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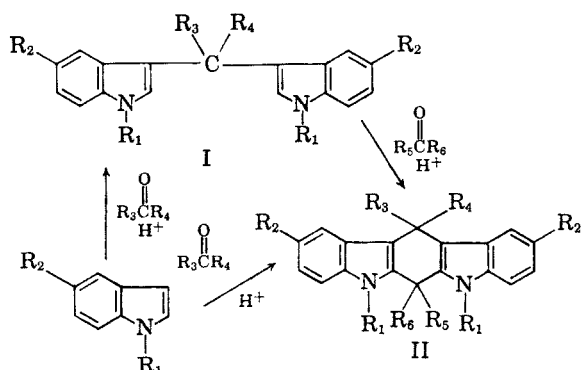
## Cyclizative Condensations. IV. 3,3'-Alkylidenebisindoles from Methyl Ketones and Their Conversion to Indolo[2,3-b]carbazoles<sup>1</sup>

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Condensation of acetone with 5-methylindole and 5-benzyloxyindole in refluxing acetic acid gave the bisindoles Ie and If. Similarly, condensation of acetophenone with indole, 1-methylindole, and 2-methylindole gave the corresponding bisindoles Ih, Ii, and IXc. Condensation of acetone with indole or with the corresponding bisindole (Id) in refluxing maleic acid solution gave the indolo[2,3-b]carbazole IIf, while the corresponding condensation of acetone with the bisindole (Ie) from 5-methylindole gave the indolo[2,3-b]carbazole IIg. Condensation of acetone with 1-methylindole or with the corresponding bisindole (Ig) in ethanolic hydrochloric acid gave the indolo[2,3-b]carbazole IIh. Condensation of indole with acetophenone in ethanolic hydrochloric acid gave the polymer VI and what is believed to be the related cyclic dimer, the indolo[3,2-b]carbazole VII, as indicated by its alternate method of synthesis from 3-(1-phenylvinyl)indole (IV) in ethanolic hydrochloric acid. Condensation of 1-methylindole with acetophenone in ethanolic hydrochloric acid gave only the bisindole Ii. Factors influencing formation of the various types of products described in this and preceding papers of the series are discussed and summarized.

In Papers I,<sup>2</sup> II,<sup>3</sup> and III<sup>4</sup> of this series, as well as elsewhere,<sup>5-7</sup> it has been shown that cyclizative condensation can occur by acid-catalyzed *nucleophilic* attack on an indole nucleus at the 2- position, whether or not the 2- position contains a methyl substituent. An intermolecular analog of this intramolecular process, the acid-catalyzed dimerization of indoles, does not occur, however, when the 2- position contains a methyl substituent, as in the attempted dimerization of 2- methylindole.<sup>8</sup> That an unsubstituted 2- position of an indole nucleus can also undergo *electrophilic* attack by a carbonyl group (leading to 2,2'-alkylidenebisindoles, for example), when the more nucleophilic 3- position is blocked by a substituent such as a methyl group, has been established previously.<sup>9</sup> By application of this principle to 3,3'-methylenebisindole (Ia) or



- Ia.  $R_1 = H, R_2 = H, R_3 = H, R_4 = H$   
 Ib.  $R_1 = CH_3, R_2 = H, R_3 = H, R_4 = H$   
 Ic.  $R_1 = H, R_2 = H, R_3 = p-(CH_3)_2NC_6H_5, R_4 = H$   
 Id.  $R_1 = H, R_2 = H, R_3 = CH_3, R_4 = CH_3$   
 Ie.  $R_1 = H, R_2 = CH_3, R_3 = CH_3, R_4 = CH_3$   
 If.  $R_1 = H, R_2 = C_6H_5CH_2O, R_3 = CH_3, R_4 = CH_3$   
 Ig.  $R_1 = CH_3, R_2 = H, R_3 = CH_3, R_4 = CH_3$   
 Ih.  $R_1 = H, R_2 = H, R_3 = C_6H_5, R_4 = CH_3$   
 Ii.  $R_1 = CH_3, R_2 = H, R_3 = C_6H_5, R_4 = CH_3$

- IIa.  $R_1 = H, R_2 = H, R_3 = H, R_4 = H, R_5 = H, R_6 = H$   
 IIb.  $R_1 = CH_3, R_2 = H, R_3 = H, R_4 = H, R_5 = H, R_6 = H$   
 IIc.  $R_1 = H, R_2 = H, R_3 = H, R_4 = H, R_5 = C_6H_5, R_6 = H$   
 IId.  $R_1 = H, R_2 = H, R_3 = H, R_4 = H, R_5 = p-(CH_3)_2NC_6H_5, R_6 = H$   
 IIe.  $R_1 = H, R_2 = H, R_3 = p-(CH_3)_2NC_6H_5, R_4 = H, R_5 = p-(CH_3)_2NC_6H_5, R_6 = H$   
 IIf.  $R_1 = H, R_2 = H, R_3 = CH_3, R_4 = CH_3, R_5 = CH_3, R_6 = CH_3$   
 IIg.  $R_1 = H, R_2 = CH_3, R_3 = CH_3, R_4 = CH_3, R_5 = CH_3, R_6 = CH_3$   
 IIh.  $R_1 = CH_3, R_2 = H, R_3 = CH_3, R_4 = CH_3, R_5 = CH_3, R_6 = CH_3$

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(2) W. E. Noland, M. R. Venkiteswaran, and C. G. Richards, *J. Org. Chem.*, **26**, 4241 (1961).

(3) W. E. Noland, M. R. Venkiteswaran, and R. A. Lovald, *J. Org. Chem.*, **26**, 4249 (1961).

(4) W. E. Noland, C. G. Richards, H. S. Desai, and M. R. Venkiteswaran, *J. Org. Chem.*, **26**, 4254 (1961).

(5) R. Robinson and J. E. Saxton, *J. Chem. Soc.*, 2596 (1953).

(6) D. A. Cockerill, R. Robinson, and J. E. Saxton, *J. Chem. Soc.*, 4369 (1955).

(7) B. Robinson and G. F. Smith, *J. Chem. Soc.*, 4574 (1960).

(8) W. E. Noland and C. F. Hammer, *J. Org. Chem.*, **25**, 1525 (1960).

(9) W. E. Noland and D. N. Robinson, *Tetrahedron*, **3**, 68 (1958).

its *N,N'*-dimethyl derivative (Ib), compounds in which the 3- positions of two indole nuclei are bridged by a carbon atom, von Dobeneck and Maas<sup>10</sup> have produced acid-catalyzed cyclizative condensation at the 2- positions with formaldehyde or aromatic aldehydes.

(10) H. von Dobeneck and I. Maas, *Chem. Ber.*, **87**, 455 (1954).

3,3'-Methylenebisindole (Ia) and formaldehyde, or indole and formaldehyde, were found to undergo cyclizative condensation in methanolic sulfuric acid to 5,6,7,12-tetrahydroindolo[2,3-b]carbazole (IIa), m.p. 408°, in 10 or 18% yields, respectively. Similarly, 1,1'-dimethyl-3,3'-methylenebisindole (Ib) and formaldehyde were found to give the *N,N'*-dimethyl derivative (IIb), m.p. 317°. In the pyrrole series, ethyl 2-methyl-3-pyrrolicarboxylate and formaldehyde yield a similar 2:2 cyclizative condensation product, m.p. 333°. 3,3'-Methylenebisindole (Ia) underwent cyclizative condensations with benzaldehyde and *p*-dimethylaminobenzaldehyde, forming the mixed indolo[2,3-b]carbazoles IIc, m.p. 306°, in 28% yield, and IID, m.p. 324°. The molecular weight of the latter was shown to be consistent with the structure assigned. Condensation of indole and *p*-dimethylaminobenzaldehyde gave the indolo[2,3-b]carbazole IIe, m.p. 394–395°, in 19% yield, along with the bisindole Ic, from which it is assumed to have formed, in 63% yield.<sup>10</sup>

We have now extended the same type of cyclizative condensation of indoles with carbonyl compounds to include a ketone, acetone. Condensation of indole with acetone, catalyzed by maleic acid in refluxing acetone solution, gave the indolo[2,3-b]carbazole IIf, m.p. 201.5–203°, in 54% yield. Condensation of the corresponding bisindole, 3,3'-isopropylidenebisindole (Id) with acetone under similar conditions gave IIg in 52% yield. Condensation of the bisindole from 5-methylindole, 5,5'-dimethyl-3,3'-isopropylidenebisindole (Ie), gave under the same conditions the indolo[2,3-b]carbazole IIg, m.p. 214–216°, in 64% yield. An attempt to prepare an analogous indolo[2,3-b]carbazole by condensation of the bisindole If, from 5-benzyloxyindole and acetone, with acetone under the same conditions gave no crystalline product. Condensation of 1-methylindole with acetone at room temperature in ethanolic hydrochloric acid containing acetone in 4.5*M* ratio excess gave the indolo[2,3-b]carbazole IIh, m.p. 183–184°, the *N,N'*-dimethyl derivative of IIf, in 13% yield after extensive purification. Condensation of the corresponding bisindole (Ig)<sup>4</sup> with acetone under similar conditions gave IIh in 31% yield.

The indolo[2,3-b]carbazoles IIf–h have typical indole ultraviolet spectra (see Experimental), with maxima similar to, and intensities ( $\epsilon$ ) twice those of 2,3-dimethylindole, which has maxima at 227  $m\mu$  ( $\log \epsilon$  4.49), 283 (3.83), and 290 (3.78) in 95% ethanol.<sup>9</sup> Compounds IIf and IIg have NH bands in their infrared spectra. The NH band of IIf shows the same doublet in chloroform solution (at 3460 and 3400  $cm^{-1}$ ) and singlet (at 3400  $cm^{-1}$ ) in Nujol as 2,3-dimethylindole. Thus, IIf and IIg, as well as IIh derived from 1-methylindole, cannot be formed by substitution at the 1-position.

Compounds IIf and IIh have molecular weights corresponding to the formulas assigned, and not to some multiple of them. Likewise, formation of an indolo[2,3-b]carbazole (IIg) from 5,5'-dimethyl-3,3'-isopropylidenebisindole (Ie), in which the nucleophilic position *para* to the nitrogen is blocked by a methyl substituent, shows that substitution cannot have occurred at the 5-position, thus bridging two or more bisindole units (Ie) through their 5-positions, and leading to a cyclic dimer or trimer which would have the same empirical composition as IIg. Failure of 2,2'-dimethyl-3,3'-isopropylidenebisindole (IXa), in which the 2-positions are blocked by methyl substituents, to undergo further condensation with acetone catalyzed by maleic acid under conditions under which IIf and IIg were formed, points to the 2-positions as the points across which cyclizative condensation with acetone has taken place. This hypothesis is in accord with the concept that an unsubstituted 2-position is the usual site of electrophilic carbonyl attack in 3-alkylindoles.<sup>9</sup>

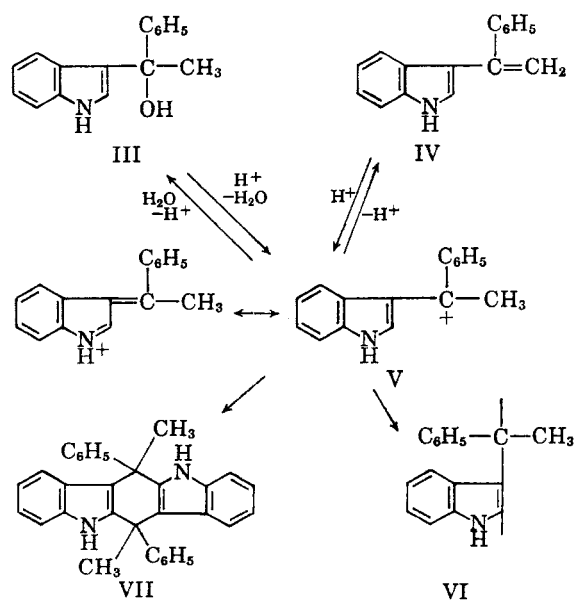
Cyclizative condensation across the 2- and 3-positions of two indole nuclei could conceivably involve either 3,3'- and 2,2'-bridging, producing indolo[2,3-b]carbazoles (II), or 3,2'- and 2,3'-bridging, producing indolo[3,2-b]carbazoles (like VII). Differentiation between these two possibilities rests partly on the argument that cyclizative condensation to the same products can be produced in as good (IIf) or better (IIh) yields, starting from 3,3'-alkylidenebisindoles (I), as from the parent indoles themselves. The possibility of reversal of formation of 3,3'-alkylidenebisindoles cannot be rigorously excluded under the acidic conditions employed (reversal has been shown to occur, for example, in acetic anhydride<sup>2</sup> and, in the presence of strong acid, in the pyrrole series<sup>11,12</sup>), but it seems likely in any case that 3,3'-alkylidenebisindoles (I) are true intermediates in the cyclizative condensation process. In this event, a bridging group is already in place across what are certainly the easiest positions for electrophilic substitution, the 3,3'-positions, and the remaining bridge must go across the 2,2'-positions, thus establishing the indolo[2,3-b]carbazole structures II for the products.

Attempts to prepare indolo[2,3-b]carbazoles by condensation of the bisindoles from acetophenone and indole (Ih) or 1-methylindole (II) with more acetophenone in ethanolic hydrochloric acid gave unchanged bisindole starting materials as the only crystalline products. Condensation of indole with an excess of acetophenone in ethanolic hydrochloric acid, however, gave a polymeric substance from which a relatively soluble, lower molecular weight fraction was isolated in pure form in 2–11% yields. The substance has the

(11) A. Treibs and H. G. Kolm, *Ann.*, **614**, 199 (1958).

(12) A. Treibs and E. Herrman, *Z. physiol. Chem., Hoppe-Seyler's*, **299**, 168 (1955).

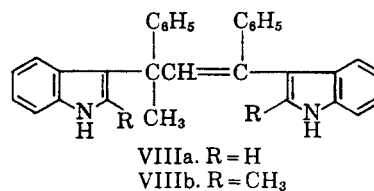
empirical composition corresponding to a 1:1 condensation product of indole and acetophenone. The ultraviolet spectrum is that of a typical indole, and is similar to that of 2,3-dimethylindole. The infrared spectrum contains NH absorption, with a doublet in chloroform solution similar to that of 2,3-dimethylindole. The NMR spectrum in carbon tetrachloride solution, with tetramethylsilane as an internal reference, contains a single sharp peak in the aliphatic region at 8.00  $\tau$ , attributed to a methyl group on a quaternary carbon atom, and a single broad peak at 2.97  $\tau$ , attributed to the aromatic protons in the molecule. These observations are consistent with polymer structure VI, which is completely analogous to the structure proposed by Leete and Marion<sup>13</sup> for the polymer resulting from action of hydrochloric acid on 3-indolemethanol. Also isolated from the condensation of indole with acetophenone, in 22% yield, was a colorless crystalline solid, m.p. 259–261°, believed to be the cyclic dimeric form (VII) of the polymer structure VI. This cyclic dimer (VII) was also isolated in 22% yield from action of ethanolic hydrochloric acid on 3-(1-phenylvinyl)indole<sup>14</sup> (IV). The dimer VII was recovered unchanged from attempted low pressure hydrogenation, suggesting the absence of olefinic unsaturation such as would be present in an alternative structure VIIIa. The typical indole ultraviolet spectrum of VII differs from that of the dimer (VIIIb)<sup>2</sup> of the 2-methyl derivative, 2-methyl-3-(1-phenylvinyl)indole, which was formed under identical conditions, in that there is no ill-defined absorption in the 236–268-m $\mu$  region, such as was present in VIIIb.



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

(14) W. E. Noland and M. R. Venkiteswaran, unpublished work (to be reported later), 1958.

Polymer structure VI or the indolo[3,2-b]-carbazole structure of the dimer VII could result from alkylation by carbonium ion V at the 2-position of its possible precursors, either the vinylogous carbinolamine III (formed by acid-catalyzed addition of indole at its 3-position to acetophenone) or the dehydration product, 3-(1-phenylvinyl)indole (IV). Formation of polymer VI and dimer VII requires that all free indole in the system be consumed rapidly in the formation of III, IV, and V, a likely event in the strongly acid medium employed. This is a necessary condition, since it is assumed that carbonium ions, such as V (or their conjugate bases, 3-alkylideneindolenines) are also intermediates in formation, in the presence of free indole molecules, of 3,3'-alkylidenebisindoles such as Ih. Because of the much greater nucleophilicity of the 3- over the 2- position of an indole nucleus, bisindole formation would predominate in the presence of free indole.



During the course of this work we have prepared several new 3,3'-alkylidenebisindoles (I), with the primary intention of using them as starting materials for preparation of indolo[2,3-b]carbazoles (II). Bisindoles from condensation of acetone with indole (Ia)<sup>15–19</sup> and with 2-methylindole (IXa)<sup>2,15,17</sup> have been reported previously, although spectral data for Ia are recorded here for the first time. The corresponding bisindoles from 1-methylindole (Ig)<sup>4</sup> and 1,2-dimethylindole (IXb)<sup>2</sup> are described in earlier papers of this series. Condensation with acetone in refluxing acetic acid gave the corresponding bisindoles from 5-methylindole (Ie, 84% yield) and from 5-benzyloxyindole (If, 65% yield). Condensation with acetophenone under similar conditions gave bisindoles from indole (Ih, 45% yield), 1-methylindole (Ii, 29% yield), and 2-methylindole (IXc, 64% yield). Condensation of 1-methylindole with acetophenone was much more effective in ethanolic hydrochloric acid, giving the bisindole Ii in 98% yield.

In contrast to the colorless crystalline product, m.p. 237–239°, to which we assign the bisindole structure IXc, a dark red powder, decomposing at

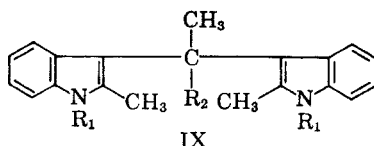
(15) M. Scholtz, *Ber.*, **46**, 1082 (1913).

(16) R. Majima and M. Kotake, *Ber.*, **55**, 3865 (1922); *Rept. Inst. Phys. Chem. Research (Japan)*, **2**, 82 (1923); *J. Chem. Soc. Japan*, **43**, No. 12 (1922); *Chem. Abstr.*, **17**, 2285 (1923).

(17) B. Oddo and L. Perotti, *Gazz. chim. ital.*, **60**, 13 (1930).

(18) T. Hoshino, *Chem. Ber.*, **85**, 858 (1952).

(19) H. Erdtman and Å. Jönsson, *Acta Chem. Scand.*, **8**, 119 (1954).



- IXa.  $R_1 = H, R_2 = CH_3$   
 IXb.  $R_1 = CH_3, R_2 = CH_3$   
 IXc.  $R_1 = H, R_2 = C_6H_5$   
 IXd.  $R_1 = H, R_2 = p\text{-}CH_3\text{-}C_6H_5$

130–132°, for which only a nitrogen analysis was reported, and for which structure IXc was claimed, has been reported to form in unstated yield from heating 2-methylindole Grignard reagent with acetophenone.<sup>17</sup> Three attempts<sup>20</sup> to obtain a homogeneous product according to the procedure described<sup>17</sup> were unsuccessful. Unchanged 2-methylindole was recovered in up to 78% yield in pure form, along with unchanged acetophenone and a dark red tar, from which no crystalline or homogeneous product could be obtained. Similarly, a dark yellow powder, m.p. 187°, for which only a nitrogen analysis was reported, and for which the bisindole structure IXd was claimed, has been reported to form in unstated yield from heating 2-methylindole Grignard reagent with *p*-methylacetophenone.<sup>17</sup> In this case, as well as in the preceding case, since the products were reported to be colored, it is very improbable that they have the bisindole structures claimed. Attempts<sup>21</sup> to prepare the bisindole IXd from 2-methylindole and *p*-methylacetophenone by (a) refluxing in glacial acetic acid solution for four or twenty-four hours; (b) refluxing for an hour in chloroform solution saturated with hydrogen chloride; or (c) passing dry hydrogen chloride into a dry ether solution, gave only reddish oils. Likewise, attempted condensation of equimolar quantities of 2-methylindole and propiophenone in refluxing acetic acid for four hours produced only an oil.<sup>22</sup>

In contrast to several reports of the formation of strongly colored bisindoles,<sup>17,23</sup> which we have been unable to confirm<sup>21</sup> and which cannot be considered correct, all authentic reports of the formation of bisindoles from ketones have so far involved methyl ketones<sup>24</sup> or benzoyl cyanide.<sup>25</sup> Even with methyl ketones, the scope of the bisindole-formation reaction appears to be limited. In contrast to the case with acetone, our attempts to form crystalline bisindoles from condensation of methyl ethyl ketone with indole<sup>26</sup> or with 2-methylindole<sup>22</sup> in refluxing acetic acid solution have been unsuccessful.

(20) By Milton H. Fischer, 1956.

(21) By Chiu-Ying Wong, 1958.

(22) Donald N. Robinson, Ph.D. thesis, University of Minnesota, March 1959, pp. 98–100, 163–165, 170.

(23) Q. Mingoa, *Gazz. chim. ital.*, **56**, 446 (1926); **58**, 673 (1928).

(24) See, for example: W. E. Noland and D. N. Robinson, *J. Org. Chem.*, **22**, 1134 (1957).

(25) A. K. Kiang and F. G. Mann, *J. Chem. Soc.*, 594 (1953).

(26) With Donavon F. Beaver, 1957.

ful. Under similar conditions, however, bisindoles are formed from acetylacetone with indole, from phenylacetone with 2-methylindole,<sup>24</sup> and from benzoyl cyanide<sup>25</sup> and acetophenone with indoles. These facts suggest that, while bisindole formation is undoubtedly sensitive to steric hindrance, electrophilicity of the attacking carbonyl group is an important factor. It is also suggested that conjugated unsaturation, such as that provided by the phenyl group attached to the potential bridging carbon atom, stabilizes the intermediate 3-alkylideneindolenine<sup>24</sup> or its conjugate acid (such as V), and thus favors bisindole formation.

From the results reported in the present paper and in the three preceding papers of this series<sup>2–4</sup> several further generalizations may be drawn concerning condensation of indoles with methyl ketones:

(1) *Relative reactivities of indoles.* Relative reactivities of indoles in formation of 3,3'-alkylidenebisindoles (I or IX) from acetone or acetophenone in refluxing acetic acid are in the order: 2-methylindole > 5-methylindole ≥ 5-benzyloxyindole ≥ indole > 1-methylindole > 1,2-dimethylindole. The yield of bisindoles from 1-methylindole was increased with acetone (I<sub>g</sub>) from 19 to 56%<sup>4</sup> and with acetophenone (I<sub>i</sub>) from 29 to 98% by changing the medium to ethanolic hydrochloric acid at room temperature.<sup>4</sup> 1,2-Dimethylindole did not form a bisindole from acetone in refluxing acetic acid, but did form the bisindole IXb in 59% yield in ethanolic hydrochloric acid.<sup>2</sup>

(2) *Bisindole formation requires lower acidities than cyclizative condensation.* Bisindole formation requires the simultaneous presence of free indole molecules (acting as nucleophiles) and of their 1:1 condensation products with carbonyl compounds (such as V or its conjugate base, acting as electrophilic reagents). This requires that the acidity of the medium be sufficiently low, for the indole involved, that the rate of acid-catalyzed formation of 1:1 condensation products does not substantially exceed the rate of bisindole formation from them. Otherwise, the reaction products will be derivatives formed by self-addition of the 1:1 condensation products, such as the cyclized dimers described in Paper I (formulas V–VI, XVI in Paper I),<sup>2</sup> Paper III (formulas I–II in Paper III),<sup>4</sup> or the polymer VI or the dimer VII described in the present paper.

(3) *Indolo[2,3-*b*]carbazole formation is favored by higher acidities than for bisindoles.* As the acidity is increased, bisindole products (I) which have open 2-positions become vulnerable to acid-catalyzed electrophilic attack by acetone at these positions, resulting in cyclizative condensation to indolo[2,3-*b*]carbazoles (II). Maleic acid solution provides the necessary acidity for cyclizative condensation of the bisindoles derived from acetone and indole (Id) or 5-methylindole (Ie). Ethanolic

hydrochloric acid was a successful medium for cyclizative condensation of the bisindole (Ig) from acetone and 1-methylindole. This reaction pathway is not available to bisindoles derived from 2-methylindoles (IX).

(4) *Cyclizative dimerization requires high acidities.* In strongly acidic media, such as ethanolic hydrochloric acid, where indoles are most likely to be rapidly converted to their 1:1 condensation products with methyl ketones (like V or its conjugate base), dimerization of the condensation product, followed by acid-catalyzed cyclization, yields cyclized dimers. According to the mechanism proposed in Paper I,<sup>2</sup> one type of cyclizative dimerization (to formulas V-VI and XVI in Paper I,<sup>2</sup> and I-II in Paper III<sup>3</sup>) requires protonation of the indole nucleus of the dimer (formulas X-XI in Paper I), which would be favored by increasing basicity of the indole nucleus involved. In accordance with this prediction, *2-methylindole is the most reactive indole, even through cyclization appears to require nucleophilic attack at a 2-position already containing a 2-methyl substituent.* Indole and 1-methylindole, which are less basic, undergo this type of cyclizative condensation with acetone, but less readily and in lower yield<sup>4</sup> than 2-methylindole.<sup>2</sup> 1,2-Dimethylindole forms only the bisindole IXb from acetone under these conditions.<sup>2</sup>

The other type of cyclizative dimerization, which is described in the present paper (III or IV → V → VI or VII), involves exclusively electrophilic alkylation of the indole nucleus and occurs only with indoles having an unsubstituted 2-position, such as with the 1:1 condensation product (IV) of indole with acetophenone, which forms the indolo-[3,2-b]carbazole VII and the related polymer VI.

#### EXPERIMENTAL

*3,3'-Isopropylidenebisindole (Id)* (with Milton H. Fischer, 1956). The reaction of indolemagnesium iodide with acetone, according to the method of Majima and Kotake,<sup>16</sup> who reported a 23% yield, gave a 34% yield, m.p. 164-165°. The work-up procedure was modified so that, after steam distillation of the indole, the solidified residue was ground in a mortar and then extracted with cyclohexane in a Soxhlet extractor for 3 hr. The undissolved residue was treated with charcoal and recrystallized three times from ethanol; reported: m.p. 163°,<sup>19</sup> 163-164°,<sup>17</sup> 163-165°,<sup>16</sup> 165°<sup>15</sup>, 165-166°,<sup>18</sup> mol. wt. 240<sup>16</sup>;  $\lambda_{\max}$  in 95% ethanol: 224 m $\mu$  (log  $\epsilon$  4.79), 276 inflection (4.02), 283 (4.04), 291 (3.99);  $\nu_{\text{NH}}$  3500s, 3440w in chloroform, 3450vw, 3400s cm.<sup>-1</sup> in Nujol.

*Anal.* Calcd. for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub> (274.35): C, 83.17; H, 6.61; N, 10.21. Found: C, 83.28; H, 6.87; N, 10.24.

*5-Methylindole.* The sample was purchased from the Regis Chemical Co.  $\lambda_{\max}$  in 95% ethanol: 220 m $\mu$  (log  $\epsilon$  4.49), 270 (3.76), 284 (3.71), 295 (3.53).

*5,5'-Dimethyl-3,3'-isopropylidenebisindole (Ie).* A solution of 5-methylindole (3.25 g., 0.0247 mole) and acetone (10 cc.) in glacial acetic acid (15 cc.) was refluxed for 3 hr. The unchanged acetone and the acetic acid were removed under reduced pressure. Crystallization of the residue from ethanol gave white needles (3.15 g., 0.0104 mole, 84%). Three recrystallizations from ethanol yielded the analytical sample as white needles, m.p. 185-186°;  $\lambda_{\max}$  in 95% ethanol: 227

m $\mu$  (log  $\epsilon$  4.77), 282 (4.00), 289 (4.01), 299 inflection (3.91);  $\nu_{\text{NH}}$  3380 cm.<sup>-1</sup> in Nujol.

*Anal.* Calcd. for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub> (302.40): C, 83.40; H, 7.33; N, 9.26. Found: C, 83.61; H, 7.52; N, 9.19.

*5,5'-Benzoyloxy-3,3'-isopropylidenebisindole (If).* A solution of 5-benzoyloxyindole (from Regis Chemical Co., 3.35 g., 0.0150 mole) and acetone (10 cc.) in glacial acetic acid (15 cc.) was refluxed for 4 hr. The unchanged acetone and the acetic acid were removed under aspirator pressure. Crystallization of the residue from ethanol gave white rhombic crystals (2.37 g., 0.00486 mole, 65%), m.p. 189-190°. Three recrystallizations from ethanol yielded the analytical sample as white rhombic crystals, m.p. 190-191°;  $\lambda_{\max}$  in 95% ethanol: 224 m $\mu$  inflection (log  $\epsilon$  4.72), 280 (4.08), 298 inflection (3.96) 310 inflection (3.82);  $\nu_{\text{NH}}$  3400 cm.<sup>-1</sup> in Nujol.

*Anal.* Calcd. for C<sub>23</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub> (486.59): C, 81.45; H, 6.21; N, 5.76. Found: C, 81.72; H, 6.35; N, 5.81.

An attempt to condense the above product with a second molecule of acetone was unsuccessful. Refluxing the compound with maleic acid (0.0020 mole each) in acetone (10 cc.) solution for 12 hr., evaporation of the acetone under reduced pressure, and extraction of the maleic acid with aqueous sodium bicarbonate solution, left a red tar which could not be crystallized.

*3,3'-( $\alpha$ -Methylbenzylidene)bisindole (Ih).* A. *From indole-magnesium bromide and acetophenone, and subsequent warming with 6N acetic acid* (with Milton H. Fischer, 1956). A solution of acetophenone (5.7 g., 0.047 mole) in diethyl ether (5 cc.) was added dropwise, with stirring, at room temperature to a mixture of indolemagnesium bromide (0.047 mole, prepared by adding a solution of indole in dry ether to a previously prepared solution of ethyl bromide and magnesium in dry ether) in ether (38 cc.). A taffy-like lump of addition product formed. Stirring was continued for 0.5 hr. and then the mixture was cooled in an ice bath and hydrolyzed with a mixture of ice (85 g.) and concentrated sulfuric acid (4.9 g.). The ether layer was separated and the aqueous layer was extracted with ether. The combined ether solutions were dried over anhydrous sodium sulfate and concentrated under reduced pressure to a yellow oil (11.0 g.), which did not crystallize. This oil was warmed for 2 hr. on a steam bath with 6N acetic acid (110 cc.), and then kept at room temperature. After 5 days the oil had become a slightly tacky solid. Trituration of the solid with ethanol left a granular residue (7.5 g.), which was dissolved in hot benzene, treated with charcoal, and precipitated by addition of petroleum ether (b.p. 60-68°). Trituration of the precipitate with ethanol left a solid (5.61 g., 0.0168 mole, 72%), m.p. 187.5-190°. Two recrystallizations from absolute ethanol yielded white crystals, m.p. 191-193°;  $\lambda_{\max}$  in 95% ethanol: 224 m $\mu$  (log  $\epsilon$  4.81), 277 inflection (4.05), 283 (4.09), 291 (4.03);  $\nu_{\text{NH}}$  3460s, 3400 w, 3340vw in chloroform, 3440, 3420, 3390 cm.<sup>-1</sup> in Nujol.

*Anal.* Calcd. for C<sub>24</sub>H<sub>20</sub>N<sub>2</sub> (336.42): C, 85.68; H, 5.91; N, 8.33. Found: C, 85.53; H, 5.91; N, 8.55.

It seems likely that the 6N acetic acid treatment may have had an important effect in increasing the yield, possibly by catalyzing the condensation of unchanged indole with acetophenone in the hydrolyzed reaction product. In a similar reaction of acetophenone with indolemagnesium bromide (except that the reaction mixture was warmed for 0.5 hr. on a steam bath and then hydrolyzed with saturated aqueous ammonium chloride solution and worked up promptly without further acid treatment), only an 18% yield of product was obtained.

B. *From indole and a stoichiometric amount of acetophenone, with acetic acid* (with Donald N. Robinson, 1956). A solution of indole (5.0 g., 0.043 mole) and acetophenone (2.5 g., 0.021 mole) in the minimum amount of glacial acetic acid was refluxed for 2 hr. The red solution was diluted with water and kept for 2 days, causing separation of a dark oil. The mixture was neutralized with sodium bicarbonate and extracted with ether. The ether was evaporated and the residue dissolved

in ethanol. After 2 days colorless crystals (1.4 g., 0.0042 mole, 20%), m.p. 192–194°, appeared.

C. *From indole and an 11-fold excess of acetophenone, with acetic acid.* A solution of indole (2.34 g., 0.0200 mole) and acetophenone (14.4 g., 0.120 mole) in glacial acetic acid (25 cc.) was refluxed for 1 hr. The acetic acid was removed from the brown solution on a steam bath under aspirator pressure, and the unchanged acetophenone was removed with the aid of a vacuum pump. The residue was treated with charcoal and crystallized from ethanol, yielding white crystals (1.52 g., 0.00451 mole, 45%), m.p. 189–190°. The mixed melting point with the sample prepared from a stoichiometric amount of acetophenone was undepressed.

An attempt to prepare 6,12-dimethyl-6,12-diphenyl-5,6,7,12-tetrahydroindolo[2,3-b]carbazole by condensation of 3,3'-( $\alpha$ -methylbenzylidene)bisindole with acetophenone in ethanolic hydrochloric acid, according to the procedure successfully employed with 1,1'-dimethyl-3,3'-isopropylidenebisindole (Ig) and acetone, gave unchanged bisindole starting material as the only crystalline product isolated.

1,1'-Dimethyl-3,3'-( $\alpha$ -methylbenzylidene)bisindole (Ii).

A. *From acetic acid* (with Donald N. Robinson<sup>22</sup>). A solution of 1-methylindole (5.2 g., 0.040 mole) and acetophenone (2.4 g., 0.020 mole) in glacial acetic acid (20 cc.) was refluxed for 4 hr. After the cooled, dark red solution had been kept at room temperature for 1 hr., crystals started to form. The next day the colorless crystals were filtered (2.1 g., 0.0058 mole, 29%), m.p. 212–218°. Five recrystallizations from acetone-water or ethanol-benzene yielded colorless crystals, m.p. 228–230°;  $\lambda_{\max}$  in 95% ethanol: 226 m $\mu$  (log  $\epsilon$  4.87), 291 (4.10).

Anal. Calcd. for C<sub>28</sub>H<sub>24</sub>N<sub>2</sub> (364.47): C, 85.68; H, 6.64; N, 7.69. Found: C, 85.98; H, 6.91; N, 7.69.

From a similar reaction in which the same amount of 1-methylindole and six times as much acetophenone in twice the previous volume of acetic acid were refluxed for 2 hr., a 24% yield of the bisindole was obtained.

B. *From ethanolic hydrochloric acid* (with Lawrence A. Stassel, 1961).<sup>27</sup> Concentrated hydrochloric acid (6.25 g.) was added, with swirling, to a solution of 1-methylindole (6.56 g., 0.0500 mole) and acetophenone (15.02 g., 0.125 mole) in 95% ethanol (25 cc.). Crystals started to form almost immediately, but the mixture was kept overnight (17 hr.). The light yellow crystals (8.9 g., 0.0244 mole, 98%), m.p. 222–224°, were filtered, washed with cold acetone to remove the yellow color, and recrystallized from ethanol-benzene, yielding two crops of white crystals (7.8 g., 83%) melting point and mixed melting point with the sample prepared in acetic acid, 228–230°.

2,2'-Dimethyl-3,3'-( $\alpha$ -methylbenzylidene)bisindole (IXc) (with Donald N. Robinson<sup>22</sup>). A solution of 2-methylindole (5.0 g., 0.038 mole) and acetophenone (2.28 g., 0.0190 mole) in glacial acetic acid (20 cc.) was refluxed for 2 hr. and then kept at room temperature for 2 days. The mass of crystals which had formed in the dark red solution was filtered and a second crop was obtained by adding water to the filtrate. Recrystallization from acetone-water yielded small white crystals (4.45 g., 0.0122 mole, 64%) m.p. 237–239°;  $\lambda_{\max}$  in 95% ethanol: 228 m $\mu$  (log  $\epsilon$  4.83), 276 inflection (4.11), 284 (4.15), 292 (4.12);  $\nu_{\text{NH}}$  3460 in CHCl<sub>3</sub>, 3390 cm.<sup>-1</sup> in Nujol.

Anal. Calcd. for C<sub>28</sub>H<sub>24</sub>N<sub>2</sub> (364.47): C, 85.68; H, 6.64; N, 7.69. Found: C, 85.83; H, 6.35; N, 7.89.

5,6,7,12-Tetrahydro-6,6,12,12-tetramethylindolo[2,3-b]carbazole (IIf). A. *From indole.* A solution of indole (7.03 g., 0.0600 mole) and maleic acid (6.96 g., 0.0600 mole) in acetone (50 cc.) was refluxed for 24 hr. Most of the acetone was removed from the deep red solution under aspirator pressure and the residue was kept overnight with ether and aqueous sodium bicarbonate solution to remove maleic acid. Evaporation of the ether layer gave a red tar (10.0 g.) containing whitish crystals. This residue was chromatographed on alumina with benzene. The material eluted with benzene was

treated with charcoal and crystallized from ethanol-water, yielding yellowish material (5.1 g., 0.0162 mole, 54%). Four recrystallizations from ethanol-water yielded yellowish white crystals, m.p. 201.5–203°;  $\lambda_{\max}$  in 95% ethanol: 229 m $\mu$  (log  $\epsilon$  4.76), 283 (4.19), 290 inflection (4.14);  $\nu_{\text{NH}}$  3460, 3400 in chloroform, 3400 cm.<sup>-1</sup> in Nujol.

Anal. Calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub> (314.41): C, 84.04; H, 7.05; N, 8.91. Found: mol. wt. (Rast), 294; C, 83.81; H, 6.95; N, 8.69.

B. *From 3,3'-isopropylidenebisindole.* A solution of 3,3'-isopropylidenebisindole (1.1 g., 0.0040 mole) and maleic acid (0.47 g., 0.0040 mole) in acetone (12.5 g.) was refluxed for 20 hr. The unchanged acetone was removed under aspirator pressure and the red tarry residue was taken up in ether (300 cc.) and kept with aqueous sodium bicarbonate solution for 4 hr. to remove maleic acid. The ether layer was washed with water, dried, and the ether evaporated. The residual reddish tar contained whitish crystals. Trituration with ethanol and a few drops of water and warming on a steam bath produced yellowish white crystals (0.65 g., 0.00206 mole, 52%). Three crystallizations from ethanol yielded a sample, m.p. 203–205°, mixed melting point with the sample prepared from indole, 202–204° (undepressed). The infrared spectra of the two samples in chloroform and Nujol were identical.

2,6,6,10,12,12-Hexamethyl-5,6,7,12-tetrahydroindolo[2,3-b]carbazole (IIg). A solution of 5,5'-dimethyl-3,3'-isopropylidenebisindole (1.51 g., 0.0050 mole) and maleic acid (1.16 g., 0.0100 mole) in acetone (10 cc.) was refluxed for 4 hr. The unchanged acetone was removed under aspirator pressure and the maleic acid extracted from the residue with aqueous sodium bicarbonate solution. Crystallization of the residue from ethanol, with charcoal, gave white crystals (1.1 g., 0.0032 mole, 64%). Three recrystallizations from ethanol yielded the analytical sample as white needles, m.p. 214–216°;  $\lambda_{\max}$  in 95% ethanol: 231 m $\mu$  (log  $\epsilon$  4.74), 282 inflection (4.13), 288 (4.14), 297 inflection (4.06);  $\nu_{\text{NH}}$  3360 cm.<sup>-1</sup> in Nujol.

Anal. Calcd. for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub> (342.46): C, 84.17; H, 7.65; N, 8.18. Found: C, 83.71; H, 7.98; N, 7.97.

5,6,6,7,12,12-Hexamethyl-5,6,7,12-tetrahydroindolo[2,3-b]carbazole (IIh). A. *From 1-methylindole* (with Heinz Sorger-Domenigg, 1955). A solution of 1-methylindole (4.29 g., 0.0326 mole), acetone (10.50 g., 0.181 mole), and concentrated hydrochloric acid (5.00 g.) in 95% ethanol (20 g.) was kept at room temperature for 1 day, at the end of which time an orange-red oil had separated. The mixture was diluted with a large amount of water, producing a brick red precipitate. The precipitate was dissolved in ethanol and made alkaline by the addition of 10% aqueous sodium bicarbonate, causing the solution to turn light brown. Concentration and cooling precipitated a flaky material. This flaky precipitate was dissolved in ethanol, and the solution treated with charcoal and diluted with water. The solution was then severely concentrated, causing precipitation of much reddish brown tar. The largely aqueous supernatant solution was decanted and the residue was triturated repeatedly with boiling petroleum ether (b.p. 60–68°). Evaporation of the petroleum ether extracts left an orange-red oil, which slowly developed small rosettes of white crystals. This residue was redissolved in boiling petroleum ether (b.p. 60–68°) and placed hot on an alumina chromatographic column packed wet with light petroleum. Elution with petroleum ether (b.p. 60–68°) removed first several small rosettes of white crystals, m.p. 193.5°. Further elution with petroleum ether and with chloroform removed material which crystallized in large rosettes of white needles, but which usually tended to oil out, requiring trituration with methanol to induce crystallization (0.73 g., 0.0021 mole, 13%), m.p. 169–177°. Recrystallization<sup>28</sup> from ethanol-water yielded white crystals, m.p. 180–181°. Rechromatography<sup>29</sup> on alumina with petroleum ether (b.p.

(28) By Donald N. Robinson, 1957.

(29) By John J. Baldwin, 1957.

(27) Section added to manuscript, May 1, 1961.

60–68°) raised the m.p. to 183–184°;  $\lambda_{\max}$  in 95% ethanol: 227  $m\mu$  (log  $\epsilon$  4.80), 287 inflection (4.13), 293 (4.15).

*Anal.* Calcd. for  $C_{24}H_{26}N_2$  (342.46): C, 84.17; H, 7.65; N, 8.18. Found: mol. wt. (Rast), 286;<sup>28</sup> C, 84.18; H, 8.04; N, 7.98.

B. *From 1,1'-dimethyl-3,3'-isopropylidenebisindole.* A mixture of 1,1'-dimethyl-3,3'-isopropylidenebisindole<sup>4</sup> (1.0 g., 0.0033 mole), acetone (4.0 g., 0.069 mole), and concentrated hydrochloric acid (1.2 g.) in ethanol (10 cc.) was prepared at room temperature. Some precipitate formed in the deep reddish orange solution. Additional acetone (3 cc.) was added and the mixture was shaken occasionally, but the crystalline precipitate persisted. After 6 hr. at room temperature the mixture was warmed on a steam bath long enough to cause the precipitate to dissolve. After a total reaction time of 20 hr. at room temperature, the whitish crystalline precipitate (0.35 g., 0.00102 mole, 31%), m.p. 176–179°, which had reformed, was filtered. Four recrystallizations from ethanol yielded clusters of thick white needles, m.p. 179–181°. The mixed melting point with the sample prepared from 1-methylindole was undepressed, and the infrared spectra of the two samples in potassium bromide and in Nujol were identical.

*Anal.* Found: C, 84.08; H, 7.83; N, 8.31.

*Attempted reaction of 2,2'-dimethyl-3,3'-isopropylidenebisindole with acetone in presence of maleic acid.* A solution of 2,2'-dimethyl-3,3'-isopropylidenebisindole<sup>4,15</sup> (3.02 g., 0.0100 mole) and maleic acid (1.16 g., 0.0100 mole) in acetone (5 cc.) was refluxed for 24 hr. The unchanged acetone was removed under aspirator pressure and the maleic acid was removed by extraction with aqueous sodium bicarbonate solution. The brown residue was treated with charcoal and crystallized from ethanol, yielding unchanged 2,2'-dimethyl-3,3'-isopropylidenebisindole (2.75 g., 91%), having a melting point which was undepressed upon admixture with starting material.

*3-(1-Phenylvinyl)indole polymer (VI)* (with James H. Osborn, 1955). A solution of indole (16.6 g., 0.142 mole), acetophenone (68.3 g., 0.568 mole), and concentrated hydrochloric acid (16.6 g.) in ethanol (67 g.) was kept at room temperature for 3 days. The dark red solution was then added to sufficient saturated aqueous sodium carbonate solution to neutralize all the hydrochloric acid present. The resulting mixture was extracted several times with ether. An attempt to wash the combined ether extracts with water produced an emulsion, which was broken by addition of solid sodium carbonate. The ether layer was separated and the ether evaporated on a steam bath. The residue was distilled at 78–79° (13 mm.) to remove unchanged acetophenone. The resulting deep red residue, a glassy solid at room temperature, was dissolved in ethanol, treated several times with charcoal, and then precipitated as a red oil by addition of water. The red oil was dried on a steam bath and then extracted repeatedly with petroleum ether (b.p. 60–68°). Concentration and cooling in an ice bath of the yellow petroleum ether extracts precipitated a yellow solid. This solid was dissolved in ethanol, treated with charcoal, and the filtrate evaporated to dryness and the residue reprecipitated twice from petroleum ether (b.p. 60–68°), yielding a pale yellowish powder (0.5 g., 0.0023 mole, 2%), m.p. 135–145° (not sharp);  $\lambda_{\max}$  in 95% ethanol: 223  $m\mu$  (log  $\epsilon$  4.44), 283 (3.83), 291 (3.78);  $\nu_{\text{NH}}$  3460s, 3400w in chloroform, 3380  $\text{cm}^{-1}$  in Nujol.

*Anal.* Calcd. for  $[C_{18}H_{15}N]_n$  (219.27): C, 87.64; H, 5.98; N, 6.39. Found: C, 87.91; H, 5.74; N, 6.16.

The polymer was obtained in higher yield after chromatography, as described in Part B below.

*6,12-Dimethyl-6,12-diphenyl-5,6,11,12-tetrahydroindolo-[3,2-b]carbazole (VII).* A. *From 3-(1-phenylvinyl)indole* (with Roger A. Lovald,<sup>30</sup> 1960). A solution of the oil (4.20 g., <0.0192 mole) containing crude 3-(1-phenylvinyl)indole (from the action of phenyllithium on 3-acetylindole),<sup>14</sup> and concentrated hydrochloric acid (2.0 g.), in 95% ethanol (10 cc.), which turned red after addition of the acid, was kept at room temperature for 48 hr. The solution was neutralized with ethanolic sodium hydroxide solution, the precipitated sodium chloride filtered off, and the filtrate evaporated to dryness. The residue was extracted with ether, the ether evaporated, and the residual mixture of red oil and solid dissolved in a small amount of ethanol and placed in a refrigerator for 2 days. The brown crystalline precipitate (1.01 g.), m.p. 220–240°, was recrystallized from ethanol with cooling in a refrigerator, giving light brownish crystals (0.93 g., 0.00212 mole, 22%), m.p. 250–256°. Four recrystallizations from ethanol-water yielded white crystals, m.p. 259–261°;  $\lambda_{\max}$  in 95% ethanol: 225  $m\mu$  (log  $\epsilon$  4.83), 283 (4.22), 291 (4.16);  $\nu_{\text{NH}}$  3470 in chloroform, 3390 in potassium bromide, 3400  $\text{cm}^{-1}$  in Nujol.

*Anal.* Calcd. for  $C_{22}H_{24}N_2$  (438.54): C, 87.54; H, 5.98; N, 6.39. Found: C, 87.40; H, 6.02; N, 6.37.

The compound was recovered unchanged in 83% yield from attempted hydrogenation at 2 atm. over Raney nickel catalyst in ethanol solution.

B. *From indole and acetophenone* (with Angelina N. Yao and H. S. Desai, 1961).<sup>27</sup> Concentrated hydrochloric acid (5.0 g.) was added to a solution of indole (4.70 g., 0.0400 mole) and acetophenone (12.01 g., 0.100 mole) in 95% ethanol (20 cc.). The red solution, which gradually became darker, was kept at room temperature for 48 hr., and then poured into water. The resulting mixture was extracted with ether and the ether was distilled. The residue (16.0 g.) was washed onto the top of an alumina column with a small amount of petroleum ether (b.p. 60–68°), in which it was largely insoluble. A small amount of benzene was added, to cause more of the residue to dissolve. Elution with petroleum ether and mixtures with benzene removed first acetophenone and then a very small amount of solid (0.006 g.), m.p. 206–213°, which, after crystallization from benzene, yielded a white solid, m.p. 216–218°;  $\nu_{\text{NH}}$  3350,  $\nu_{\text{C=O}}$  1688  $\text{cm}^{-1}$  in Nujol. Further elution with benzene-petroleum ether removed yellow-orange oils, which solidified upon trituration with methanol. After reprecipitation from methanol or benzene-petroleum ether the solids had melting points of 146–180° (0.650 g., 7%) and 145–155° (0.350 g., 4%), and infrared spectra in Nujol identical with 3-(1-phenylvinyl)indole polymer.

Elution with benzene removed yellow oils, which crystallized upon trituration with methanol; elution with benzene-ethyl ether removed the same compound, which left a white crystalline solid upon evaporation of the elution solvents. Further elution with ether, acetone, and methanol removed only oils. Recrystallization of the solids from methanol, ethanol, or benzene-petroleum ether yielded white solids (1.89 g., 0.00431 mole, 22%), m.p. 255–260°, having infrared spectra in Nujol identical with that of the sample prepared from 3-(1-phenylvinyl)indole as described above in Part A.

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