added and the mixture had changed from red-brown to yellow, after which the remaining half was added rapidly. The mixture was then heated rapidly to boiling, but a tan precipitate remained undissolved. The mixture was then cooled to room temperature and kept in a refrigerator overnight. Addition of water and filtration removed the precipitate as a tan powder (48.8 g, 89%), mp 175–181°. Recrystallization from methanol–water, with charcoal, gave a whitish powder: mp 191–192°; $\lambda_{max}^{95\%\ EtOH}$ 216 mμ (log ε 4.52), 248 (4.29), 268 (4.02), and 313 (4.07); $\nu_{NH}^{Nujol}$ broad absorption around the Nujol peak and $\nu_{C=O}^{Nujol}$ 1621 s cm$^{-1}$.

*Anal.* Calcd for $C_{11}H_{11}NO$ (173.21): C, 76.27; H, 6.40; N, 8.08. Found: C, 76.09; H, 6.37; N, 8.33.

**2,3,4-Trimethylindole** (with R. J. Sperley, 1962).—The procedure is a modification of that of Leete and Marion[49] for reduction of indole-3-carboxaldehyde to skatole. A solution of lithium aluminum hydride (10.0 g, 0.264 mole) in anhydrous ether (100 ml) was added slowly to a solution of 2,4-dimethylindole-3-carboxaldehyde (25.0 g, 0.144 mole) in anhydrous ether (400 ml) under dry nitrogen. A vigorous reaction took place at first, followed by gentle bubbling. The solution was refluxed for 3 hr under nitrogen, and then moist ether (200 ml) was added to decompose unreacted hydride. The resulting yellow solution was filtered and the ether was distilled off. The residual yellow oil solidified upon cooling, to a mass of yellowish white plates (21.4 g, 93%), mp 57–62°. Recrystallization from methanol–water yielded white plates, mp 63–64.5°, which turned yellow quickly when dried in air, but seemed to keep better when dried in a vacuum desiccator over phosphorus pentoxide: $\lambda_{max}^{95\%\ EtOH}$ 230 mμ (log ε 4.51), 278 infl (3.84), 284 (3.86), and 292 infl (3.77). The infrared spectrum in Nujol was identical with that of the sublimed sample described below.

*Anal.* Calcd for $C_{11}H_{13}N$ (159.22): C, 82.97; H, 8.23; N, 8.80. Found: C, 82.03; H, 8.18; N, 8.51.

Sublimation of the crude sample in the absence of light at 65° (0.05 mm) for 48 hr gave a light pink solid, mp 56–58°, $\nu_{NH}^{Nujol}$ 3380 s cm$^{-1}$. The compound is very sensitive to air oxidation.

*Anal.* Found: C, 83.17; H, 7.61; N, 8.62.

(73) G. Plancher and R. Ciusa, *Atti Accad. Naz. Lincei Rend. Classe Sci. Fis. Mat. Nat.*, [5] **15**, 447 (1906); *Chem. Zentr.*, II, 1847 (1906); *J. Chem. Soc.*, **92**, 80 (1907).

(74) M. Dennstedt, *Chem. Ber.*, **24**, 2559 (1891).

(75) M. Dennstedt, *ibid.*, **21**, 3429 (1888).

(76) H. Booth, A. W. Johnson, and F. Johnson, *J. Chem. Soc.*, 98 (1962).

# Pyridylmethylnaphthalene and Pyridylmethylindan Derivatives

DON M. LYNCH AND WAYNE COLE

*Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago, Illinois*

*Received May 25, 1966*

Several pyridylmethylnaphthalene and piperidylmethylnaphthalene derivatives, and the corresponding indan analogs, were made for evaluation as endocrine agents. These ring systems were obtained by condensing the sodium salt of an alkylpyridine with a 1-tetralone or 1-indanone, followed by elimination and hydrogenation steps as required. Restricted rotation about the C–N amide bond of the N-acylpiperidyl compounds is evidenced by long-range shielding effects shown by nmr.

A series of pyridine and piperidine derivatives having the tricyclic ring system shown by II was made. These compounds were among those desired for biological evaluation as possible endocrine agents because their molecules offered semirigid structures in which two polar groups may assume a spacing of about 11 A, as occurs in the natural estrogens. The synthesis of a number of these structures was achieved by condensing the sodium salt of γ-picoline or 4-ethylpyridine with a substituted 1-tetralone Ia or 1-indanone Ib,c. The intermediate tertiary alcohols were not isolated but readily dehydrated to the unsaturated compounds. Although the condensation of α-picoline with 1-indanone is known to give a tertiary alcohol,[1] it appears that the presence of a methoxy substituent *para* to the carbinol function, as is present in the systems under study, facilitates the dehydration of 5-methoxy-1-indanol.[2]

The condensation of γ-picoline with 6-methoxy-1-tetralone (Ia) gave isolable material containing roughly a 50:50 mixture of the endocyclic and exocyclic double-bond isomers IIa. Integration of the vinyl hydrogen triplet at 347 cps in the nmr spectrum of the endocyclic

(1) J. Sam, J. N. Plampin, and D. W. Alwani, *J. Org. Chem.*, **27**, 4543 (1962).

(2) D. G. Lindsay, B. J. McGreevy, and C. B. Reese, *Chem. Commun.*, **16**, 379 (1965).