Tetrahedron. Vol. 26, pp. 5427 to 5435. Pergamon Press 1970. Printed in Great Britain

THE REACTION OF 3-PROPYLINDOLE WITH ALDEHYDES

PREPARATION OF 2-(α-AMINOALKYL) INDOLES

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(*Received in the USA* 30 *April* 1970; *Received in the UK for publication* 21 *July* 1970)

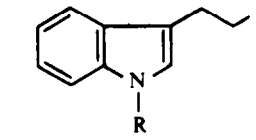
Abstract—2,2'-Benzylidenebisindoles (**5**) are produced by the condensation of 3-propylindole with aromatic aldehydes. It is shown that aromatic aldehydes react initially, but reversibly, at nitrogen. N-substituted products can be trapped as acetate derivatives (**7**) and are converted to 2,2'-benzylidenebisindoles (**5**) under the original reaction conditions. 3-Propylindole reacts with formaldehyde and piperidine under mild conditions to give 1-piperidinomethyl-3-propylindole. 2-Piperidinomethyl-3-propylindole is obtained when the reaction with formaldehyde in acetic acid is carried out at 100° in the presence of excess piperidine. The condensation of 3-propylindole with formaldehyde and primary amines involves initial attack at nitrogen followed by intramolecular substitution at the 2-position to yield 1H-imidazo[1,5*a*]indole and 2,3,4,5-tetrahydrotriazepino[1,7*a*]indole derivatives. Hydrolysis of cyclohexylimidazoindole (**11**) affords 2-cyclohexylaminomethyl-3-propylindole.

IN CONNECTION with a proposed synthetic route to cinchonamine,[2] it became of interest to achieve an intermolecular condensation at the 2-position of a 3-substituted indole. Only two examples of condensation of aliphatic aldehyde-amine adducts at the 2-position of 3-substituted indoles have been recorded. Thesing and Binger[3] described the formation of 2-dimethylaminomethyl-1,-3-methylindole by the reaction of 1,3-dimethylindole with formaldehyde and dimethylamine, while Kamal[4] reported the formation of 2-diethylaminomethyl-3-methylindole from skatole. The production of the latter compound is unexpected since the normal mode of attack in such cases involves the indole nitrogen to give N-substituted products.[3, 5, 6, 7]

3-Propylindole was chosen as a model in order to approximate the steric bulk of tryptophol.[2] The reaction of 3-propylindole with formaldehyde and piperidine following Kamal's procedure[4] gave 1-piperidinomethyl-3-propylindole (**1**) in 29% yield. When Kamal's work[4] was repeated only 1-dimethylaminomethyl-3-methylindole could be isolated from the basic products. Since the latter reaction is incomplete after 1 day, Kammal's report of NH absorption could have been due to unreacted skatole.

Various attempts to condense formaldehyde at the 2-position of 3-propylindole under mild conditions failed, and in all cases N-substituted products were obtained. Thus, reaction with formaldehyde and piperidine in excess acetic acid led to a good yield of **1**, while condensation with formaldehyde in acetic anhydride and pyridine gave 1-acetoxymethyl-3-propylindole (**2**) in nearly quantitative yield. The reaction with formaldehyde and piperidine in water proved more complicated and only 1,1'-methylene-bis (3-propylindole) and 1-hydroxymethyl-3-propylindole could be isolated in relatively pure form.

The behavior of aromatic aldehydes contrasts markedly with that of aliphatic aldehydes. As a rule aromatic aldehydes[8–10] condense at position -2 of 3-substituted

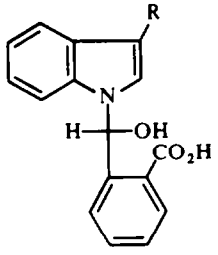


1: R = —CH_2—N

2: R = —CH_2—OAc

indoles. The Ehrlich color test for 3-substituted indoles, for example, relies on specific reaction of *p*-dimethylaminobenzaldehyde at the 2-position to form 2,2′-benzylidene-bis-indoles which are readily oxidized to colored materials.[8]

Phthaldehydic acid is an exception to this rule, affording N-substituted product **4**.[11] A rationale for these results would involve rapid, but reversible condensation at nitrogen, followed by a slower, irreversible attack at position -2. In the case of phthaldehydic acid the reversal of substitution at nitrogen is prevented by the lactonization of intermediate **3**.



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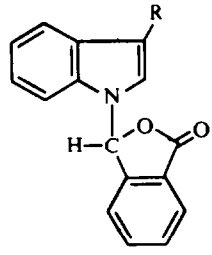
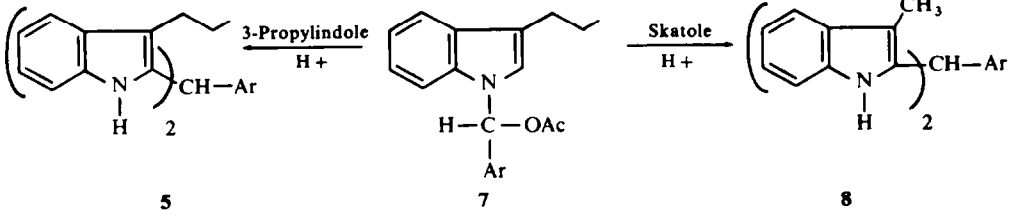


4: R = CH_3
6: R = $CH_3CH_2CH_2$

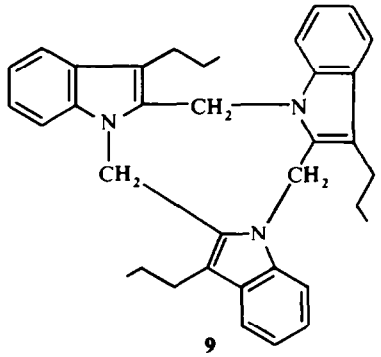
Similar behaviour is observed with 3-propylindole which is converted to 2,2′-benzylidene derivatives (**5**) when treated with aromatic aldehydes and to N-substituted lactone (**6**) when reacted with phthaldehydic acid. When the reaction of benzaldehyde or *m*-nitrobenzaldehyde with 3-propylindole is conducted in acetic anhydride, N-substituted acetates (**7**) are obtained. When acetate **7** is mixed with 3-propylindole in the presence of acid, bis-indole **5** is produced. When acetate **7** is treated with an excess of skatole under similar conditions, the bis-indole isolated is almost exclusively **8**, a product resulting from the condensation of benzaldehyde with two moles of skatole rather than a mixed bis-indole. These results confirm the premise that the condensation of aromatic aldehydes at the nitrogen atom of 3-substituted indoles is reversible. It can also be concluded that 2-substituted products do not arise by way of an intramolecular rearrangement of N-substituted derivatives.



5 **7** **8**

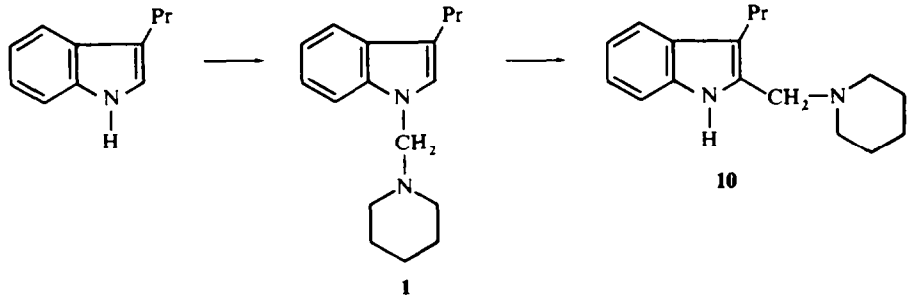
The problem of substitution of the 2-position of 3-propylindole by aliphatic aldehydes is clearly one of overcoming a large activation barrier to attack at the 2-position. Attempts to block nitrogen with acetoxymethyl, piperidinomethyl, and benzyl groups and achieve condensation at the 2-position under mild conditions have failed.

We turned next to a study of the condensations of aliphatic aldehydes under more vigorous conditions. Since 3-propylindole undergoes severe and rapid darkening to give intractible tars in acetic acid at elevated temperature, initial attempts avoided elevated temperature and merely extended the period of reaction for several weeks. From the complex mixture resulting from piperidinomethanol, 3-propylindole, and acetic acid there was isolated a neutral product having the empirical formula $C_{12}H_{13}N$ whose NMR spectrum displayed a 2 proton singlet at δ 5·22 ppm and signals for 7 propyl hydrogens and 4 aromatic protons. The mass spectrum exhibited an intense parent ion at *m/e* 513 permitting the formulation of the compound as trimer **9**. The salient feature of this compound is that condensation has occurred at the 2-position.



9

In order to prevent bis-indole formation, the reaction of 3-propylindole with formaldehyde in acetic acid was carried out at 100° in the presence of a large excess of piperidine. Only moderate darkening and polymerization took place, and the basic material isolated proved to be 2-piperidinomethyl-3-propylindole (**10**). 1-Piperidinomethyl-3-propylindole was converted into **10** by heating at 100° with excess piperidine in acetic acid, demonstrating our contention that condensation with aldehydes occurs reversibly at nitrogen and ultimately involves attack at the 2-position.

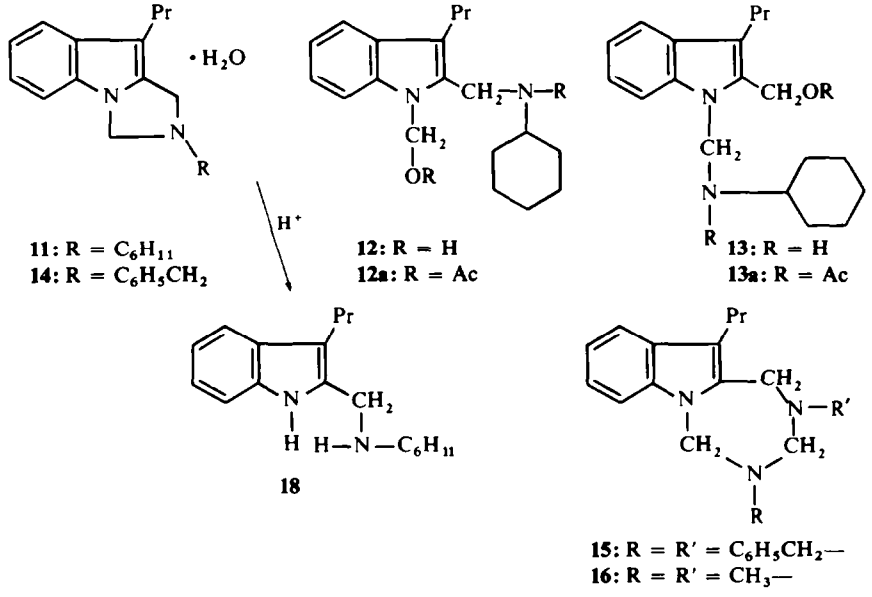


10 **1**

Whereas intermolecular substitution at position-2 occurs with some difficulty, this is not the case with intramolecular substitutions as witnessed by the many known examples of Pictet–Spengler and related cyclizations of tryptamine derivatives.[12] We

therefore considered the possibility of an intramolecular cyclization involving an N-amino-alkylindole derivative. When 3-propylindole, cyclohexylamine, and sodium acetate were treated with 2 equivalents of formaldehyde in acetic acid, the imidazo [1.5a] indole **11** was isolated in 25% yield as a stable hydrate. The water molecule was tenaciously bound and its presence was indicated by a broad 2-proton singlet in the NMR spectrum which disappeared when the sample was stirred with D_2O. An acetone solution of **11** was stable to chromium trioxide in sulphuric acid–water, while its mass spectrum displayed a parent ion at *m/e* 282 consistent with the hydrate formulation and eliminating noncyclized aminoalcohols **12** and **13**. The sample recovered from treatment with D_2O also showed a parent ion at *m/e* 282. An old sample of **11** showed an ion at *m/e* 300 suggesting hydrolysis to **12** or **13** had occurred. Another indication of the lability of the imidazole ring was provided by acetylation, which afforded a mixture of acetates formulated as **12a** and **13a** on the basis of spectral data (Experimental).

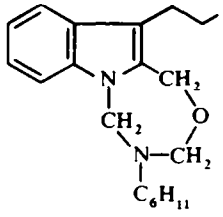
The yield of imidazo[1.5a]indole **14** from benzylamine was very low (1–3%), and instead a moderate yield (30–40%) of triazepinoindole **15** was recovered as an insoluble hydrochloride salt which formed during extraction of imidazole **14**. With methylamine an imidazoindole derivative could not be isolated and only triazepinoindole **16**, along with other unidentified basic materials, was produced.



The triazepinoindole structures were assigned on the basis of spectral data. The benzyl derivative **15** lacked NH absorption in the IR and showed 5 methylene signals in its NMR spectrum. The ratio of methyl to aromatic protons was 3:14 indicating the presence of 2 benzyl groups. The mass spectrum showed no parent ion, but displayed a strong ion at *m/e* 290 which corresponds to loss of $C_6H_5—CH_2N=CH_2$. The methyl derivative **16** displayed a parent ion at *m/e* 257.

When cyclohexylamine, formaldehyde, and 3-propylindole were combined in a 2:6:1 ratio, a solid was isolated whose NMR and mass spectrum, as well as elemental

analysis, indicated a molecular formula of $C_{20}H_{28}N_2O$ and suggests it be formulated as compound **17**.



17

Hydrolysis of the cyclohexylimidazoindole **11** with hydrochloric acid in propyl alcohol gave 2-cyclohexylaminomethyl-3-propylindole (**18**), which was characterized as its N-acetyl derivative.

In summary, it is shown that 3-substituted indoles undergo facile, but reversible condensation at nitrogen. Intermolecular condensation at position-2 by formaldehyde requires vigorous conditions and can be achieved by heating in acetic acid in the presence of excess amine. Intramolecular substitution at position-2 is also accomplished by reaction with excess formaldehyde and primary amines. The resulting imidazoindole can be hydrolyzed to the desired 2-substituted product. Various attempts[12] to demonstrate initial condensation at position-3[13] gave negative results, suggesting the likelihood that intermolecular attack occurs directly at position-2 and not *via* intramolecular rearrangement of a 3-substituted intermediate as discussed by Jackson *et al.*[13]

EXPERIMENTAL

All b.ps and m.ps are uncorrected. IR spectra were determined with a Perkin Elmer Infracord spectrometer. NMR spectra were measured with a Varian Associates A-60 Spectrometer. UV spectra were obtained with a Perkin Elmer Model 202 spectrometer. Mass spectra were determined with Hitachi RMU-6A and RMU-6D spectrometers. Microanalyses were performed by Dr. C. S. Yeh and associates.

Reaction of 3-propylindole with formaldehyde

A. With Piperidine hydrochloride in water. A mixture of 0·23 ml piperidine, 0·19 ml conc HCl, 3·7 ml water, 0·365 g 3-propylindole, best prepared from valeraldehyde phenylhydrazone,[5] 4 ml NaOAc-AcOH buffer soln, and 0·25 ml 40% formalin in 3 ml water was stirred for 1 week. The aqueous phase was decanted and neutralized with NH_4OH and extracted with ether to give a small amount of N-methylpiperidine. The original organic layer was taken up in ether, dried, and the ether removed. Chromatography on silica gel and elution with 10% ether in hexane gave an oil (3–4 components indicated by TLC) which was further purified by thick layer chromatography to give a white, crystalline solid, m.p. 84–87°, identified as 1,1'-methylenebis(3-propylindole); IR no absorption at 2·8–3·0 μ; NMR ($CDCl_3$) 0·90 (t, 6), 1·67 (m, 4), 2·6 (t, 4), 5·98 (s, 2, $-N-CH_2-N-$), 6·8 (s, 2), and 7·0–7·6 ppm (m, 8); mass spectrum, *m/e* (relative intensity) 330 (14), 300 (4), 172 (25), 159 (35), 131 (12), and 130 (100). Elution with 50% ether-hexane gave 1-hydroxymethyl-3-propylindole, IR broad 2·8–3·0μ, NMR 0·90 (t, 3), 1·67 (m, 2), 2·6 (t, 2), 3·65 (broad s, 1, —OH) 4·98 (s, 2, $-N-CH_2-O$), 6·55 (s, 1), and 6·9–7·6 ppm (m, 4). This product was identical to the alcohol prepared by LAH reduction of 1-acetoxymethyl-3-propylindole.

B. With Acetic acid-acetic anhydride. A mixture of 0·8 g 3-propylindole, 4 ml AcOH, 3·5 ml Ac_2O, and 0·8 ml 40% formalin was stirred at ambient temp for 2 days. The dark red soln was diluted with water and extracted with ether. The ether soln was washed with NaOH aq, dried ($MgSO_4$), and evaporated to leave 0·96 g yellow oil which showed a broad peak at 3·0 μ and strong CO absorption at 5·75 μ. The material was acetylated with Ac_2O-pyridine yielding an oil which no longer displayed absorption at 3·0 μ. TLC on silica showed the presence of **2** and 1,1'-methylenebis(3-propylindole).

When the original reaction was conducted in Ac_2O containing a small amount of pyridine a quantitative yield of crude **2** was obtained. Attempts to purify the compound by distillation or column chromatography led to decomposition and gave material less pure than the original crude material; IR 5·70, 8·1–8·4, 9·9, 10·6, and 13·6 μ; NMR 0·97 (t, 3), 1·75 (sextet, 2), 1·98 (s, 3, —O—CO—CH_3), 2·72 (t, 2), 6·05 (s, 2, N—CH_2—O), 7·04 (s, 1), and 7·1–7·7 (m, 4); mass spectrum, *m/e* (relative intensity) 231 (7), 202 (11), 172 (7), 130 (25), 103 (13), 73 (23), 45 (15), 43 (100).

C. With Acetic acid-piperidine. A soln of 2·35 g 3-propylindole, 1·26 g piperidine, and 1·11 ml 40% formalin in 301 ml AcOH was stirred at ambient temp overnight. NaOH aq was added and ether extraction gave 3·2 g crude product whose IR showed the presence of some unreacted starting material, N—H at 2·85 μ. Distillation gave, after a forerun of 3-propylindole, b.p. 138–150° (0·5 mm), 1·8 g of **1**, b.p. 150–155° (0·5 mm); IR shows no —NH stretching vibration; NMR (CCl_4) 0·97 (t, 3), 1·30 (s, 6), 1·72 (m, 2), 2·26 (broad s, 4, CH_2—N), 2·67 (t, 2), 4·38 (s, 2, N—CH_2—N), 6·65 (s, 1), and 6·8–7·5 ppm (m, 4). (Found: C, 69·94; H, 8·61; N, 9·50. Calcd. for $C_{17}H_{25}N_2O$: C, 69·71; H, 8·62; N, 9·57%).

The *hydrochloride salt of* 1-*piperidinomethyl*-3-*propylindole** was recrystallized from EtOH-ether and showed m.p. 160–162·5°.

The *picrate of* 1-*piperidinomethyl*-3-*propylindole** was recrystallized from EtOH and displayed m.p. 145–147°. (Found: C, 57·01; H, 5·61; N, 14·46. Calcd. for $C_{23}H_{27}N_5O_6$: C, 56·91; H, 5·67; N, 14·43%).

Hydrolysis of 1-piperidinomethyl-3-propylindole was achieved by stirring with 5 ml AcOH/NaOAc buffer (pH 5) for 1 day at ambient temp. Tlc indicated the major product was 3-propylindole. Longer treatment produced increasing amounts of 1,1'-methylenebis(3-propylindole). Hydrolysis with 1N $KHSO_4$ gave a crude product which was almost entirely 3-propylindole.

D. Prolonged reaction with piperidinomethanol, trimer **9**. A mixture of 3·18 g 3-propylindole, and 2·3 g piperidinomethanol,[14] in 20 ml AcOH was allowed to stand for 3·5 weeks. A solid (125 mg) was removed and the soln was poured into water and made basic with Na_2CO_3 aq and NaOH and extracted with ether. The ether was extracted with 5% HCl, resulting in the separation of a dark oil at the interphase. Neutralization of the acid phase gave 330 mg of **1**. Neutralization of the dark oil gave 883 mg of ether soluble material which has not yet been identified.

From the ether soln resulting after HCl extraction there was obtained 1·68 g oil. Trituration with hexane gave 110 mg solid which was identical with the solid separating from the original reaction mixture. Recrystallization from benzene-hexane gave the analytical sample of trimer **9**, m.p. 205–207°; no NH absorption in IR; NMR ($CDCl_3$) 0·97 (t, 3), 1·65 (sextet, 2), 2·79 (t, 2), 5·22 (s, 2, N—CH_2—C), 7·00–7·45 (m, 3), 7·48–7·70 ppm (m, 1); mass spectrum (75 ev) *m/e* 513, 342, 341. (Found: C, 84·30; H, 7·71; N, 8·04; M.W. 484 (C_6H_6), 484 (acetone). Calcd. for $C_{36}H_{39}N_3$: C, 84·16; H, 7·65; N, 8·18%; M.W. 513).

When the reaction described above was allowed to proceed for 1 day a 60% yield crude 1-piperidinomethyl-3-propylindole was isolated. When carried out at 90° the mixture turned black and yielded only a small amount basic material. The complex neutral products were not investigated further.

When a 500 mg sample of 1-piperidinomethyl-3-propylindole was kept for a month in AcOH there was obtained 84 mg of trimer **9**.

E. With excess piperidine-acetic acid at elevated temperature (2-*piperidinomethyl* 3-*propylindole* **10**) A soln of 1·59 g 3-propylindole, 5 ml piperidine and 0·75 ml 40% formalin in 15 ml AcOH was heated at 100° for 24 hr. The mixture turned dark red, but remained clear. The soln was cooled, neutralized with NaOH and extracted with ether. The ether soln was extracted with 1N $KHSO_4$ which in turn was neutralized with alkali and extracted with ether. Drying (K_2CO_3) and evaporation gave 0·6 g (23%) of **10** as a tacky oil; IR 3·0, 11·0 and 13·6 μ; NMR ($CDCl_3$) 0·98 (t, 3) 1·4 and 1·5 (m's, 8), 2·3 (m, 4), 2·68 (t, 2), 3·50 (s, 2, —CH_2—N), 6·9–7·2 (m, 3), 7·4–7·6 (m, 1), and 8·50 ppm (s, 1, NH).

When the reaction was stopped after 2 hr, the NMR spectrum showed singlets at 3·54 and 4·70 ppm of equal intensity indicating the formation of equal amounts of **1** and **10**.

When 4·50 g of **1**, 5·0 ml piperidine and 15 ml AcOH were heated at 100° for 24 hr, 2·15 g (44%) of tacky oil was recovered whose NMR spectrum indicated it was almost entirely **10**.

The *picrate of* 2-*piperidinomethyl*-3-*propylindole** was recrystallized from EtOH and showed m.p. 158–160°. (Found: C, 57·00; H, 5·60; N, 14·41. Calcd. for $C_{23}H_{27}N_5O_6$: C, 56·91; H, 5·67; N, 14·43%).

F. With 2 equivalents formaldehyde and 1 equivalent cyclohexylamine. A stirred mixture of 0·38 ml cyclohexylamine, 0·48 ml 40% formalin, 0·48 g 3-propylindole and 5 ml AcOH was kept under N_2 at ambient temp for 1 day. The mixture was worked-up in the usual manner and basic material was extracted with 1N $KHSO_4$. During this extraction a red oil separated at the ether-water interphase. The acidic extracts were neutralized with NaOH and extracted with ether to give 100 mg solid. Recrystallization from hexane gave

pure **11**, m.p. 108°; IR 9·6 and 13·4 μ; NMR 0·92–2·92 (m's, 18), 3·87 (s, 2), 4·25 (broad s, 2) 5·45 (s, 2) and 7·00–7·70 ppm (m, 4); mass spectrum, molecular ion at *m/e* 282. (Found: C, 77·2; H, 9·03; N, 9·53. Calcd. for $C_{19}H_{26}N_2 \cdot 0{\cdot}75\ H_2O$: C, 77·2; H, 9·35; N, 9·46%).

When a $CDCl_3$ soln of **11** was shaken with D_2O the NMR signal at 4·25 ppm disappeared. The mass spectrum of the sample recovered from this treatment still showed a molecular ion at *m/e* 282.

Attempts to increase the yield of **11** by modifying conditions and changing concentration of reactants met with little success. When the reaction was conducted for 18 hr at ambient temp in the presence of 0·8 g NaOAc the yield of **11** was increased to 209 mg (24%).

A sample of **11** in 2 ml Ac_2O and 0·5 ml pyridine was heated at 100° for 5 hr. Work-up gave an oil which showed strong absorption at 5·75 (AcO—) and 6·1 (AcN—) μ; NMR 1·98 (s, CH_3—CO), 2·18 (s, CH_3—CO—), 4·17 (s, CH_2N), 4·90 (s, CH_2—O), and 6·17 ppm (s, AcO—CH_2—N) suggesting the presence of both **12a** and **13a**.

Hydrolysis of **11**. A soln of 90 mg of **11** in 7 ml 85% propyl alcohol containing 5 drops of conc HCl was distilled slowly to remove formaldehyde as it formed. Additional propyl alcohol and water were added and the soln was kept at 80° overnight and then the solvents were removed under diminished pressure. The residue was taken up in chloroform, washed with dil NaOH aq, dried, and evaporated to give 81 mg oil which showed NH absorption in the IR. The oil was dissolved in 1·5 ml pyridine and 0·25 ml acetyl chloride and was kept overnight at ambient temp. MeOH (0·5 ml) was added and after standing 30 min, ether was added. The insoluble solids were removed and the ether soln was washed with water and dil HCl. After drying ($MgSO_4$), evaporation left 50 mg of an oil which was chromatographed on an alumina column to give 22 mg of the N-acetyl derivative of **18**; IR 3·0, 6·12 and 13·5 μ; NMR 0·75–1·99 (m's, 15), 2·20 (s, 3, N—CO—CH_3), 2·78 (t, 2), 3·54 (m, 1), 4·60 (s, 2, C—CH_2—N), 7·00–7·72 (m, 4), and 8·93 ppm (broad s, 1, NH); mass spectrum, *m/e* (rel. intensity) 312 (67), 283 (7), 279 (8), 269 (12), 230 (10), 229 (53), 187 (51), 172 (35), 171 (140), 170 (18), 167 (17), 158 (62), 149 (32), 144 (23), 143 (12), 130 (12).

G. 6 Equivalents formaldehyde and 2 equivalents cyclohexylamine—compound **17**. A mixture of 7·9 g 3-propylindole, 9·9 g cyclohexylamine, 16 g NaOAc, 150 ml AcOH and 22·5 ml 40% formalin was kept at ambient temp for 1 day. The mixture was diluted with water, neutralized with Na_2CO_3, and extracted with ether. The ether soln was extracted with 10% HCl resulting in a 3 phase mixture. The ether and water layers were separated from the intermediate red oil. NaOH aq was added to this oil and the mixture was extracted with ether. The ether soln was dried (K_2CO_3) and evaporated leaving an oil which was crystallized from a small amount of hexane at −20° affording two crops for a total of 2·4 g. The analytical sample of **17** was prepared by sublimation *in vacuo* and showed m.p. 100–102°; NMR 4·37, 4·95 and 5·72 ppm (s's, 6, 3 —CH_2—) in addition to signals for one propyl, one cyclohexyl and one indole group; molecular ion at *m/e* 312. (Found: C, 76·94; H, 9·23; N, 9·63. Calcd. for $C_{20}H_{28}N_2O$: C, 77·0; H, 8·97; N, 8·97%).

H. Benzylamine and formaldehyde—2-benzyl-2,3-dihydro-9-propyl-1H-imidazo [1.5-a] *indole* (**14**) *and 2,4-dibenzyl-11-propyl-2,3,4,5-tetrahydro-1,3,5-triazepino* [1. 7a] *indole* (**15**). A soln of 7·95 g (0·05 mol) 3-propylindole, 5·35 g (0·05 mol) benzylamine, 10 g NaOAc, and 7·5 ml (0·1 mol) 40% formalin in 150 ml AcOH was kept at ambient temp for 18 hr. The mixture was diluted with water and neutralized with solid Na_2CO_3 and 10% NaOH aq. The mixture was extracted with ether and the resulting ether soln was extracted with 5% HCl. The red oil which formed at the interphase was removed and the aqueous layer was neutralized with 10% NaOH aq and extracted with ether. The ether soln was dried and evaporated leaving an oil which partially crystallized. Recrystallization from hexane gave 200 mg of **14**, m.p. 107–109°; IR no NH absorption, 13·5 and 14·5 μ; NMR 0·90 (t, 3), 1·62 (m, 2), 2·67 (t, 2), 3·74 (s, 2), 3·90 (s, 2), 4·26 (broad s, 2, H_2O), 5·46 (s, 2), and 7·00–7·85 ppm (m, 9); molecular ion at *m/e* 290. (Found: C, 77·59; H, 7·65; N, 8·92. Calcd. for $C_{20}H_{22}N_2 \cdot H_2O$: C, 77·88; H, 7·80; N, 9·08%).

The water and ether, insoluble red oil obtained above was washed with water and shaken with ether until it crystallized yielding 3·24 g tan solid. The solid was treated with alkali and extracted with ether. The ether soln was dried, evaporated and the residue was sublimed at 120° and 0·2 mm to give **15**, m.p. 123–124·5°; IR no NH absorption, 13·4, 13·6, 13·8, and 14·3 μ; NMR 1–3 (m's, 7, —CH_2CH_3), 3·58, 3·64, 3·88, 4·07, and 5·08 (s's, 10), and 6·8–7·6 ppm (m, 14). (Found: C, 82·26; H, 7·68; N, 10·17. Calcd. for $C_{28}H_{31}N_3$: C, 82·10; H, 7·62; N, 10·26%).

The monohydrochloride of **15** was recrystallized from EtOH and showed m.p. 152–153°. (Found: C, 75·49; H, 7·22; N, 9·12; Cl, 8·20. Calcd. for $C_{28}H_{32}N_3Cl$: C, 75·43; H, 7·23; N, 9·42; Cl, 7·92%).

I. Formaldehyde and methylamine—2,4-dimethyl-11-propyl-2,3,4,5-tetrahydro-1,3,5-triazepino [1. 7a] *indole* (**16**). A mixture of 7·95 g (0·05 mol) 3-propylindole, 12 g NaOAc, 5·35 g (0·079 mol) $MeNH_2HCl$ and 7·5 ml (0·1 mol) 40% formalin in 150 ml AcOH was stirred at ambient temp for 24 hr. The mixture was

diluted with water, made basic with solid Na_2CO_3 and NaOH aq and extracted with ether. The ether soln was extracted with 10% HCl. The acidic layer was neutralized and extracted with ether to give 7·77 g red oil. Chromatography on basic alumina and elution with hexane gave 1 g oil which afforded 400 mg solid on sublimation *in vacuo*, m.p. 68–71·5°; raised to 71–73° by a second sublimation; IR no NH absorption, 13·5, and 13·8 μ; NMR 0·93 (t, 3), 1·66 (m, 2), 2·20 (s, 3, NCH_3), 2·35 (s, 3, NCH_3), 2·72 (t, 2), 3·78 (s, 4, 2 $-CH_2$), 5·07 (s, 2, CH_2), 6·90–7·30 (m, 3), and 7·40–7·67 ppm (m, 1); molecular ion at *m/e* 257. In benzene the NMR singlet at 3·78 was separated into two singlets of equal intensity. (Found: C, 74·87; H, 8·95; N, 16·22. Calcd. for $C_{16}H_{23}N_3$: C, 74·66; H, 9·00; N, 16·33%).

In another experiment using 15·9 g 3-propylindole and permitting the reaction to proceed for 2 days, the crude basic fraction was crystallized from hexane at −20° to give 3·07 g (12%) of **16**.

Reaction of 3-propylindole with benzaldehyde. A soln of 0·5 g 3-propylindole and 0·16 ml benzaldehyde in MeOH containing 1 drop H_2SO_4 was kept overnight. Ether was added and after washing with 10% NaOH aq, and drying ($MgSO_4$), the ether was removed to give 721 mg tacky yellow solid. Chromatography on an alumina column using 20% ether-hexane as an eluant gave a yellow oil identified as 2,2'-benzylidene-bis(3-propylindole); IR 2·85, 13·4, and 14·25 μ; NMR 0·87 (t, 6), 1·60 (sextet, 4), 2·67 (t, 4), 6·05 (s, $CH{-}C_6H_5$), and 7·05–7·58 ppm (m, 15).

Reaction of 3-propylindole with benzaldehyde in acetic anhydride-pyridine—1-(α-acetoxybenzyl)-3-propylindole, **7** (Ar=C_6H_5). A soln of 3·18 g 3-propylindole, 2·12 g benzaldehyde, and 3 ml pyridine in 15 ml AcO was kept at ambient temp for 9 days. The mixture was taken up in ether and washed with water and 10% NaOH aq. After drying (K_2CO_3), the ether was removed and the residue was crystallized from hexane at −78°. Several recrystallizations gave 1-(α-acetoxybenzyl)-3-propylindole, m.p. 59–66°; IR no NH absorption, strong 5·80 μ; NMR ($CDCl_3$) 0·95 (t, 3), 1·67 (m, 2), 2·12 (s, 3, $CO{-}CH_3$), 2·68 (t, 2), 6·80 (s, 1, $HC(OAc)C_6H_5$), 7·08–7·68 (m, 9), and 8·00 ppm (s, 1). (Found: C, 78·21; H, 7·11; N, 4·72. Calcd. for $C_{20}H_{21}NO_2$: C, 78·14; H, 6·90; N, 4·56%).

Reaction of 3-propylindole with phthalaldehydic acid. A mixture of 7·95 g 3-propylindole and 7·5 g phthalaldehydic acid was heated to 40° and as water vapor was evolved the temp was slowly raised to 180°. The mixture was cooled, dissolved in EtOH (decoloring carbon) and cooled to −20° affording 5·2 g solid, m.p. 103–104·5°. Recrystallization from methylene chloride-hexane afforded 3·0 g of **6**, m.p. 105·5–108·5°; IR no NH absorption, 5·65, 10·9, 13·3, and 13·5 μ; λ_{max} 222 and 275 mμ (ε 40,500 and 8,000); NMR 0·92 (t, 3), 1·65 (m, 2), 2·62 (t, 2), 6·47 (s, 1), 7·00–8·11 ppm (m, 9). (Found: C, 77·8; H, 5·70; N, 4·77. Calcd. for $C_{19}H_{17}NO_2$: C, 78·3; H, 5·88; N, 4·81%).

3-Propylindole and p-nitrobenzaldehyde. A soln of 318 mg 3-propylindole, 151 mg *p*-nitrobenzaldehyde and 3 drops H_2SO_4 in 5 ml abs EtOH was kept 1 day. The usual work-up and several recrystallizations from benzene-hexane gave 2,2'-(*p*-nitrobenzylidene)-bis(3-propylindole), m.p. 185–186°, which crystallized with an equivalent of benzene, mass spectrum, *m/e* (rel. intensity) 451 (100), 422 (43), 293 (59), 292 (65), 217 (31), 170 (25), and 158 (31).

3-Propylindole and m-nitrobenzaldehyde. A soln of 318 mg 3-propylindole, 151 mg *m*-nitrobenzaldehyde and 3 drops H_2SO_4 in 5 ml EtOH was kept 1 day, diluted with water and extracted with ether. The ether soln was washed with NaOH aq, dried ($MgSO_4$) and evaporated. The residue was washed with hexane and the solid was recrystallized from benzene-hexane to give 150 mg of **5**, yellow needles, m.p. 184·5–185°, IR 2·90, 6·60, 13·4, 13·6, 13·8, and 13·9 μ; NMR 0·87 (t, 6), 1·58 (m, 4), 2·65 (t, 4), 6·10 (s, 1), 6·89–7·75 (m, 12), and 7·98–8·15 ppm (m, 2); mass spectrum, *m/e* (rel. intensity) 451 (100), 422 (44), 293 (66), 292 (61), 217 (22), 170 (27), and 158 (27). (Found: C, 76·92; H, 6·48; N, 9·06. Calcd. for $C_{29}H_{29}N_3O_2$: C, 77·13; H, 6·48; N, 9·30%).

The hexane soluble material isolated above showed NMR signals at 5·54 and 6·43 ppm. The former signal was attributed to the diethyl acetal of *m*-nitrobenzaldehyde, while the latter was possibly due to N,N'-bisindole. The major component of the hexane fraction was isolated after repeated column chromatography on alumina and showed no NH absorption in the IR and was assigned as N-(α-ethoxy-3-nitrobenzyl)-3-propylindole on the basis of its NMR spectrum: 1·00 (t, 3), 1·30 (t, 3, $O{-}CH_2{-}\underline{CH_3}$), 2·12 (m, 2), 2·83 (t, 2), 3·67 (q, 2), 6·76 (s, 1), 7·15–8·05 (m, 7), 8·20–8·77 ppm (m, 2).

1-(α-Acetoxy-m-nitrobenzyl)-3-propylindole (**7**). A mixture of 1·59 g (0·01 mol) 3-propylindole, 1·51 g (0·01 mol) *m*-nitrobenzaldehyde, 1 ml pyridine and 10 ml Ac_2O was allowed to stand at ambient temp for 1 day. The usual work-up gave an oil whose IR showed weak NH, strong CO absorption at 5·70 and weak absorption at 5·89 μ. The oil was triturated with hexane leaving 0·80 g yellow solid. Recrystallization from EtOH gave pure **7** as bright yellow needles, m.p. 105–107°; IR no NH absorption, 5·70 and 6·52 μ; NMR 0·95 (t, 3), 1·70 (m, 2), 2·14 (s, 3), 2·68 (t, 2), 6·85 (s, 1), and 7·0–7·7 and 8·0–8·2 ppm (m's, 9). (Found: C, 68·25; H, 5·89; N, 7·73. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68·20; H, 5·72; N, 7·95%).

Tlc analysis of the hexane-soluble fraction isolated above demonstrated the presence of unreacted 3-propylindole.

Reaction of 1-(α-*acetoxy*-m-*nitrobenzyl*)-3-*propylindole with* 3-*propylindole.* A soln of 218 mg (1·37 mmols) 3-propylindole and 484 mg (1·37 mmols) 3-propylindole and 484 mg (1·37 mmols) of **7** in 8 ml abs EtOH was treated with 3 drops of H_2SO_4 and allowed to stand at ambient temp for 2 days. Usual work-up gave a yellow oil which on treatment with hexane left 335 mg yellow solid identified as **5** (Ar=*m*-nitro) on the basis of its IR and NMR spectra. The presence of a singlet at 5·45 ppm in the NMR of the crude product suggested the probable presence of the diethyl acetal of *m*-nitrobenzaldehyde.

Reaction of 1-(α-*acetoxy*-m-*nitrobenzyl*)-3-*propylindole with skatole.* A soln of 236 mg (0·67 mmol) of **7**, 425 mg (3·25 mmols) skatole, and 7 drops H_2SO_4 in 10 ml EtOH was kept at ambient temp for 1 day. The usual work-up gave a yellow oil which was dissolved in benzene and treated with hexane to give a gummy solid. The hexane-benzene soln was evaporated and spectral examination of the residue indicated it was composed largely of skatole. The solid was chromatographed on a silica gel column to give 140 mg solid, m.p. 212–215°, which showed strong NH absorption at 3·0 and a 6·6 μ peak attributed to a nitro group. The NMR spectrum indicated the absence of a propyl group and permitted the structural assignment to the product as **8**.

When **7** was reacted with one equivalent of skatole the crude bisindole showed propyl, as well as Me NMR signals indicating the predominant formation of a mixed bisindole.

A pure sample of **8** was obtained from skatole and *m*-nitrobenzaldehyde and was recrystallized from benzene-hexane and showed m.p. 217–220°; NMR 2·18 (s, 6), 6·05 (s, 1), and 7·0–8·2 ppm (m, 14); molecular ion at *m/e* 395 (100%).

Reaction of 3-*propylindole with salicylaldehyde.* A mixture of 1·59 g 3-propylindole and 1·22 g salicylaldehyde did not react on standing for 1 day, but on adding a few crystals *p*-toluenesulphonic acid and standing 2 days, the mixture solidified. After washing with benzene, 1·49 g white powder remained. This solid was treated with 5 ml Ac_2O and 0·5 ml pyridine. On work-up and crystallization from hexane-chloroform, white crystals of the acetate derivative of the 2,2'-benzylidene derivative were obtained, m.p. 214·5–215·5°; IR 2·9 and 5·70 μ; NMR (dioxan) propyl signals and 1·88 (s, 3, O—CO—CH_3), 6·12 (s, 1, H—C—Ar), 6·8–8·0 (m, 12), and 8·85 ppm (s, 2); mass spectrum, *m/e* (% rel. abund.) 464 (100), 435 (32), 421 (26), 306 (23), 305 (32), 264 (20), 262 (20), 234 (24), 220 (16), and 43 (80).

1,3-*Bis(dimethylaminomethyl)indole.* Enough EtOH was added to a mixture of 3·22 g (0·04 mol) of $Me_2NH \cdot HCl$, 4 ml NaOH aq, 1·17 g (0·01 mol) indole, and 3 ml (0·04 mol) 40% formalin, to make it homogeneous. The soln was refluxed overnight and worked-up to give an oil whose NMR spectrum showed the presence of 61% bis adduct and 39% mono adduct on the basis of the ratio of singlets at 3·58 and 4·57. The crude material was heated again with formalin and dimethylamine for 24 hr resulting in an oil which was essentially pure 1,3 bis(dimethylaminomethyl)indole, NMR 2·07 (s, 6), 2·18 (s, 6), 3·53 (s, 2), 4·43 (s, 2), 6·8–7·4 (m, 4), and 7·5–7·8 ppm (m, 1).

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