Synthesis of Piperidylindoles

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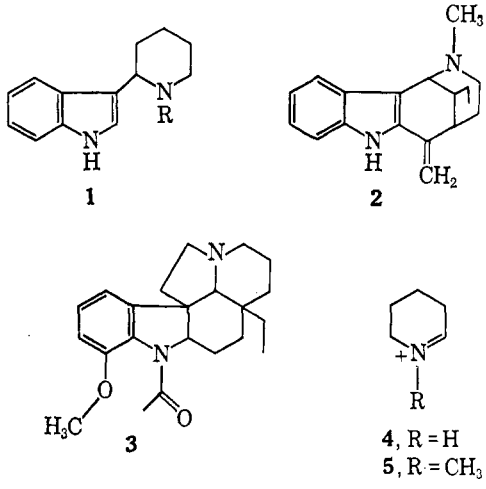
As an approach to the synthesis of various indole alkaloids, several methods of constructing simple 3-(2-piperidyl)indole systems have been developed. The first involved nucleophilic attack of indole on 1-piperideine salts to yield the desired piperidylindoles. Another method utilized the reaction of the Vilsmeyer salt of N-methylpiperidone with indole. The product, an amino ketone, was reductively cyclized to a piperidylindole. A third approach consisted of the reaction of pyridinium salts with indole. The indole Grignard reagent reacted with 2-chloropyridines to yield 3-(2-pyridyl)indoles. Reduction of these gave another synthesis of piperidylindoles. As a final approach the pyridine ylid formed by decarboxylation of picolinic acid was added to N-benzylisatin to give a dioxindole.

The 3-(2-piperidyl)indole skeleton **1** is common to a large number of indole alkaloids. The alkaloids uleine **2**[2] and aspidospermine **3**[3] are but two examples of the many interesting structures which are constructed around this backbone. Despite the apparent dissimilarity, parallel synthetic approaches to these and other indole alkaloids can be visualized which involve fabrication of the basic piperidylindole system followed by a further series of reactions designed to complete the individual alkaloid structures. This paper outlines several syntheses of the fundamental piperidylindole ring system.



Discussion

Nucleophilic Attack of Indole on 1-Piperideine Salts.—The one previously known synthetic route to simple piperidylindoles is that of van Tamelen[4] who formed this skeleton by nucleophilic attack of indole on the imonium salts **4** and **5**. He prepared the imonium salt **4** *in situ* by reaction of 1-piperideine trimer with aqueous acid; the N-methyl salt **5**, on the other hand, was generated from N-methyl-2-piperidone by lithium aluminum hydride reduction followed by treatment with aqueous acetic acid. This reaction of indole and 1-piperideine salts seemed ideally suited for the synthesis of piperidylindoles properly substituted for the construction of complex indole alkaloids. The only obstacle seemed to be the preparation of the necessary 1-piperideine salts since neither of van Tamelen's methods for generating the imonium salts **4** and **5** appeared applicable to more complex systems.

In order to prepare the necessary appropriately substituted 1-piperideine salts, the reaction of pyridinium salts with dithionite was utilized. Sodium dithionite (hydrosulfite) reduces N-alkylnicotinamide salts[5] to N-alkyl-1,4-dihydronicotinamides.[6,7] When this reduction was tried with pyridine methiodide and β-picoline methiodide, no reaction was observed. In view of the observed reduction of nicotinamide and not of simple pyridine methiodides, it seemed evident that an electronegative substituent is necessary for this reaction to take place.[8] In order to test this hypothesis and at the same time prepare a synthetically useful intermediate, the reduction of methyl nicotinate methiodide **6** was investigated. The reaction of the methiodide **6** with sodium dithionite proceeded smoothly to yield the unstable 1,4-dihydropyridine **7** which was immediately hydrogenated over platinum to a separable mixture of the tetrahydropyridine **8** and the piperidine **9**. The structure of the tetrahydropyridine **8** was substantiated by its proton magnetic resonance spectrum which showed a one-proton singlet at τ 2.72 (vinyl hydrogen), a three-proton singlet at τ 6.38 (CH_3OCO–), and a three-proton singlet at τ 7.03 (N–CH_3).

Treatment of the tetrahydropyridine **8** with dilute acid gave the protonated species **11** as shown by the ultraviolet investigations. The tetrahydropyridine has absorption in the ultraviolet region at 240 and 295 mμ. The addition of acid caused an instantaneous

(1) Department of Chemistry, University of California, Los Angeles, Calif. 90024.

(2) G. Büchi and E. W. Warnhoff, *J. Am. Chem. Soc.*, **81**, 4433 (1959).

(3) J. F. D. Mills and S. C. Nyburg, *J. Chem. Soc.*, 1458 (1960).

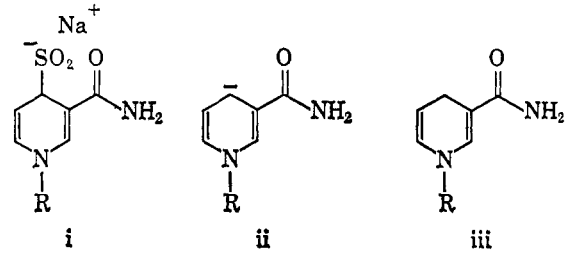
(4) E. E. van Tamelen and G. G. Knapp, *J. Am. Chem. Soc.*, **77**, 1860 (1955).

(5) P. Karrer and F. Blumer, *Helv. Chim. Acta*, **30**, 1157 (1947).

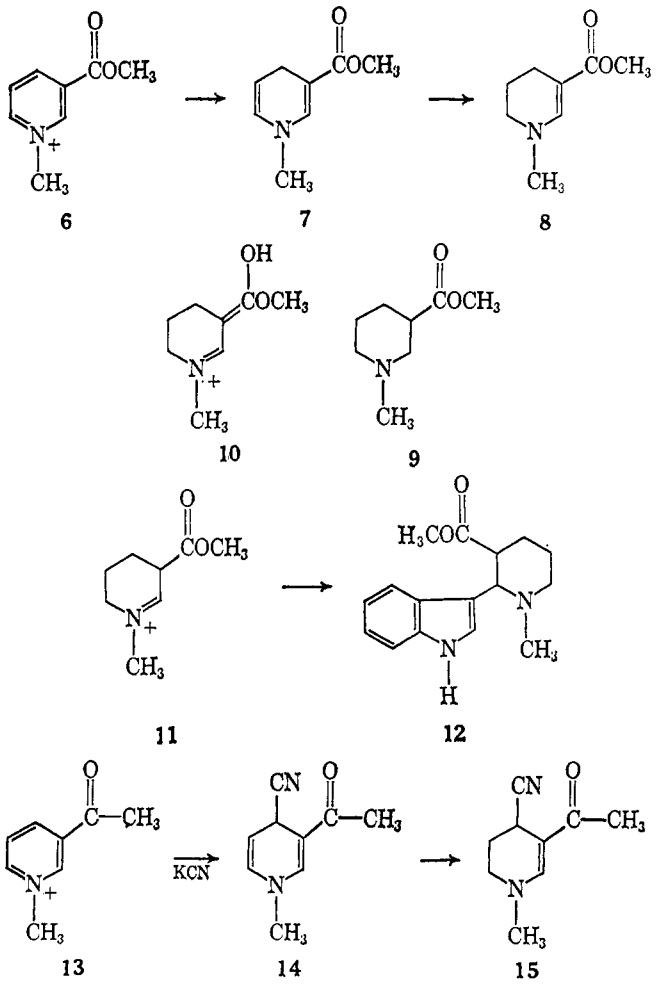
(6) R. F. Hutton and F. W. Westheimer, *Tetrahedron*, **3**, 73 (1958).

(7) K. Wallenfels and H. Schüly, *Ann.*, **621**, 178 (1959).

(8) Wallenfels and Schüly[7] have demonstrated that dithionite reduction of N-alkylnicotinamide salts occurs by initial addition of dithionite ion to yield an adduct i which probably decomposes in neutral or acidic solution to the dihydropyridine iii by way of a carbanion (ii). The presence of electron-withdrawing substituents would assist the reaction by making the pyridine ring more electrophilic and by stabilizing the initially formed adduct (i).

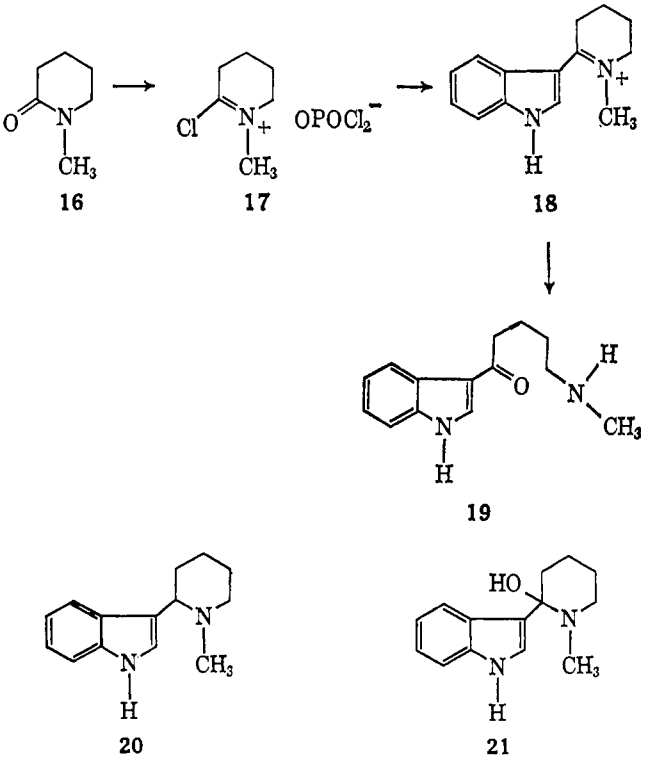


loss of all except weak end absorption. This is ample evidence that **8** is protonating on carbon rather than oxygen since the oxygen protonation would lead to the salt **10** which should have much more intense ultraviolet absorption[9,10] than the imonium salt **11** (carbon protonation). Nitrogen protonation would yield a system which should have strong end absorption in the ultraviolet. Indole smoothly condensed with **11** in acetic acid solution to give the tricyclic ester **12** isolated in good yield as its hydrochloride. The ester showed a typical indolic chromophore in the ultraviolet and had bands in the infrared characteristic of a saturated ester (1735 cm.$^{-1}$), indolic N–H (3200 cm.$^{-1}$), and those characteristic of a hydrogen adjacent and *trans* to the lone pair of a tertiary amine (2800 and 2850 cm.$^{-1}$).[11] Since approach to the imonium salt is certainly less hindered from the side opposite the carbomethoxy group, the adduct probably possesses an all-*trans* stereochemistry. The preferred conformation, therefore, will be that in which both substituents are equatorial with respect to the piperidine ring.



The further applicability of this reaction was tested by trying to condense indole with the cyano ketone **15**. This was prepared by the addition of potassium cyanide to 3-acetylpyridine methiodide (**13**),[12] followed by immediate reduction of the intermediate dihydropyridine **14** with hydrogen over platinum to give the cyano ketone **15**. The intermediate dihydropyridine **14**, an unstable yellow solid, had a carbonyl band in the infrared at 1680 cm.$^{-1}$; the cyano ketone **15** on the other hand had its carbonyl absorption at 1630 cm.$^{-1}$. This low-frequency carbonyl absorption is consistent with a vinylogous amide formulation for **15**.[9] Introduction of an additional double bond, as in **14**, delocalizes the nitrogen lone pair of electrons, consequently diminishing their interaction with the carbonyl group and giving absorption at a higher frequency. The proton magnetic resonance spectrum of **15** showed a one-proton singlet at τ 2.67 (vinyl hydrogen), a three-proton singlet at τ 6.90 (CH_3CO–), and a three-proton singlet at τ 7.84 (CH_3–N). No change was observed in the ultraviolet spectrum of **15** when run in dilute acid. Indole failed to react with the cyano ketone in acetic acid; acidic conditions sufficiently severe to assure protonation of the ketone[9] caused elimination of the cyano group as evidenced by lack of nitrile absorption in the infrared spectra of the uncharacterized products.

Reaction of Vilsmeyer Salts with Indole.—A very fruitful procedure for the synthesis of piperidylindoles was based on the known electrophilicity of Vilsmeyer salts toward the indole ring.[13,14] The Vilsmeyer salt **17**, which should be formed by the reaction of N-methylpiperidone (**16**) with phosphorus oxychloride, can be envisioned to react with indole to give a piperidylindole derivative **18** which would be capable of further transformations. However, neither the desired imonium salt **18** nor its tautomeric enamine were isolated when the reaction was performed; instead, there was obtained in good yield the amino ketone **19**. This was



(9) N. J. Leonard and J. A. Adamcik, *J. Am. Chem. Soc.*, **81**, 595 (1959).
(10) K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 1960 (1959).
(11) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).
(12) M. L. Lamborg, R. M. Burton, and N. O. Kaplan [*J. Am. Chem. Soc.*, **79**, 6173 (1957)] and K. Wallenfels and H. Diekmann [*Ann.*, **621**, 166 (1959)] investigated the effect of potassium cyanide on the ultraviolet spectra of various pyridinium methiodides.
(13) O. Bayer in "Methoden der Organische Chemie," Vol. VII (1), E. Muller, Ed., 4th Ed., G. Thieme Verlag, Stuttgart, 1954, p. 29.
(14) G. F. Smith, *J. Chem. Soc.*, 3842 (1954); H. Rapoport and N. Castagnoli, Jr., *J. Am. Chem. Soc.*, **84**, 2178 (1962); H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960).

TABLE I

ULTRAVIOLET SPECTRA OF INDOLES

Compd.	λ_{max}^{EtOH} (log ϵ), mμ				
Indole		272 (3.9)	278 (3.8)	287 (3.8)	
1-Methylindole	224 (4.3)	272 (3.8)	282 (3.8)	288 (3.7)	294 (3.7)
3-Methylindole	224 (4.4)	275 (3.66)	283 (3.69)	290 (3.61)	
3-Acetylindole[a]			241 (4.09)	258 (3.93)	297 (4.09)
Indole-3-carboxaldehyde		210 (4.4)	245 (4.1)	260 (4.1)	300 (4.1)
19		207 (4.49)	242 (4.04)	256 (3.94)	297 (3.96)
Hydriodide of N-ethyl **19**		210 (4.6)	240 (4.18)	258 (3.98)	297 (4.1)
34	210 (4.0)	255 (3.95)		309 (3.67)	
32	223 (4.44)	267 (4.06)		311 (4.09)	
33	217 (4.49)	258 (3.91)	267 (3.93)	316 (4.16)	
33 methiodide	212 (4.78)	275 (4.02)	284 (3.97)	370 (3.76)	
38	207 (4.68)		268 (4.11)	320 (4.08)	

[a] See ref. 15.

probably formed in the work-up by hydrolysis of the imonium salt **18**. The amino ketone was shown to possess a 3-acylindole structure by its ultraviolet spectrum which was identical with that of 3-acetylindole[15] (see Table I) and by infrared absorption at 3250 (N–H), 1630 (>C=O), 1580, 1540, 790, and 750 cm.$^{-1}$ (indole ring).[16] Reaction of **19** with ethyl iodide yielded the hydriodide of N-ethyl **19** with identical spectral characteristics.

The amino ketone **19** was surprisingly stable. Attempted cyclization to an enamine was unsuccessful and starting material was recovered. This probably reflects the decreased carbonyl reactivity caused by interaction with the indole nitrogen lone pair of electrons. Indeed 3-acylindoles can be treated as vinylogous amides and this is reflected in their low carbonyl absorption in the infrared and their chemical behavior.

Hydrogenation of **19** over platinum in ethanol gave a good yield of 3-(N-methyl-2-piperidyl)indole (**20**). Formation of the cyclic amine indicates the existence of an equilibrium between the ketone **19** and the corresponding carbinolamine **21**. Hydrogenolysis of the benzylic hydroxyl, possibly assisted by the lone pair on nitrogen,[17] would give the observed **20**. The melting point of the reduction product (**20**) was identical with the product obtained by van Tamelen[4] from the reaction of indole with the immonium salt **5**.

Pyridinium Salts and Indole.—Quaternization of pyridines leads to pyridinium salts which are considerably more electrophilic than the parent heterocycles. N-Acylpyridinium salts react smoothly with aldehydes, ketones, and indole to give dihydropyridines.[21-23] If indole could be made to react with these salts at the α-position, potentially valuable intermediates for the synthesis of substituted piperidylindoles would be formed. In spite of a report that the reaction with indole occurred only in the γ-position,[23] some addition was expected to take place to give the desired α-substituted products. There are many analogous reactions in which attack by nucleophiles occurs predominantly at the α-position of pyridinium salts; for example, sodium borohydride and sodium hydroxide add to give initially 1,2-dihydropyridines.

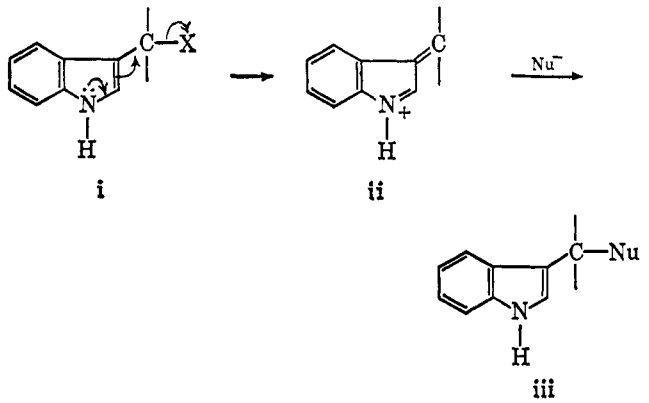
Cyanogen bromide reacted with excess pyridine to give the N-cyanopyridinium salt **22** which was too unstable to isolate. Reaction of this salt (**22**) with indole was expected to yield a mixture of **24** and the desired α-substituted product **26**. Indeed, if indole was present when **22** was formed, a white crystalline compound having the elemental composition of the desired adduct could be isolated from the reaction mixture. The adduct showed absorption typical of an unconjugated indole chromophore in the ultraviolet and had bands in the infrared at 3450 (N–H) and 2260 cm.$^{-1}$ (N–CN). The adduct was assigned the 1,4-dihodropyridine structure **24** since the n.m.r. spectrum showed a two-proton doublet at τ 3.88 (J = 8 c.p.s.) for the α-proton on the pyridine ring further split (2 c.p.s.) by the methine proton, a two-proton doublet at τ 4.9 (J = 8 cps) for the β-pyridine ring proton also split (4 c.p.s.) by the methine proton, and a one-proton multiplet at τ 5.54 for the methine proton. An adduct with the analogous structure **25** was isolated from the reaction of indole, ethyl chlorocarbonate, and pyridine.

A dark orange crystalline compound was also isolated from the cyanogen bromide reaction. It was shown to be the aldehyde **27** by its elemental composition, its infrared spectrum which had bands at 3350 (N–H) and 1670 (>C=O) cm.$^{-1}$, and its n.m.r. spectrum which had a one-proton doublet at τ 0.31 for the aldehydic proton split (8 c.p.s.) by the adjacent

(15) J. W. Baker, *J. Chem. Soc.*, 461 (1946).

(16) 3-Acetylindole has bands in the infrared at 3180 (N–H), 1620 (>C=O), 1610, 1575, 1524, and 1492 cm.$^{-1}$ (indole ring).[15]

(17) The lone pair of electrons on the indole nitrogen readily assists in the ionization of i to the imonium salt ii which smoothly adds nucleophiles to give the substitution product iii. This is illustrated by the reduction of indole-3-carboxylic acid derivatives to skatole ($Nu^- = H^-$) and by the ease with which gramine [i, X = $N(CH_3)_2$] alkylates assorted nucleophiles.[18-20]



(18) A. P. Gray, *J. Am. Chem. Soc.*, **75**, 1252 (1953).

(19) K. T. Potts and R. Robinson, *J. Chem. Soc.*, 2675 (1955).

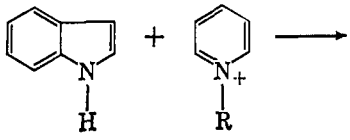
(20) H. R. Snyder and E. L. Eliel, *J. Am. Chem. Soc.*, **71**, 663 (1949).

(21) W. von E. Doering and W. E. McEwen, *ibid.*, **73**, 2104 (1951).

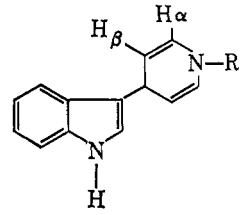
(22) F. Kröhnke, *Ann.*, **600**, 176 (1956).

(23) H. von Dobeneck and W. Goltzsche, *Chem. Ber.*, **95**, 1484 (1962).

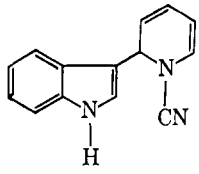
vinyl hydrogen, a one-proton singlet at τ 2.02 for the 2-proton on the indole ring, a one-proton quartet at τ 3.70 for one vinyl hydrogen, and a six-proton multiplet centered at τ 2.60 (vinyl and aromatic protons). The aldehyde **27** was probably formed from the desired adduct **26** during the acidic work-up. The adduct **26** is undoubtedly more labile than the isomeric **24** since ring cleavage of the α-substituted product (**26**) can be assisted by the lone pair of electrons on the indolic nitrogen.[17]



22, R = CN
23, R = $CO_2C_2H_5$



24, R = CN
25, R = $CO_2C_2H_5$



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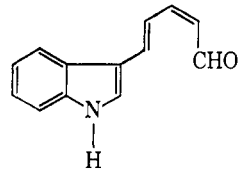
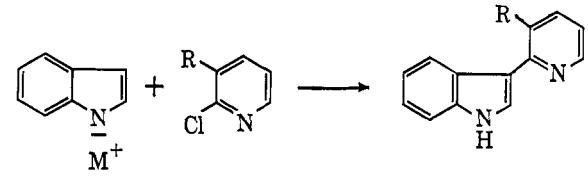


27

The cleavage of the α-substituted adduct **26** to the aldehyde **27** is analogous to the formation of glutaconic dialdehyde derivatives by ring cleavage of pyridinium salts by nucleophiles.[24] Konig obtained a highly colored compound from the reaction of indoles with pyridine and cyanogen bromide.[25] He assigned this a pentamethinediindole structure. If this is correct it could be formed by condensation of indole with the unsaturated aldehyde **27**. Since he reported no physical properties, we were unable to compare our compounds with his.

Addition of the Indole Grignard Reagent to 2-Halopyridines.—Another fertile approach to the synthesis of piperidylindoles involved constructure of the pyridylindole system followed by reduction. Organometallics readily displace halide from 2-halopyridines to yield substitution products. Therefore, a metallic salt of indole should react to give a pyridylindole. Since pyridine and pyridinium rings are more reducible than indoles,[26] selective reduction of these pyridylindoles ought to give the corresponding piperidylindoles.

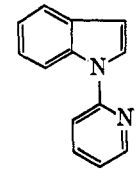
When the sodium salt of indole (**28**) was allowed to react with 2-chloropyridine (**30**), an adduct was isolated which showed ultraviolet absorption at a much higher wave length than simple indoles (see Table I). Since the adduct had no N–H absorption in the infrared, it was assigned a N-pyridylindole structure **34** which is in accord with the well-known propensity of the sodium salts of indoles to give predominantly N-alkylation. The Grignard reagent of indole[27] (**29**), on the other hand, reacted with 2-chloropyridine to give the isomeric adduct **32**. This possessed an N–H band in the infrared at 3200 cm.$^{-1}$ and ultraviolet absorption characteristic of an extended indolic system. The Grignard reagent **29** reacted likewise with 2-chloro-3-cyanopyridine **31** to yield the cyanopyridylindole **33**.



28, M = Na
29, M = MgI

30, R = H
31, R = CN

32, R = H
33, R = CN



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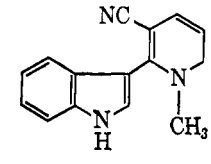

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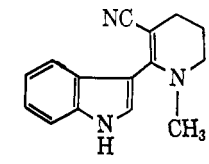

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The pyridylindole **32** formed a methiodide upon reaction with excess methyl iodide and this was reduced with hydrogen over platinum to the corresponding N-methylpiperidylindole **20**. The analogous methiodide formed from **33** proved to be more resistant to hydrogenation. Reduction with sodium borohydride gave the dihydropyridine **35** which could be further hydrogenated to the tetrahydro derivative **36**. All attempts to saturate the pyridine ring completely by further hydrogenation of **36** led to products in which the nitrile had reacted.

The Grignard reagent of indole **29** reacted with 2-chloro-4-cyanopyridine to give an entirely unexpected product. The adduct which was isolated from the reaction had a band in the infrared at 3200 cm.$^{-1}$ (N–H) and an ultraviolet spectrum which was very similar to that of the cyanopyridylindole **33** (see Table I). This compound, however, still contained chlorine as evidenced by an elemental analysis and was thus assigned the chloro ketone structure **38**. The astonishingly low carbonyl frequency (1605 cm.$^{-1}$) cast some doubt on the structure even though 3-acylindoles are characterized by low-frequency carbonyl absorption.[16] Thus, an independent synthesis of this system was carried out. The indole Grignard reagent **29** reacted at 0° with the mixed anhydride formed from isonicotinic acid and ethyl chloroformate to yield the ketone **39**. This likewise had its carbonyl band at the extremely low frequency of 1605 cm.$^{-1}$. Reduction of the chloro ketone **38** with hydrogen over palladium gave a good yield of the ketone **39**.

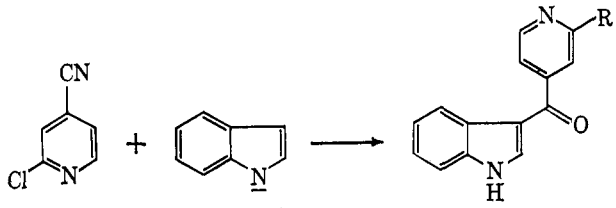
(24) H. S. Mosher in "Heterocyclic Compounds," Vol. 1, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 424–432.

(25) W. Konig and R. Schreckenbach, *J. prakt. Chem.*, [No. 2] **87**, 241 (1913).

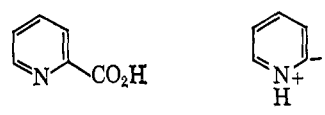
(26) A. P. Gray and H. Kraus, *J. Org. Chem.*, **26**, 3368 (1961).

(27) M. G. Reinecke, H. Johnson, and J. F. Sebastian, *Tetrahedron Letters*, 1183 (1963).

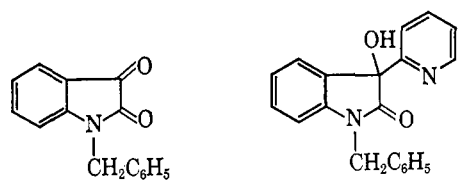
Addition of Pyridine Ylids to Isatins.—Picolinic acid **40** readily decarboxylates to pyridine. This reaction has been shown to go by way of the carbanionic intermediate **41** which will add to ketones.[28,29] As a final mode for attaching a pyridine ring to an indole, picolinic acid was decarboxylated in the presence of N-benzylisatin **42**. The ylid **41** added to ketonic carbonyl and the dioxindole **43** was isolated in good yield. All attempts to reduce the dioxindole **43** to the corresponding indole were unsuccessful.



37 **29** **38**, R = Cl; **39**, R = H



40 **41**



42 **43**

Experimental

Microanalyses were performed by Dr. S. Nagy and associates, Massachusetts Institute of Technology, Microanalytical Laboratory, and by Miss Heather King, University of California at Los Angeles. Melting points were determined on a Kofler hot-stage microscope or with a Büchi melting point apparatus and are corrected. Boiling points are uncorrected. Ultraviolet spectra were measured on a Cary recording spectrophotometer, Model 11; infrared spectra were measured on a Perkin-Elmer recording spectrophotometer, Model 21, with a sodium chloride prisms, or on a Perkin-Elmer Model 127 Infracord. The listings of infrared bands include those which are relevant to the structural argument and other medium and strong bands. A Varian Associates A-60 instrument was used for recording n.m.r spectra. Peak positions are given in τ values. The alumina used for chromatography was Alcoa F-20. The gas–liquid partition chromatograms were obtained with 0.6 × 215 cm. columns packed with 10–20% by weight suspensions of Dow Corning silicone oil, no. 550, on a support of 48–100-mesh firebrick. The fractions, eluted with helium, were detected with a thermal conductivity cell.

Methyl 1-Methyl-1,4,5,6-tetrahydronicotinate (8).—To a solution of 220 g. of sodium dithionite (hydrosulfite) and 170 g. of sodium carbonate in 2 l. of water was added 220 g. of methyl nicotinate methiodide. The resulting solution was stirred for 1 hr. and then extracted with four 100-ml. portions of methylene chloride to give, after drying over magnesium sulfate and evaporation, 89 g. of the oily dihydropyridine (**7**). This was hydrogenated over 5 g. of platinum oxide in 300 ml. of ethanol. The reaction was interrupted after 15,000 cc. of hydrogen (theoretical, 14,200 cc.) had been absorbed. The catalyst was removed by filtration and, after evaporation of the ethanol, the remaining oil was distilled through a spinning-band column yielding 21.6 g. of methyl 1-methylhexahydronicotinate (**9**),[30] b.p. 60–70° (2 mm.), and 34 g. (28%) of methyl 1-methyl-1,4,5,6-tetrahydronicotinate (**8**), b.p. 100–105° (2 mm.). The tetrahydronicotinate had bands in the infrared spectrum (film) at 1680 and 1625 cm.$^{-1}$ and λ_{max}^{EtOH} 240 and 295 mμ (ϵ 1900 and 23,600, respectively) which disappeared on addition of acid. The n.m.r. spectrum exhibited a proton singlet at τ 2.72, a three-proton singlet at τ 6.38, and a three-proton singlet at τ 7.03.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.99; H, 8.45; N, 9.04. Found: C, 61.82; H, 8.63; N, 9.27.

3-(3-Carbomethoxy-1-methyl-2-piperidyl)indole Hydrochloride.—A mixture of 6 g. of indole, 6 g. of methyl 1-methyl-1,4,5,6-tetrahydronicotinate (**8**), and 20 ml. of acetic acid was stirred at 35° for 2 days under nitrogen. The reaction mixture was poured into 10% aqueous hydrochloric acid and the solution was extracted rapidly with chloroform. On standing for a few minutes the hydrochloride precipitated and was collected by filtration. Recrystallization from chloroform–methanol gave 8 g. of product, m.p. 231–234° (sublimes). An analytical sample recrystallized from methanol had bands in the infrared (Nujol) at 3200, 2700, and 1735 cm.$^{-1}$ and λ_{max}^{EtOH} 217, 274, 280, and 287 mμ (ϵ 41,000, 6500, 6800, and 5600, respectively).

Anal. Calcd. for $C_{16}H_{23}ClN_2O_3$: C, 62.19; H, 6.85; N, 9.07. Found: C, 62.27; H, 6.77; N, 8.65.

A solution of the salt in a small amount of ethanol was made basic with dilute sodium hydroxide solution. Extraction with chloroform, evaporation, and recrystallization from benzene gave the free base **12**, m.p. 109–114°. It had bands in the infrared (film) at 3400, 2850, 2800, and 1730 cm.$^{-1}$.

3-Acetyl-4-cyano-1-methyl-1,4,5,6-tetrahydropyridine (15).—A solution of 4.0 g. of potassium cyanide in 5 ml. of water was added slowly to a solution of 4.0 g. of 3-acetylpyridine methiodide[30] in 4 ml. of water. The precipitated dihydropyridine (**14**) was collected on a filter and washed once with water. It was unstable but could be recrystallized from acetone to give yellow needles: m.p. 113–123°; infrared bands at 2240, 1680, 1645, and 1590 cm.$^{-1}$. The partially dried solid dihydropyridine was usually not purified further and was immediately dissolved in hot ethyl acetate. Hydrogenation of the dried ethyl acetate solution over 500 mg. of platinum oxide resulted in the uptake of 90% of the theoretical amount of hydrogen. The catalyst was filtered and removal of the solvent from the filtrate gave a solid which was recrystallized from acetone–ether to give 1.33 g. (58%) of product. The analytical sample was recrystallized from acetone: m.p. 120–122°; λ_{max}^{EtOH} 298 mμ (ϵ 30,000), no change in acid; infrared 2230, 1630, and 1590 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.91; H, 7.38; N, 17.08. Found: C, 65.61; H, 7.30; N, 17.00.

3-(5-Methylaminovaleryl)indole (19).—Phosphorus oxychloride (9 g.) was added to a solution of 6 g. of indole and 6 g. of N-methyl-δ-valerolactam (**16**) in 100 ml. of chloroform. The resulting solution was refluxed for 3 hr. and poured into 10% hydrochloric acid in water. The organic layer was extracted with dilute hydrochloric acid and the combined acid layers were washed with methylene chloride. The acid solution was poured into excess dilute sodium hydroxide solution and the resulting yellow precipitate was filtered and washed with water. Recrystallization from methanol–ether gave 3.83 g. of product. An analytical sample recrystallized from acetone had m.p. 108–113°; bands in the infrared (Nujol) at 3250, 1630, 1580, 1540, 790, and 740 cm.$^{-1}$; and λ_{max}^{EtOH} 207, 242, 256, and 299 mμ (ϵ 31,000, 11,000, 8650, and 9100, respectively).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.10; H, 7.89; N, 12.18. Found: C, 73.13; H, 7.65; N, 12.04.

3-(5-Ethylmethylaminovaleryl)indole Hydroiodide.—A mixture of 200 mg. of 3-(5-methylaminovaleryl)indole (**19**), 1 ml. of ethyl iodide, and 3 ml. of ethanol was allowed to reflux for 24 hr. The reaction mixture was cooled and the precipitated product (150 mg.) was collected on a filter. An analytical sample was recrystallized from ethanol to give white needles, m.p. 189–199°. The hydriodide had bands in the infrared (Nujol) at 3200, 1635, 1590, 1530, 780, and 750 cm.$^{-1}$ and λ_{max}^{EtOH} 210, 240, 258, and 297 mμ (ϵ 40,000, 15,000, 9500, and 12,500, respectively).

Anal. Calcd. for $C_{16}H_{23}IN_2O$: C, 49.78; H, 6.01; N, 7.26. Found: C, 49.78; H, 6.36; N, 7.25.

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3-(1-Methyl-2-piperidyl)indole (20).—A solution of 1 g. of 3-(5-methylaminovaleryl)indole (**19**) in ethanol was hydrogenated over 250 mg. of platinum oxide. Hydrogen uptake was complete after 80% of the theoretical amount had been absorbed. Filtration, evaporation of the ethanol, and recrystallization of the residue from acetone gave 670 mg. of white cubes. An analytical sample recrystallized from acetone had m.p. 160–162° (sublimes); bands in the infrared (Nujol) at 3100, 1620 (w), 780, and 745 cm.$^{-1}$; and λ_{max}^{EtOH} 218, 274, 280, and 288 mμ (ε 38,000, 6400, 6600, and 5500, respectively).

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.57; H, 8.48; N, 13.09. Found: C, 78.51; H, 8.29; N, 13.24.

3-(1-Cyano-1,4-dihydro-2-pyridyl)indole (24).—A solution of 10 g. of cyanogen bromide in 30 ml. of ether was added dropwise to a cooled solution of 6 g. of indole in 50 ml. of pyridine. The resulting mixture was allowed to stand at room temperature for 15 min. and was poured into dilute hydrochloric acid solution. This mixture was then extracted several times with chloroform; the combined extracts were dried and concentrated to give a residue which was chromatographed on alumina. Elution with benzene gave a solid which was recrystallized from benzene to give 3.4 g. of white needles with m.p. 143–144° dec.; λ_{max}^{EtOH} 220, 273, 280, and 290 mμ (ε 38,700, 6300, 6400, and 5300, respectively); and infrared bands (Nujol) at 3470, 2260, 1690 (w), and 1640 (w) cm.$^{-1}$. The n.m.r. spectrum exhibited a pair of doublets at τ 3.88 (J = 8 and 2 c.p.s.), a pair of doublets at τ 4.9 (J = 8 and 4 c.p.s.), and a one-proton multiplet at τ 5.54.

Anal. Calcd. for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 76.11; H, 5.04; N, 19.12.

5-(3-Indolyl)-2,4-pentadienal (27).—Continued elution with chloroform of the above chromatogram gave an orange-yellow solid which was recrystallized from ethanol containing a little acetone to yield 1.3 g. of product with m.p. 212–213.5°; λ_{max}^{MeOH} 226, 270, 278, and 390 mμ (ε 9550, 5750, 5600, and 12,400, respectively); and infrared bands (Nujol) at 3350, 1670, and 1590 (br) cm.$^{-1}$; ($CHCl_3$) 1685 1620, 1590, and 1530 cm.$^{-1}$. Thin layer chromatograms of the product could be visualized either with Ehrlich reagent (green spot) or with dinitrophenylhydrazine (red spot). The n.m.r. spectrum showed a one-proton doublet at τ 0.31 (J = 8 c.p.s.), a one-proton singlet at τ 2.02, a one-proton quartet at τ 3.70, a six-proton quartet at τ 3.70, and a six-proton multiplet centered at τ 2.60.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.87; H, 5.54; N, 7.34.

3-(1-Carboethoxy-1,4-dihydro-2-pyridyl)indole.—Ethyl chloroformate (2.16 g.) was added slowly to a solution of 2.34 g. of indole in 40 ml. of pyridine. After 36 hr. at room temperature, the mixture was poured into 10% hydrochloric acid in water. This mixture was extracted with ether and the combined ether extracts were washed with 10% hydrochloric acid. The ether was dried and evaporated to yield an oil which crystallized on standing. Two crystallizations from ethanol gave 0.6 g. of a white solid: m.p. 136–138°; infrared bands (Nujol) at 3400, 1650, and 1605 cm.$^{-1}$; λ_{max}^{EtOH} 223, 275 (br), and 290 mμ (ε 55,000, 10,000, and 8400, respectively).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C,71.70; H, 6.02; N, 10.45. Found: C, 72.04; H, 6.30; N, 10.36.

1-(2-(Pyridyl)indole (34).—A mixture of the sodium salt of indole prepared from 1.5 g. of indole and sodium hydride, 3 ml. of 2-chloropyridine, and 4.5 ml. of dioxane was heated in a sealed tube at 170° for 8 hr. The reaction mixture was poured into water and extracted with chloroform; the chloroform extracts were dried and evaporated to give a residue which was chromatographed twice on alumina. Elution with pentane gave a liquid with λ_{max}^{EtOH} 210, 255, and 309 mμ (ε 10,000, 8900, and 4700, respectively) and infrared bands (film) at 1590, 1520, 780, 760, 740, and 720 cm.$^{-1}$. Treatment with picric acid in ethanol gave a picrate with m.p. 101.5–103.5° after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{13}N_5O_7$: C, 53.95; H, 3.10; N, 16.56. Found: C, 53.87; H, 3.24; N, 16.21.

3-(2-Pyridyl)indole (32).—The Grignard reagent prepared in the usual way from 1.5 g. of indole was placed in a sealed tube with 5 ml. of 2-chloropyridine. After heating for 12 hr. at 160°, the reaction mixture was poured into water and extracted with chloroform. The residue obtained on drying and concentrating the chloroform extracts was chromatographed on alumina. After excess indole had been eluted with benzene, a solid material was eluted with chloroform. Several crystallizations from benzene followed by sublimation gave 300 mg. of white crystals, m.p. 150–154°. The product had λ_{max}^{EtOH} 223, 267, and 311 mμ (ε 27,500, 11,600, and 12,300, respectively) and showed bands in the infrared (Nujol) at 3200, 1595, 785, 740, 710, and 3550 cm.$^{-1}$ (chloroform).

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.48; H, 5.20; N, 14.44. Found: C, 80.50; H, 5.09; N, 14.60.

3-(2-Pyridyl)indole Methiodide.—A solution of 1.05 g. of 3-(2-pyridyl)indole and 5 ml. of methyl iodide in 25 ml. of acetone was allowed to stand at room temperature for 2 days. Filtration yielded 1.55 g. of the methiodide: m.p. 215–216°; λ_{max}^{MeOH} 216, 268, and 365 mμ (ε 29,000, 7000, and 6600, respectively).

Anal. Calcd. for $C_{14}H_{13}IN_2$: C, 50.01; H, 3.90; N, 8.33. Found: C, 50.14; H, 3.86; N, 8.12.

Reduction of 3-(2-Pyridyl)indole Methiodide.—A solution of 500 mg. of 3-(2-pyridyl)indole methiodide and 500 mg. of potassium carbonate in 25 ml. of methanol and 5 ml. of water was hydrogenated over 100 mg. of reduced platinum oxide. Hydrogen uptake stopped after the absorption of 4.1 equiv. of hydrogen. The solid which had formed was filtered and dissolved in hot methanol and separated from the platinum catalyst by filtration. Evaporation of the methanol and recrystallization of the residue from benzene–acetone gave 162 mg. of 3-(1-methyl-2-piperidyl)indole (**20**) identified by comparison of the infrared spectra and R_f on silica gel G thin layer chromatograms with an authentic sample.

3-(3-Cyano-2-pyridyl)indole (33).—A solution of the Grignard reagent of indole in ether was prepared from 12.9 g. of indole, 2.64 g. of magnesium, and methyl iodide. Using a Soxhlet extractor, 2-chloro-3-cyanopyridine (**31**) was added. After the addition was complete the ether was distilled off slowly with rapid stirring. The reaction mixture foamed and solidified. It was then heated in an oil bath at 170–171° for 3 hr. The flask was then broken, the residue was digested with hot methanol, and the methanol solution was filtered and concentrated. The residue was sublimed and recrystallized from methanol to give 6.5 g. (52%) of product. An analytical sample, m.p. 199–200.5°, had λ_{max}^{EtOH} 217, 258, 267, and 316 mμ (ε 31,000, 8200, 8500, and 14,600, respectively) and bands in the infrared (Nujol) at 3200 and 2220 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_8N_3$: C, 76.68; H, 4.14; N, 19.19. Found: C, 76.34; H, 4.17; N, 19.26.

3-(3-Cyano-2-pyridyl)indole Methiodide.—A solution of 1.4 g. of **33**, 5 ml. of methyl iodide, and 15 ml. of acetone was heated in a sealed tube at 85° for 2 days. Filtration of the reaction mixture yielded 2.1 g. of product, m.p. 197–205° dec. An analytical sample was crystallized from methanol–acetone and had λ_{max}^{EtOH} 212, 275, 284, and 370 mμ (ε 61,000, 10,500, 9600, and 5800, respectively).

Anal. Calcd. for $C_{15}H_{12}IN_3$: C, 49.90; H, 3.39; N, 11.64. Found: C, 49.88; H, 3.44; N, 11.63.

Dihydropyridine (35).—Sodium borohydride (1 g.) was added to a solution of 1.3 g. of the methiodide of **33** methanol in batches with cooling. A yellow crystalline product separated slowly. This was collected and the filtrate was concentrated and added to water to yield a second crop (total yield 400 mg.). An analytical sample was recrystallized from methanol–acetone, m.p. 180–200° dec.; λ_{max}^{EtOH} 213, 263, 279, 288, and 360 mμ (ε 39,000, 11,000, 7000, 1500, and 6700, respectively); infrared bands (chloroform) at 3470, 3300, and 2200 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{13}N_3$: C, 76.66; H, 5.58; N, 17.88. Found: C, 76.61; H, 5.76; N, 17.52.

Tetrahydropyridine (36).—A solution of 1 g. of the methiodide **35** in ethanol was hydrogenated over platinum oxide. Uptake of hydrogen was complete after 2 moles was absorbed. The reaction mixture was filtered and evaporated. The white solid was sublimed and recrystallized from acetone–methanol (yield 350 mg.). It had m.p. 200–203° (sublimes) and λ_{max}^{EtOH} 222, 273, and 300 mμ (ε 11,000, 9000, and 6500, respectively) and showed bands in the infrared (chloroform) at 3500 and 2200 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{15}N_3$: C, 76.01; H, 6.38; N, 17.73. Found: C, 76.12; H, 5.87; N, 18.00.

3-Indolyl 4(2-Chloropyridyl) Ketone (38).—A solution of 1.50 g. of indole in 20 ml. of ether was added to an ether solution of the Grignard reagent prepared from 2.16 g. of magnesium and 16.35 g. of ethyl iodide. To this mixture was added 6 g. of 2-chloro-4-cyanopyridine by means of a Soxhlet extractor. The reaction mixture was then placed in an oil bath, the temperature was slowly increased, and the ether was allowed to distil off. After all the ether had been removed, the resulting mixture was heated at 150–180° for 3 hr. Upon cooling, the reaction mix-

ture was treated with methanol and then filtered from an insoluble material. Evaporation of the methanol gave a residue which was chromatographed on activity III Woelm alumina. Elution with benzene gave a solid. Crystallization from benzene–acetone gave 300 mg. of light yellow plates with m.p. 234.5–236.5°; λ_{max}^{MeOH} 207, 268, and 320 mμ (ε 48,000, 13,000, and 12,000 respectively); and infrared bands (Nujol) at 3200, 1605 1580, 1535, 1515, and 1495 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_9ClN_2O$: C, 65.42; H, 3.53; Cl, 13.80; N, 10.90. Found: C, 65.51; H, 3.73; Cl, 14.08; N, 10.82.

Reduction of 3-Indolyl 4-(2-Chloropyridyl) Ketone.—Hydrogenation of 250 mg. of 3-indolyl 4-(2-chloropyridyl) ketone in a suspension of 100 mg. of reduced palladium chloride, 900 mg. of barium carbonate, and 25 ml. of ethanol resulted in the uptake of 1.1 equiv. of hydrogen. Filtration of the mixture into chloroform removal of the ethanol by means of an aqueous washing, desiccation over magnesium sulfate, and evaporation gave a solid. When recrystallized from acetone this had an infrared spectrum, melting point, mixture melting point, and an R_f value on silica gel G thin layer chromatograms (eluent, 1% ethanol in chloroform) identical with that of 3-indolyl 4-pyridyl ketone (**39**).

3-Indolyl 4-Pyridyl Ketone (39).—To a suspension of 5 g. of isonicotinic acid in methylene chloride was added 4.1 g. of triethylamine. This was cooled to 0° in an ice bath and ethyl chloroformate was added over a period of 10 min. The solution was stirred at 0° for 30 min. to complete formation of the mixed anhydride and was rapidly added to a solution of the Grignard reagent of indole in ether prepared from 10.5 g. of indole. The resulting mixture was stirred at room temperature for 2 hr. and then decomposed by the addition of ammonium chloride solution. Extraction with chloroform, followed by desiccation and evaporation, gave a residue which was dissolved in chloroform. Extraction with dilute hydrochloric acid gave an aqueous phase which was washed once with chloroform and then poured into sodium hydroxide solution to give a solid. Filtration and crystallization from acetone gave 850 mg. of yellow needles. An analytical sample was recrystallized twice from acetone to give white needles with m.p. 235–236°; λ_{max}^{MeOH} 208, 258, and 310 mμ (ε 35,500, 23,000, and 11,000, respectively); and infrared bands (Nujol) at 3200, 1605, 1575, 1550, and 1520 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.58; H, 4.48; N, 12.55.

1-Benzyl-3-(2-pyridyl)dioxindole (43).—A mixture of 9 g. of picolinic acid and 5 g. of 1-benzylisatin was melted under nitrogen. The melt was then allowed to stand in an oil bath at 180–200° for 2 hr. while carbon dioxide was evolved. The cooled reaction mixture was then dissolved in chloroform and this was extracted several times with 10% aqueous hydrochloric acid. The acidic extracts were basified with sodium hydroxide and then extracted with chloroform. Drying and evaporation of the chloroform gave a solid which was recrystallized from ethanol to give 1.6 g. of product: m.p. 192.5–194°; λ_{max}^{MeOH} 211, 258, and 290 mμ (ε 26,000, 6400, and 1050, respectively); infrared (Nujol) at 3450, 1700, 1620, 1590, and 1495 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.18; N, 8.86. Found: C, 75.92; H, 5.10; N, 8.80.

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The Base-Catalyzed Alkylation of Fluorene and Indene with Alcohols and Diols

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Fluorene can be alkylated in the 9-position with alcohols, using alkali metal hydroxide as catalyst. If the alkylating agents are diols, 9-(hydroxyalkyl)fluorenes as well as bis(9-fluorenyl)alkanes are obtained as products. Products of the reaction of fluorene with several alcohols and diols are described, as are a number of derivatives of bis(9-fluorenyl)alkanes. The alkylation reaction is also applicable to indene, which is alkylated in the 1- and 3-positions.

Schoen and Becker[1] reported in 1955 that sodium alkoxide in a solution of the corresponding alcohol will alkylate fluorene in the 9-position. The alkylation of fluorene with sodium ethoxide in ethanol, for example, yielded 9-ethylfluorene. Later Rubin and Becker extended the reaction to include diols. They prepared 1,2-bis(9-fluorenyl)ethane from fluorene, sodium, and ethylene glycol.[2] In all these experiments the amount of alkali metal used was in stoichiometric excess of the amount of fluorene added.

We have pursued the study of the alkylation of fluorene with alcohols and can report that it is not necessary to use as strong a base as alkali metal alkoxide, but that alkali metal hydroxides will do. Also, it is not necessary to use stoichiometric quantities of base; catalytic quantities will do. Four 9-alkylfluorenes were prepared, using methanol, ethanol, 1-butanol, and 2-ethylhexanol. A mixture of C_{10} alcohols[3] was also treated with fluorene, giving a mixture of 9-isodecylfluorenes.

The reactions were conducted at temperatures of 180–250°, usually in a rocker autoclave, but some reactions of high-boiling alcohols could be carried out in flasks at atmospheric pressure. Data from a number of runs are given in Table I. The data show that catalytic amounts of potassium hydroxide and sodium hydroxide work equally as well as stoichiometric amounts of sodium alkoxide in effecting the reaction of fluorene with alcohols. They also show that lithium hydroxide, calcium oxide, and tributylamine are not catalysts for the reaction.

Like Rubin and Becker,[2] we found that, when a diol is used instead of an alcohol, a bis(9-fluorenyl)alkane (I) is formed. With potassium hydroxide or sodium hydroxide as catalyst, however, there is also an appreciable yield of 9-(hydroxyalkyl)fluorene (II), and the yield of this product increases with increasing catalyst concentration. Alkylation of fluorene with ethylene glycol in the presence of potassium hydroxide

(1) K. L. Schoen and E. I. Becker, *J. Am. Chem. Soc.*, **77**, 6030 (1955).
(2) I. D. Rubin and E. I. Becker, *J. Org. Chem.*, **22**, 1623 (1957).
(3) Union Carbide's C_{10} alcohols, trade name "iso-Decanol."