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Synthesis of Indoles from 4-Oxo-4,5,6,7-tetrahydroindoles. II.[1] Introduction of Substituents into the 4 and 5 Positions

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A new general method for the synthesis of indoles is described. In this method 4-oxo-4,5,6,7-tetrahydroindoles, which have suitable blocking groups on the nitrogen, are substituted at the 5 position by groups such as alkyl, phenyl, alkylthio, bromo, and cyano. Most of these transformations (except bromination) were effected by the use of a 5-hydroxymethylene substituent. Heterocyclic rings, such as isoxazole and aminothiazole, could be fused to the 4,5 positions. Other substituents were introduced at the 4 position by reaction of the carbonyl group with Grignard, Reformatsky, and Wittig reagents. Certain of the novel substituted 4-oxotetrahydroindoles and 6,7-dihydroindoles prepared by these reactions were then dehydrogenated to the fully aromatic indoles. In order to obtain indoles unsubstituted on nitrogen, various removable blocking groups were examined. Of these groups, benzyl and benzoyl were the most useful.

In a previous communication[1a] we suggested that a versatile new method of indole synthesis was available based upon transformations of 4-oxotetrahydroindoles. Since then, we have expanded the method to include a wide variety of substituents at the 4 and 5 positions. The present article describes the introduction of these substituents, considers the use of blocking groups on nitrogen to further extend the method, and points out important limitations in the method.

The most generally useful method for the preparation of 4-oxotetrahydroindoles is due to Stetter and Lauterbach.[3] In this method 1,3-cyclohexanediones (**1**), including those substituted at the 6 position, are alkylated with α-halo ketones and the resulting triones **3** are condensed with ammonia or primary amines. Products with a variety of alkyl and aryl groups at 1, 2, 3, and 6 are obtained. A useful variant of this procedure is based upon alkylation of 1,3-cyclohexanedione with ethyl bromopyruvate. Treatment of the resulting 4-oxotetrahydrobenzofuran-3-carboxylic acid (**2**) with ammonia at 153° gives the parent 4-oxotetrahydroindole **5**.[3] There are also three other known methods for the preparation of 4-oxotetrahydroindole derivatives.[4-7]

The usefulness of 4-oxotetrahydroindoles in indole synthesis is determined by two factors inherent in their structures. One of these factors is the conjugation between the pyrrole nitrogen and the carbonyl group (which deactivates both functions). Thus the carbonyl group is less reactive than normal carbonyl groups toward nucleophiles, and the pyrrole ring is less susceptible to electrophilic attack (and consequently more stable in acid) than ordinary pyrroles. Physical evidence for this conjugation is provided by the ir spectra of the 4-oxotetrahydroindoles. In the N-alkyl derivatives the carbonyl stretch is at 6.38 μ and in N-H derivatives it is at 6.25 μ (KBr disks). Chemical evidence for this deactivation is found in the failure of **5** to undergo reaction with sodium bisulfite, potassium cyanide in acetic acid, or pyrrolidine and p-toluenesulfonic acid. However, the carbonyl group of **5** does retain sufficient ketonic character to allow oxime and hydrazone formation. As discussed below, 4-oxotetrahydroindoles blocked on nitrogen also react with certain Grignard and Wittig reagents.

The second important feature of 4-oxotetrahydroindoles which determines their usefulness in indole synthesis is the relatively acidic hydrogen possessed by those derivatives unsubstituted on nitrogen. Treatment of these compounds (*e.g.*, **5**) with bases affords a pyrrolyl-type anion which recieves additional stabilization due to conjugation with the carbonyl group. This conjugation decreases the reactivity of the carbonyl group to a level where it is unreactive toward carbanions. Furthermore, the methylene group adjacent to this carbonyl group does not participate in base-catalyzed condensations.[8] However, if the nitrogen is substituted with an alkyl or benzyl group, both of these reaction types can be effected.

We have examined several different types of substituents, including removable blocking groups, for the nitrogen of 4-oxotetrahydroindoles. The ethyl group was particularly important in the synthesis of indoloquinone analogs of the mitomycin antibiotics. This

(1) (a) The first paper in this series is considered to be the preliminary communication by W. A. Remers and M. J. Weiss, *J. Amer. Chem. Soc.*, **87**, 5262 (1965). (b) A brief discussion of this method is given by M. J. Weiss, G. R. Allen, Jr., G. J. Gibs, J. F. Poletto, and W. A. Remers in "Topics in Heterocyclic Chemistry," R. C. Castle, Ed., Wiley-Interscience, New York, N. Y., 1969.

(2) To whom inquiries should be addressed at the Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, Ind. 47907.

(3) H. Stetter and R. Lauterbach, *Justus Liebigs Ann. Chem.*, **655**, 20 (1962).

(4) A. H. Kost, L. J. Ovseneva, and T. G. Shuvaeva, *Khim. Geterosikl. Soedin*, 717 (1966) [*Chem. Abstr.*, **66**, 115537 (1967)]; K. Schoen, I. J. Pachter, and A. A. Rubin, Abstracts, 153rd National Meeting of the American Chemical Society, Division of Medicinal Chemistry, April 1967, No. 46.

(5) S. Hauptmann, M. Blume, G. Hartmann, D. Haendel, and P. Franke, *Z. Chem.*, **6**, 107 (1966).

(6) K. E. Schulte, J. Reisch, and H. Lang, *Chem. Ber.*, **96**, 1470 (1963).

(7) J. M. Bobbitt and C. P. Dutta, *Chem. Commun.*, 1429 (1968).

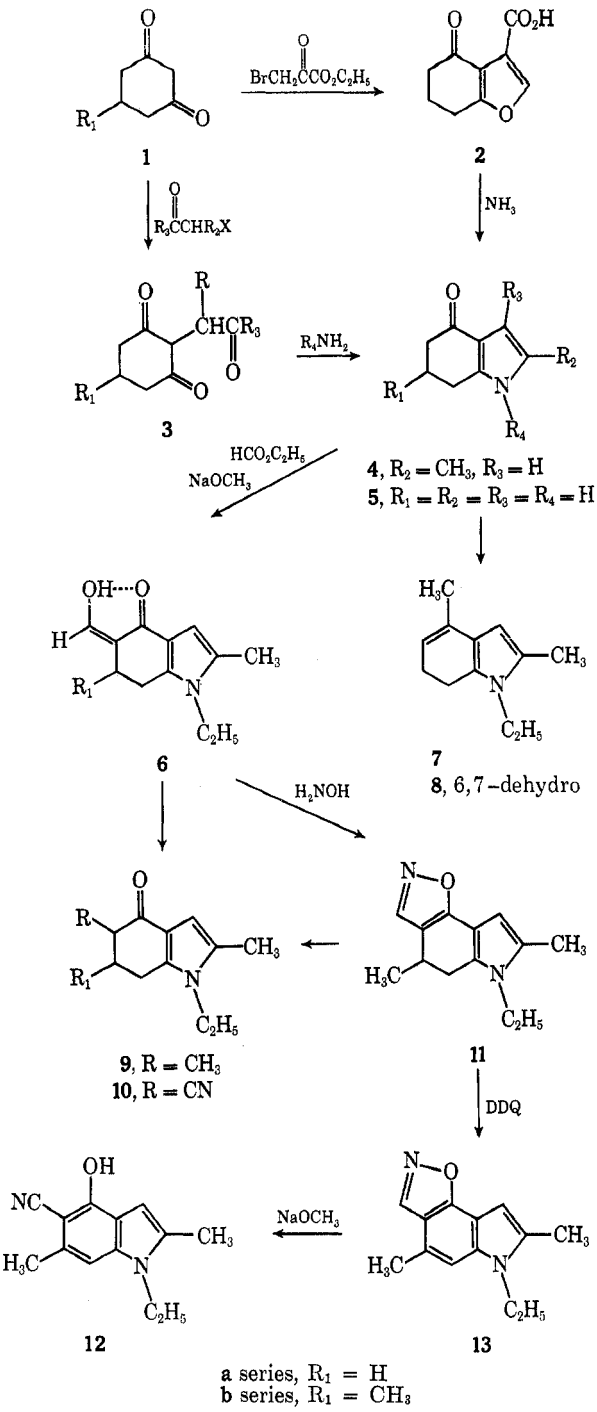
(8) This aspect of the chemistry of 4-oxotetrahydroindoles was first investigated by F. J. McEvoy, J. M. Smith, Jr., and D. S. Allen, Jr., U. S. Patent 3,404,157 (1968); see *Chem. Abstr.*, **65**, 20134c (1966).

work has been reported previously.[9] Additional indole syntheses with *N*-ethyl compounds were based upon the preparation of 5-hydroxymethylene derivatives **6a** and **6b**, by formylation of **4a** and **4b** with ethyl formate in the presence of sodium methoxide.[10] These hydroxymethylene derivatives afford the means for introduction of various substituents into the 5 position, as well as for the fusion of an additional ring to the 4,5 positions. For example, **6a** was converted into the corresponding nitrile **10a** upon treatment with bis-*O*,*N*-trifluoroacetylhydroxylamine.[11] Under mild conditions, **6b** and hydroxylamine afforded the 4,5-dihydroisoxazolo[5,4-*e*]indole **11**. However, prolonged heating of the reaction mixture resulted in opening of the isoxazole ring of **11**, affording nitrile **10b**.[8] The pyrroloindazole system was obtained by treatment of **6b** and **10b** with a variety of hydrazine derivatives.[8] The hydroxymethylene groups of **6a** and **6b** were also useful for the introduction of 5-methyl groups. Products **9a** and **9b** were obtained in good yields by treatment of these compounds with methyl iodide and potassium carbonate followed by methoxide-catalyzed deformylation (Scheme I).

The *N*-benzyl blocking group can be introduced in the formation of the 4-oxotetrahydroindole[3] or, alternatively, it can be introducted by alkylation with benzyl chloride of the anion formed by the action of base on the N-unsubstituted 4-oxotetrahydroindole. The most satisfactory method for this alkylation was treatment of the 4-oxotetrahydroindole with 1 equiv of methylsulfinyl carbanion in dimethyl sulfoxide[12] followed by benzyl chloride. As noted below, the benzyl blocking group was readily removed from the ultimate indole product by reduction with sodium in ammonia.[8]

The 1-benzyl compound **17** was converted into its 5-hydroxymethyl derivative **21**, which was further transformed into 5-methyl derivative **20**. The carbonyl groups of 4-oxotetrahydroindoles blocked on nitrogen are reactive toward certain Wittig reagents. Thus treatment of **20** with triphenylmethylene phosphorane afforded a mixture of the 5-methyl-4-methylenetetrahydroindole **25** and the isomeric 4,5-dimethyl-6,7-dihydroindole **22** in approximately equal amounts, as shown by the nmr spectrum of this mixture (Experimental Section). Observations of isomers in the products of Wittig reactions are extremely rare,[13] and the reasons for their occurrence in the present example (and that of

SCHEME I



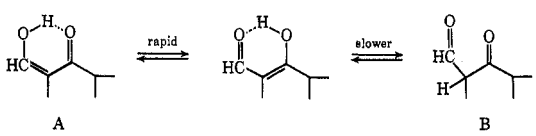
4 noted below) are not apparent. Excess base was present, but this is true in many Wittig reactions.

Isomerization was also noted in the reaction of **4** with triphenylmethylene phosphorane. In this case the only product isolated was the isomeric 4-methyl-6,7-dihydroindole **7**. Treatment of **4** with methylmagnesium iodide also afforded **7**.

Hydroxymethylene derivative **21** was also useful for the introduction of a 5-phenyl substituent. When it was treated with potassium *tert*-butoxide and diphenyliodonium chloride, followed by deformylation with methanolic sodium methoxide,[14] a good yield of the 5-phenyl-4-oxotetrahydroindole **19** was obtained.

(9) (a) W. A. Remers and M. J. Weiss, *J. Amer. Chem. Soc.*, **88**, 804 (1966); (b) R. H. Roth, W. A. Remers, and M. J. Weiss, *J. Org. Chem.*, **31**, 1012 (1966).

(10) In the case of the 6-unsubstituted compound **6a**, two tautomeric forms could be isolated. In methylene chloride, the lower melting monocarbonyl form A (6.03 μ) predominated in the ratio 9:1 according to the nmr spectrum of this solution (see Experimental Section) and A could be obtained upon concentration of this solution. However, when A was carefully crystallized from methanol, the higher melting decarbonyl form B (6.05, 6.15 μ) was obtained.



(11) Method of J. H. Pomeroy and C. A. Craig, *J. Amer. Chem. Soc.*, **81**, 6340 (1959).

(12) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(13) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, p 134.

(14) F. M. Beringer and S. A. Galton, *J. Org. Chem.*, **28**, 3417 (1963); J. F. Poletto, G. R. Allen, Jr., and M. J. Weiss, *J. Med. Chem.*, **10**, 106 (1967).

Attempts to reduce the carbonyl group of **5** with sodium borohydride were unsuccessful, probably because of salt formation due to the acidic NH group of this compound.[15] In contrast, *N*-benzyl derivative **19** could be reduced with this reagent under vigorous conditions. The product was not the anticipated alcohol. Rather, it was the corresponding tetrahydroindole **16** in which the carbonyl group was reduced to a methylene group.[16] This same product was obtained by treatment of **19** with lithium aluminum hydride in ether.

The carbonyl group of a 4-oxotetrahydroindole can also be reduced to a methylene group by the Wolff–Kishner method (*e.g.*, **17** was converted into **15**).[17] However, in this example it was necessary to isolate the intermediate hydrazone prior to heating with potassium hydroxide. Otherwise the only product found was the azine **14**.

Finally, the methylthio group was introduced into the 5 position by treating hydroxymethylene derivative **21** with methyl thiotosylate[18] in ethanolic sodium ethoxide. Under these conditions the carboxaldehyde group was cleaved directly and work-up afforded the 5-methylthio-4-oxotetrahydroindole **18** (Scheme II).

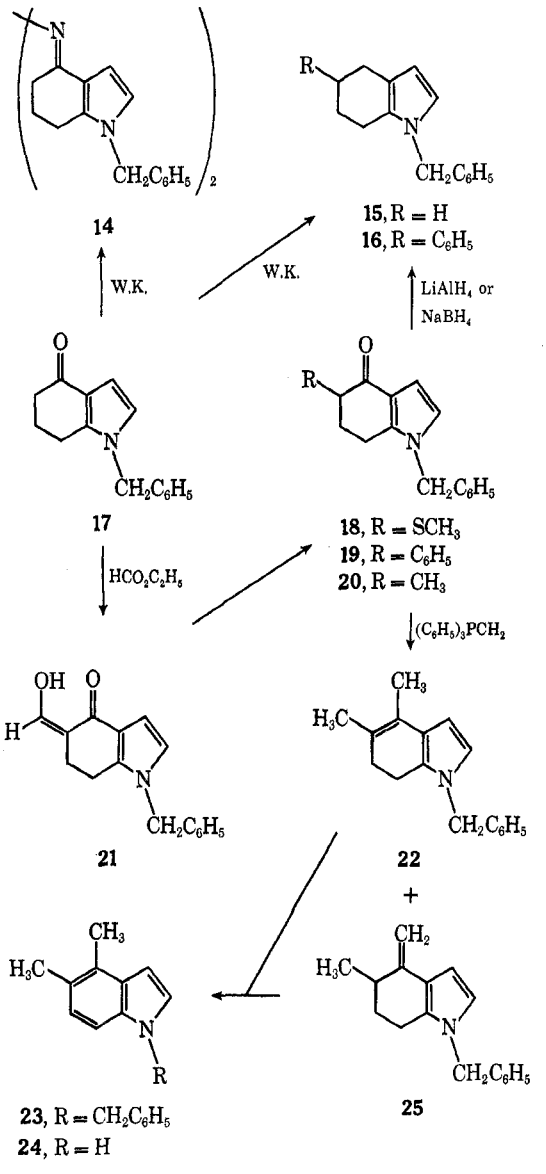
The foregoing results demonstrate the wide range of substituents which have been introduced into the 4 and 5 positions when the nitrogen is substituted. As described below, certain of the resulting compounds afford the corresponding fully aromatic indoles upon dehydrogenation. However, the versatility of these procedures is limited by the difficulty in removing the substituent from nitrogen. In several examples, one of which is discussed below, the benzyl group was removed by reduction with sodium in ammonia.[8] Unfortunately, this method is limited to compounds which are compatible with such a vigorous reductive cleavage. Therefore, we examined several more labile blocking groups.

The 1-benzenesulfonyl derivative **28** was readily prepared and it could be hydrolyzed back to **5** by heating with potassium hydroxide in methanol. Although stable under midly acidic conditions, the benzenesulfonyl group of **28** proved too readily cleaved by bases to allow preparation of a 5-hydroxymethylene derivative. However, a Reformatsky reaction with ethyl bromoacetate and zinc afforded the anticipated 4-carbethoxymethyl-4-hydroxy derivative **26** in nearly quantitative yield. Upon storage at room temperature **26** gradually underwent dehydration to the corresponding 4-carboxymethylene derivative **27**. This assignment of the double bond to the exocyclic position is supported by its nmr spectrum, which shows no significant splitting of the peak for the vinyl hydrogen (δ 5.88 ppm).

The benzenesulfonyl group of **28** was ideally suited to the introduction of bromine at C_5. In the absence of an electron-withdrawing substituent on nitrogen (*e.g.*, compound **5**), bromination, even with selective reagents such as phenyltrimethylammonium tribromide, takes place preferentially in the pyrrole ring.[19,20] However, the benzenesulfonyl group so deactivates the pyrrole ring (and presumably activates the carbonyl group by inhibiting electron release to it) that bromination adjacent to the carbonyl group is favored. Thus, treatment of **28** with phenyltrimethylammonium tribromide in tetrahydrofuran afforded the bromo ketone **29** in 59% yield.

Our initial attempt to convert bromo ketone **29** into the aminothiazole derivative **37**, by heating it with thiourea and triethylamine in ethanol, afforded the bromine-containing carbonyl derivative **34**. However, an attempted recrystallization of **34** from methanol induced its cyclization to **36**. Repetition of the experiment with methanol instead of ethanol led to the direct isolation of **36**. It is known that in the presence of dilute acid carbonyl derivatives such as **34** are some-

SCHEME II



(15) As anticipated, the carbonyl group of **5b** was readily reduced by diborane (ir evidence); however, only amorphous solid was obtained from this reduction.

(16) Related reductions of 1-tetralone derivatives to the corresponding tetrahydronaphthalenes fiy sodium borohydride were reported by K. H. Bell, *Aust. J. Chem.*, **22**, 601 (1969).

(17) The Wolff–Kishner reduction of 4-oxotetrahydroindoles has been reported by Kost, Ovseneva, and Shuvaeva (ref 4).

(18) We wish to thank Dr. M. L. Scheinbaum for sending us a detailed procedure for the preparation of potassium thiotosylate from his Ph.D. dissertation, Harvard University, 1965 [*Dissertation Abstr.*, **26**, 713 (1965)]. Methyl thiotosylate was prepared from it by the method of D. T. Gibson, *J. Chem. Soc.*, 2637 (1931).

(19) W. A. Remers and M. J. Weiss, *J. Org. Chem.*, **36**, 1241 (1971).

(20) Introduction of bromine at C_5 by way of the hydroxymethylene derivative appeared to be an attractive method; however, treatment of **6a** with bromine and sodium acetate afforded extensive decomposition.

times isolated in attempts to form aminothiazoles.[21] However, the excess triethylamine present in our experiment should have effectively scavenged any traces of liberated HBr. We are unable to offer a reason for the unusual difference in solvent effect between ethanol and methanol.

Despite the facile hydrolysis of the benzenesulfonyl group of **28**, it was difficult to remove this blocking group from **36**. Acid hydrolysis or alkaline hydrolysis under mild conditions was unsuccessful and strong alkaline conditions destroyed the molecule. Lithium-in-ammonia reduction also decomposed **36**. Rather than pursue these experiments further, we decided to change blocking groups.

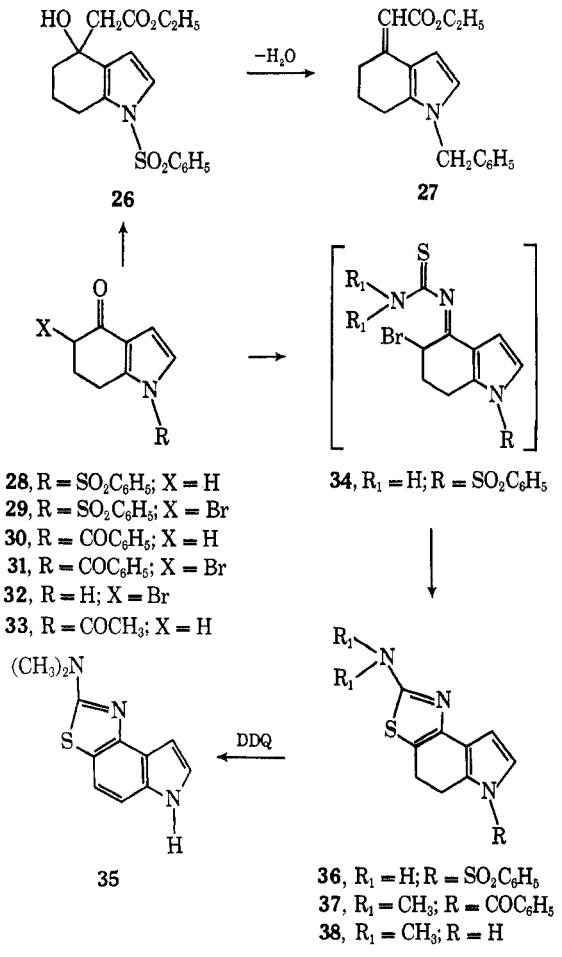
The benzoyl group offered an attractive possibility since it appeared sufficiently electron withdrawing to direct bromination at C_5 and more labile to hydrolysis than the benzenesulfonyl group. Preparation of 1-benzoyl-4-oxotetrahydroindole **30** was straightforward, and it was readily brominated at C_5 by phenyltrimethylammonium tribromide or pyridinium bromide perbromide. The resulting 5-bromo derivative **31** was hydrolyzed to 5-bromo-4-oxo-4,5,6,7-tetrahydroindole (**32**) by brief treatment with methanolic sodium hydroxide. Attempted condensations of the bromo ketones **31** and **32** with thiourea were fruitless since extensive decomposition occurred in both cases. On the supposition that the successful reaction with benzenesulfonyl derivative **29**, but failure with benzoyl derivative **31**, was due to rapid methanolysis of the latter compound under the experimental conditions, a less reactive solvent was sought for the aminothiazole synthesis. Tetrahydrofuran was a good solvent for **31** but not for thiourea. However, it readily dissolved substituted thioureas such as 1,1-dimethylthiourea. When a solution of this thiourea derivative, bromo ketone **31**, and triethylamine in tetrahydrofuran was heated at reflux temperature, the desired aminothiazole derivative **37** formed in good yield. Treatment of **37** with 1 equiv of sodium hydroxide in methanol then furnished the corresponding debenzoylated compound **38** (Scheme III).

The acetyl group was briefly investigated as a potential blocking group for 4-oxotetrahydroindoles, but it proved too labile for general use. For example, the 1-acetyl derivative **33**, prepared by heating **5** with acetic anhydride and sodium acetate, reverted to **5** upon attempted recrystallization from methanol.

To complete the synthesis of indoles, it was necessary to find suitable means for the dehydrogenation and the removal (where required) of certain blocking groups from nitrogen of the intermediates described above. In some cases dehydrogenation was facile, but in other cases it could not be accomplished. These difficulties in dehydrogenation impose important limitations upon this general method of indole synthesis.

Catalytic dehydrogenation, with palladium on charcoal in an aromatic hydrocarbon solvent[22] such as cumene, was a useful method for conversion of 4-oxotetrahydroindoles to the corresponding 4-hydroxyindoles except when a 5 substituent was present. As shown in Table I the yields for a series of methyl-

SCHEME III



substituted 4-oxotetrahydroindoles were acceptable (although not high) for the compounds unsubstituted at the 5 and 6 positions, or substituted only at the 6 position, but the yields were decreased when a 5 substituent was present.[23,24] 4-Oxotetrahydroindoles with 5-phenyl and 5-methylthio substituents (*e.g.*, **19** and **18**) also failed to undergo catalytic dehydrogenation. Steric inhibition of enolization is probably important in at least some of these 5-substituted compounds.

Dehydrogenation of the parent 4-oxotetrahydroindole (**5**) was attempted with palladium on charcoal in cumene, but repeated attempts afforded only low yields of the 4-hydroxyindole. Since our initial communication[1] on this method, Plieninger and Klinga reported the dehydrogenation of **5** in high yield using the same type of catalyst in mesitylene.[25] We repeated this experiment and confirmed their result, except that our product was contaminated with a small amount of starting material. As catalytic dehydrogenation is quite sensitive to the catalyst, it is probable that our particular sample of catalyst was inferior in activity.

The two 6,7-dihydroindoles with alkyl substituents, **7** and **22**, were readily dehydrogenated to the corresponding indoles **8** and **23**, respectively, by palladium on charcoal (Table II). In the case of **22** the 5-methyl

(21) J. M. Sprague and A. H. Land, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, p 579.

(22) Method of E. C. Horning, M. G. Horning, and G. N. Walker, *J. Amer. Chem. Soc.*, **71**, 169 (1949).

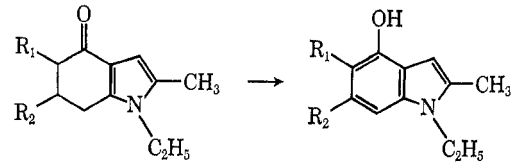
(23) Extensive efforts to obtain optimum yields were not made.

(24) Catalytic dehydrogenation of ten different 3-alkyl- and 2,3-dialkyl-4-oxotetrahydroindoles in yields of 26–65% was reported by S. Hauptmann, G. Blume, G. Hartmann, D. Haendel, and P. Franke, *Z. Chem.*, **6**, 183 (1966).

(25) H. Plieninger and K. Klinga, *Chem. Ber.*, **101**, 2605 (1968).

TABLE I[a]

DEHYDROGENATION OF 4-OXO-4,5,6,7-TETRAHYDROINDOLES



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Compd	Product	R_1	R_2	R_3	Method	Yield, %	Mp,[b] °C
4a	39a	H	H	H	Pd/C	38	98–102
4b	39b	H	CH_3	H	Pd/C	20–45	141–143
9a	39c	CH_3	H	CH_3	Pd/C	13	110–112
9b	39d	CH_3	CH_3	CH_3	Pd/C	0[c]	
6a	39e	=CHOH	H	CHO	DDQ	12	95–96
6b	39f	=CHOH	CH_3	CHO	DDQ	51	129–131

[a] Satisfactory analytical values (±0.35% in C, H, and N) were reported for all compounds in the table: Ed. [b] Recrystallized from hexane. [c] For a successful preparation from 6, see ref 9b.

TABLE II[a]

DEHYDROGENATION OF 6,7-DIHYDROINDOLES

Compd	Product	Method	Yield, %	Mp, °C
7	8	Pd/C	42	Oil
22 + 25	23	Pd/C	60	87
11	13	DDQ	40	148–153
38	35	DDQ	15	255 dec

[a] Satisfactory analytical values (±0.35% in C, H, and N) were reported for all compounds in the table: Ed.

group did not inhibit the dehydrogenation as it did in the related 4-oxo compounds.

We attempted dehydrogenation of certain of the above 4-oxotetrahydroindoles by 5,6-dichloro-2,3-dicyanobenzoquinone[26] (DDQ), but we obtained only polymeric products. It seems likely that dehydrogenation occurred, but the products were unstable in the presence of DDQ. In contrast, when the product indoles were stabilized by the carboxaldehyde group at C_5 or a heterocyclic ring fused to the 4 and 5 positions, DDQ generally afforded crystalline products. Thus 5-hydroxymethylene-4-oxotetrahydroindoles **6a** and **6b** were converted to the corresponding 4-hydroxyindole-5-carboxaldehydes **39e** and **39f** (Table I), and the 6,7-dihydroindoles substituted with isoxazole and aminothiazole rings (**11** and **38**, respectively) afforded the fully aromatic tricyclic systems **13** and **35** (Table II). An attempt to dehydrogenate **11** by palladium on charcoal had given only the 5-cyano-4-oxotetrahydroindole **10**.

Certain 4-oxotetrahydroindoles proved resistant to dehydrogenation by both catalytic and quinone methods. They were subjected to a variety of their dehydrogenating agents such as diphenyl picryl hydrazyl, trityl perchlorate, selenium dioxide, and sulfur without success. No method was found for dehydrogenation of the 5-phenyl derivative **19** or the related 5-phenyltetrahydroindole **16**. Dehydrogenation of the 5-methylthio derivative **18** was also unsuccessful, except that when heated with sulfur it gave a very small amount of 1-benzyl-4-hydroxyindole. In several examples 5-substituted 4-hydroxyindoles, which could not be prepared directly from the 4-oxotetrahydroindoles, were obtained by transformation of other dehydrogenation products. Thus the 5-cyano-4-hydroxyindole **12** was formed by base-catalyzed ring opening of isoxazole **13**, and catalytic hydrogenation of the carboxaldehyde group of **6b** afforded the desired 5,6-dimethyl-4-hydroxyindole **39d**.[9b]

Finally, the removal of blocking groups must be considered. The benzoyl group of the aminothiazole derivative **37** was removed prior to dehydrogenation since, at least with DDQ, it prevented this process. In the synthesis of 4,5-dimethylindole (**24**)[27] it was desirable to dehydrogenate the isomeric dihydroindoles **22** and **25** prior to cleavage of the benzyl group. This cleavage was effected in good yield by sodium in liquid ammonia.[28]

In this paper we have partially outlined the potential scope of indole synthesis from the 4-oxotetrahydroindoles by describing the introduction of a variety of substituents including fused heterocycles[8] into the 4 and 5 positions. In the accompanying publication we extend this scope by electrophilic substitution of the pyrrole ring and the α-methylenecarbonyl system of the 4-oxotetrahydroindole.[19]

Experimental Section

General.—Melting points were determined on a Mel-Temp apparatus and are corrected. Ultraviolet spectra were determined in methanol using a Cary recording spectrophotometer. Infrared spectra were determined in potassium bromide disks or as films between salt plates on a Perkin-Elmer spectrophotometer (Model 21). Nuclear magnetic resonance spectra were determined in deuteriochloroform on a Varian A-60 spectrometer with tetramethylsilane as an internal standard. Solutions were dried over magnesium sulfate and concentrated under reduced pressure on a rotary evaporator.

4-Oxo-4,5,6,7-tetrahydroindole Oxime.—A mixture of 2.70 g (20 mmol) of **5**,[3] 5 ml of ethanol, 5 ml of pyridine, and 1.39 g (20 mmol) of hydroxylamine hydrochloride was heated on a steam bath for 2 hr. The mixture was concentrated and the residue was treated with brine and ethyl acetate. The organic layer was concentrated to a viscous oil which crystallized on standing. Two recrystallizations from acetone gave a low yield of colorless prisms, mp 174–179°.

(26) E. A. Braude, A. G. Brooke, and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954); J. A. Edwards, J. C. Orr, and A. Bowers, *J. Org. Chem.*, **27**, 3378 (1962).

(27) 4,5-Dimethylindole is a new compound, one of the three isomeric dimethylindoles not reported by L. Marion and C. W. Oldfield, *Can. J. Chem.*, **25**, 1 (1947), in their systematic attempt to prepare all of the possible dimethylindoles.

(28) M. Julia, P. Manoury, and J. Igolen, *C. R. Acad. Sci., Paris*, **251**, 294 (1960).

Anal. Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.95; H, 6.90; N, 18.45.

A superior procedure was the following. A solution of 18 g of **5** in 150 ml of hot water was treated with a solution of 45 g (excess) of hydroxylamine hydrochloride in 180 ml of 10% sodium hydroxide, and the mixture was heated on a steam bath for 30 min. At this time crystals began to appear. Just enough ethanol was added to dissolve them and the hot solution was filtered. Upon cooling, the filtrate gave 18.9 g of crystals. Recrystallization from ethanol–water gave 12.4 g (62%) of colorless needles, mp 168.5–170.5°. This product was sufficiently pure for use in subsequent preparations.

1-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydroindole (4a).—This compound was prepared by a procedure analogous to that utilized by Stetter and Lauterbach for the corresponding 1,2-dimethyl compound,[3] with the additional feature of washing a methylene chloride solution of the crude product two times with 5% sodium hydroxide solution. In this manner we obtained from 33 g of 2-acetonyl-1,3-cyclohexanedione and 2 g of anhydrous ethylamine, after recrystallization from cyclohexane, 18.8 g (54%) of **4a** as white prisms: mp 74–75°; λ_{max} 6.10 μ, 252 mμ (ϵ 10,500) 284 mμ (7200).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.20; H, 8.80; N, 8.02.

2,6-Dimethyl-1-ethyl-4-oxo-4,5,6,7-tetrahydroindole (4b).—This compound was prepared by a procedure analogous to that used by Stetter and Lauterbach[3] for the corresponding 1,2-dimethyl compound. From 87.4 g (0.47 mol) of 2-acetonyl-5-methyl-1,3-cyclohexanedione[3] and 68.8 g of anhydrous ethylamine, after adsorption chromatography on a column of 1 kg of magnesia–silica gel 60/100 with methylene chloride as the eluent, 52.76 g (58.7%) of product was obtained. This material was recrystallized from cyclohexane to give white needles: mp 77–79°; λ_{max} 6.08 μ, 252 mμ (ϵ 10,400), 285 mμ (7200).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.30. Found: 74.80; H, 9.05; N, 7.17.

2,4-Dimethyl-1-ethylindole (8).—To a suspension of 9.40 g (25 mmol) of methyltriphenylphosphonium bromide in 80 ml of hexane was added 2.8 g (25 mmol) of potassium *tert*-butoxide. This mixture was stirred 30 min and treated with a suspension of 885 mg (5 mmol) of **4a** in 10 ml of ether. The mixture was stirred 16 hr and poured into water, and the organic layer was separated. The aqueous layer was extracted with methylene chloride and the combined organic layers were dried and concentrated. A benzene solution of the residue was passed through a silica gel column. Concentration of the eluate (50 ml) afforded 620 mg of **7**, an amber oil that had λ_{max} 13.2 μ, 231 mμ, 270 mμ, identical in infrared absorption spectrum with a sample prepared by treatment of **4a** with methylmagnesium bromide (see below).

A solution of 20 mmol of methylmagnesium iodide in 25 ml of ether was treated with a suspension of 3.54 g (20 mmol) of **4a** in 30 ml of ether, and the mixture was stirred 16 hr and treated with water and ammonium chloride solution. The ether layer was dried and concentrated to afford 2.08 g of **7**, identical in ir and uv absorption spectra with the sample described above. The ir spectrum had absorptions(s) at 13.2 μ characteristic of a trisubstituted double bond but had no absorptions in the regions 3.2–3.3 and 10.9–11.1 μ characteristic of terminal olefins. Without further purification this sample was converted to the corresponding indole **8**.

A mixture of 2.08 g of **7**, 8 ml of cumene, and 500 mg of 10% palladium on charcoal was heated at reflux temperature for 3 hr, cooled, and filtered. Concentration of the filtrate gave 850 mg of **8** as brownish oil: bp 84° (0.5 mm); λ_{max} 236 mμ (ϵ 28,000) 278 (5820), 282 (5820), 294 (4800); nmr δ 7.0 (three-proton multiplet, benzene-ring protons), 6.22 (singlet, C-3 proton), 3.95 (two-proton quartet, CH_2CH_3), 2.47 (three protons, 4-methyl), 2.33 (three protons, 2-methyl), 1.2 ppm (three-proton triplet, CH_2CH_3). The analytical data are given in Table II.

1-Ethyl-5-hydroxymethylene-2-methyl-4-oxo-4,5,6,7-tetrahydroindole (6a).—An ice-cooled suspension of 1.08 g (20 mmol) of sodium methoxide in 10 ml of dry benzene, under nitrogen, was treated with a solution of 1.48 g (20 mmol) of ethyl formate in 5 ml of benzene and a solution of 885 mg (5 mmol) of **4a** in 10 ml of benzene. The mixture was stirred at room temperature overnight, and was then cooled in an ice bath and treated with 20 ml of 5% sodium hydroxide solution. The combined alkaline extracts were cooled in an ice bath, layered with 20 ml of benzene, and acidified with 6 *N* hydrochloric acid. A pale yellow solid separated. This solid (230 mg) had λ_{max} 6.05, 6.15 μ, indicating tha it was **6a** in a dicarbonyl form. When a methylene chloride solution of this solid was concentrated, it afforded **6a** as the monocarbonyl form, λ_{max} 6.03 μ.

Concentration of the benzene layer, from which the above yellow solid had separated, gave a pale yellow oil that crystallized on standing, affording an additional 400 mg of monocarbonyl form, mp 65–70°. Thus, the total yield of product was 670 mg (65%). Recrystallization from methanol afforded white prisms: mp 82–90°; λ_{max} 6.05, 6.15 μ (dicarbonyl form), 265 (ϵ 7770) mμ, 281 mμ (7800), 329 mμ (10,600); nmr δ 10.08 (5% HC(=O)CHC(=O)), 7.80 ppm (95% HC(OH)=CC(=O) $\rightleftarrows$ HC(=O)C=C(OH)) (in CH_2Cl_2).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.71; H, 7.75; N, 6.63.

On a 10-g scale this reaction afforded a 70% yield of **6a**, mp 91–95° (from ether).

2,6-Dimethyl-1-ethyl-5-hydroxymethylene-4-oxo-4,5,6,7-tetrahydroindole (6b).—This compound was prepared by the procedure described for **6a**. When 65.67 g (34 mmol) of **4b** was treated with 64.8 g of sodium methoxide and 88.8 g of ethylformate in dried benzene under nitrogen, 70.2 g (96.1%) of **6b** was obtained as a tan solid which was of sufficient purity to be used in subsequent reactions. Recrystallization from petroleum ether gave gray-tinged needles: mp 71–74°; λ_{max} 6.16 μ, 221 mμ (ϵ 10,400), 203 mμ (7700), 283 mμ (7800), 330 mμ (10,600); nmr 2.20 ppm (HC(OH)=CC(=O) $\rightleftarrows$ HC(=O)C=C(OH)).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.38; H, 7.86; N, 6.48.

2,5-Dimethyl-1-ethyl-4-oxo-4,5,6,7-tetrahydroindole (9a).—A mixture of 1.0 g of **6a**, 3.0 g of powdered potassium carbonate, 30 ml of acetone, and 4 ml of methyl iodide was stirred at room temperature overnight. It was then concentrated and the residue was treated with water and methylene chloride. The organic layer was washed with 1% sodium hydroxide solution and brine, dried, and concentrated, affording a pale yellow oil: λ_{max} 5.8 μ, 6.1 μ, 285 mμ. Without further purification this oil was converted to the deformylated product by heating it with 270 mg of sodium methoxide in 20 ml of methanol at reflux temperature for 2 hr. The resulting solution was concentrated and the residue was treated with water and methylene chloride. The organic layer was washed with water, dried, and concentrated, and the residue was purified by adsorption chromatography on silica gel with ether as eluent. Concentration of the eluate gave **9a** as white crystals: mp 44–47°; λ_{max} 6.08 μ, 255 mμ (ϵ 10,500), 285 mμ (ϵ 7200).

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.39; H, 8.68; N, 7.29.

1-Ethyl-4-oxo-2,5,6-trimethyl-4,5,6,7-tetrahydroindole (9b).—This compound was prepared by the procedure described for **9a**, with the intermediate 5-carboxaldehyde being converted directly to **9b**. From treatment of 2.19 g of **6b** with potassium carbonate and methyl iodide in aetone, followed by treatment of the intermediate with methanol and sodium methoxide, and subsequent purification by adsorption chromatography on magnesia–silica gel, 1.18 g (57.5%) of **9b** was obtained as off-white solid. A 425-mg sample of this product was recrystallized from 10 ml of hexane to give 228 mg of pale tan needles: mp 97–99.5°; λ_{max} 6.09 μ, 210 mμ (ϵ 12,200), 252 mμ (9300), 285 mμ (6600).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 75.72; H, 9.35; N, 6.77.

1-Ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-5-indolecarbonitrile (10a).—A mixture of 1.03 g (5 mmol) of **6a**, 1.13 g (5 mmol) of *O,N*-bistrifluoroacetylhydroxylamine,[11] 0.79 g (10 mmol) of pyridine, and 10 ml of benzene was heated at reflux temperature for 20 min and then left at room temperature for 18 hr. It was treated with water, and the benzene phase was washed with water and sodium bicarbonate solution, dried, and concentrated to a brown solid. Two recrystallizations of this solid from acetone–hexane afforded 360 mg (35%) of **10a** as white prisms: mp 141–145°; λ_{max} 4.4 μ, 6.05 μ, 255 mμ (ϵ 11,000), 291 mμ (7300).

Anal. Calcd for $C_{12}H_{14}NO$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.20; H, 6.89; N, 14.03.

2,6-Dimethyl-1-ethyl-4-oxo-4,5,6,7-tetrahydro-5-indolecarbonitrile (10b).—A mixture of 2.19 g (10 mmol) of **6b**, 765 mg (10 mmol) of hydroxylamine hydrochloride, and 50 ml of ethanol was refluxed for 18 hr. The resulting dark brown solution was filtered and concentrated to give 2.59 g of a dark brown semisolid which was dissolved in methylene chloride and chromatographed on 30 g of magnesia–silica gel. A total of 1.04 g (48%) of **10b** (tan solid)

was obtained. A 170-mg sample of this solid was recrystallized from boiling methanol (3 ml) to give 107 mg of white solid: mp 140–143°; λ_{max} 4.45 μ, 6.03 μ, 210 mμ (ϵ 13,300), 255 mμ (10,800), 289 mμ (6500).

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 71.69; H, 7.43; N, 13.48.

When a mixture of 2 g of isoxazoloindole **11**, 0.5 g of 10% palladium on charcoal, and 10 ml of cumene was heated at reflux for 4 hr and then filtered and cooled, crystals of **10b** separated from the filtrate. They had mp 141–144°, undepressed upon admixture with the sample described above.

4,5-Dihydro-4,7-dimethyl-6-ethyl-6*H*-isoxazolo[5,4-*e*]indole (11).—A solution of 16.9 g (77 mmol) of **6b** in 100 ml of warm ethanol was treated with a solution of 5.37 g (77 mmol) of hydroxylamine hydrochloride in 15 ml of water. Within a few minutes crystals of the product appeared. The mixture was cooled and filtered, and the crystals were washed with aqueous ethanol. This procedure gave 14.8 g (88%) of **11** as a nearly white product which had mp 135–138° after recrystallization from ethanol–water: λ_{max} 234 mμ (ϵ 8100), 380 mμ (12,400).

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.65; H, 7.92; N, 12.95.

2,6-Dimethyl-1-ethyl-4-hydroxy-5-indolecarbonitrile (12.)—To an ice-cooled suspension of 0.38 g (7 mmol) of sodium methoxide in 10 ml of dry benzene, under nitrogen, was added a solution of 1.51 g (7 mmol) of **13** in 50 ml of benzene. The mixture was stirred for 4 hr and then treated with 5% NaOH solution. The benzene layer was extracted with additional 5% NaOH and the combined alkaline solutions were acidified to pH 2 with HCl, whereupon the product precipitated. It was washed with water and dried under vacuum. A yield of 0.6 g (40%) of **12** as white solid with mp 230–243° was obtained. Recrystallization from acetonitrile gave needles: mp 243–248°; λ_{max} 3.1 μ (OH), 4.5 (CN).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.38; H, 6.21; N, 12.96.

1-Benzyl-4-oxo-4,5,6,7-tetrahydroindole (17).—A solution of 0.133 mol of methylsulfinyl carbanion in dimethyl sulfoxide,[12] prepared from 5.8 g of 55% sodium hydride in mineral oil and 50 ml of dimethyl sulfoxide, was cooled to 18° and treated with a solution of 16.4 g (0.12 mol) of **5**[3] in 50 ml of dimethyl sulfoxide. The mixture was stirred under nitrogen for 2 hr and then treated with 15.4 g (0.12 mol) of benzyl chloride. The resulting solution was stirred at room temperature for 17 hr and then diluted gradually with water. The white crystals which separated were washed with water and dissolved in methylene chloride, and this solution was washed with water, dried, filtered, and concentrated on a steam bath as hexane was added. When most of the methylene chloride had boiled off the solution was cooled. This procedure gave 20.8 g (76%) of **17** as white prisms, mp 80–81.5°.

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.57; H, 6.63; N, 6.14.

This preparation could also be carried out with potassium *tert*-butoxide as the base, but the yields were variable and sometimes the product was difficult to separate from starting material.

1-Benzyl-4,5,6,7-tetrahydroindole (15).—A mixture of 5.62 g of **17**, 18 ml of hydrazine hydrate, and 200 ml of benzene was heated in a Dean–Stark apparatus for 21 hr and then was concentrated. The residue (hydrazone) was treated for 1 hr at 100° with 5 g of powdered potassium hydroxide and 3 ml of hydrazine hydrate in 150 ml of diethylene glycol. The temperature was then increased until the mixture began to distil. After 50 ml of water and solvent were removed, the remaining solution was heated at reflux temperature for 5 hr. It was then cooled and extracted with benzene. This extract was washed with water and brine and concentrated. Distillation of the residual oil (5.38 g) afforded 4.35 g (83%) of **15** as a colorless oil, bp 185–188° (8 mm).

Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 84.37; H, 8.06; N, 7.03.

When the Wolff–Kishner reduction was run without isolation of the intermediate hydrazone, the product (1.35 g, 25%) was bis[4-(1-benzyl-4,5,6,7-tetrahydroindole)] azine (**14**), mp 221.5–224.5°.

Anal. Calcd for $C_{30}H_{30}N_4$: C, 80.68; H, 6.77; N, 12.55. Found: C, 80.22; H, 6.86; N, 12.25.

1-Benzyl-5-hydroxymethylene-4-oxo-4,5,6,7-tetrahydroindole (21).—This compound was prepared by the procedure described for **6a**. However, no indication of the tautomeric equilibrium noted for **6a** was found. From 20 g of **17** was obtained 18.0 g (80%) of white prisms, mp 45–48°.

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.53; H, 5.72; N, 5.59.

1-Benzyl-5-methylthio-4-oxo-4,5,6,7-tetrahydroindole (18).—To a solution of 115 mg (5 mmol) of sodium in 5 ml of ethanol was added, under nitrogen, 1.265 g (5 mmol) of **21**. The mixture was stirred 20 min and then treated with 1.10 g (5 mmol) of methyl thiotosylate.[18] After 16 hr the mixture was neutralized with 5 mmol of acetic acid and concentrated under reduced pressure. The residual solid was treated with methylene chloride and 2.5% sodium hydroxide solution. The resulting organic layer was washed with brine, dried, and concentrated. Recrystallization of the residual solid from methanol gave 604 mg (45%) of **18** as colorless prisms, mp 94–96°. An analytical sample, recrystallized once more from methanol, had mp 95–97°, λ_{max} 6.08 μ.

Anal. Calcd for $C_{16}H_{17}NOS$: 70.83; H, 6.32; N, 5.16; S, 11.79. Found: C, 71.09; H, 6.46; N, 5.19; S, 11.83.

In larger scale experiments, yields of **18** up to 83% were obtained.

1-Benzyl-4-oxo-5-phenyl-4,5,6,7-tetrahydroindole (19).—To a solution of sodium *tert*-butoxide in *tert*-butyl alcohol (made from 0.69 g(30 mg-atoms) of sodium and 250 ml of *tert*-butyl alcohol) was added 6.76 g (30 mmol) of **21**. To the resulting solution was added 9.50 g (30 mmol) of diphenyliodonium chloride and the mixture was stirred at reflux temperature under nitrogen for 22 hr. It was then concentrated and the residue was treated with dilute hydrochloric acid and methylene chloride. The organic layer was washed with brine, dried, and concentrated. A solution of the residual brown liquid in 250 ml of methanol was treated with 4.0 g of sodium methoxide at reflux temperature for 2 hr. After concentration of the resulting solution, the residue was treated with water and methylene chloride. The organic layer was washed with brine, dried, and concentrated. Trituration of the residue with ether afforded 4.33 g (54%) of **19** with mp 92–98°. Recrystallizations from ether–methylene chloride and from methanol–water gave an analytical sample with mp 109–111°.

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.32; N, 4.65. Found: C, 83.18; H, 6.45; N, 4.85.

1-Benzyl-5-phenyl-4,5,6,7-tetrahydroindole (16).—A suspension of 6.0 g of **19** in 400 ml of ether was treated with 1.0 g of lithium aluminum hydride. The mixture was stirred for 21 hr and then treated with 6.5 ml of saturated potassium sodium tartrate solution. It was filtered and the filtrate was dried and concentrated. The residual oil was further concentrated under higher vacuum (1 mm) until became glassy. Trituration with ether then afforded **16** as white solid (5.4 g, 94%) with mp 63–72°. Recrystallization from methanol gave white crystals, mp 70–72°.

Anal. Calcd for $C_{21}H_{21}N$: C, 87.76; H, 7.36; N, 4.88. Found: C, 87.33; H, 7.39; N, 4.80.

Reduction of 602 mg of **19** with 380 mg of sodium borohydride in 10 ml of ethanol at reflux temperature for 4 hr gave 483 mg of **16** identical in ir spectrum (no carbonyl group remained) with the sample described above.

1-Benzyl-5-methyl-4-oxo-4,5,6,7-tetrahydroindole (20).—This compound was prepared by the procedure described for **9a**. From 16.0 g of **21** was obtained 12.4 g (82%) of **20** as an amber oil which solidified upon storage at 5°. Recrystallization from ether–hexane gave white plates, mp 57–58°.

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.25; H, 6.87; N, 6.12.

1-Benzyl-4,5-dimethylindole (23).—To a suspension of 18.0 g (47.5 mmol) of methyltriphenylphosphonium bromide in 150 ml of hexane was added 5.3 g (47.5 mmol) of potassium *tert*-butoxide. The mixture was stirred 30 min and then treated with a solution of 2.3 g (9.5 mmol) of **20** in 10 ml of benzene and 10 ml of ether. The mixture was stirred under nitrogen for 16 hr and treated with water and methylene chloride, and the organic layer was dried and concentrated. Treatment of the residue with ether induced crystallization of the phosphine oxides. The mixture was filtered and the filtrate was concentrated. Extraction of the residue with hexane, followed by concentration of this extract, gave 1.27 g of a mixture of **1-benzyl-4-methylene-5-methyl-4,5,6,-7-tetrahydroindole (25)** and **1-benzyl-4,5,dimethyl-6,7-dihydroindole (22)** in a ratio of approximately 1:1, as indicated by its nmr spectrum: five protons 7.6–6.2 (phenyl), 5.25 and 5.04 (one-half proton each, $=CH_2$), 4.95 (two protons, benzyl CH), 2.46 and 2.33 (one and one-half proton each, methyl groups on

double bond), 1.78 (one and one-half proton doublet, J = 8 Hz, methyl group of **25**), aliphatic protons 2.65–1.67 ppm. This mixture of isomers was treated directly with 300 mg of 10% palladium on charcoal and 10 ml of cumene at reflux temperature for 3 hr. The resulting mixture was cooled, filtered, and concentrated, and the residual oil was purified by adsorption chromatography on Florisil with methylene chloride as eluent. Concentration of the eluate gave a colorless oil which crystallized upon cooling. Recrystallization from hexane gave 750 mg (34% from 20) of **23** as waxy white prisms, mp 87°. The analytical data are given in Table II.

4,5-Dimethylindole (24).—To a solution of 2.04 g of sodium in 250 ml of liquid ammonia was added a solution of 3.48 g of **23** in 60 ml of ether. The mixture was stirred 5 min and then decolorized with ammonium chloride. After evaporation of the solvents, the residue was treated with water and methylene chloride. The organic layer was washed with water, dried, concentrated, and heated under vacuum to remove toluene. The white solid product (1.50 g, 69%) had, upon recrystallization from hexane, mp 106.5–108°: λ_{max} 222 mμ (ε 29,000), 269 (7110), 284 (5010), 296 (3420).

Anal. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.57; H, 7.54; N, 9.78.

1-Benzenesulfonyl-4-oxo-4,5,6,7-tetrahydroindole (28).—Potassium *tert*-butoxide was freshly prepared from 7.8 g (0.2 g-atom) of potassium and 400 ml of *tert*-butyl alcohol. The excess *tert*-butyl alcohol was removed under reduced pressure and benzene was added to the residue and removed under reduced pressure to further decrease the adhering *tert*-butyl alcohol. The residual solid was suspended in 300 ml of dry benzene and treated with a suspension of 27.0 g (0.2 mol) of **5** in 100 ml of benzene. An atmosphere of nitrogen was introduced and the mixture was stirred for 1 hr at reflux temperature. It was then cooled and treated with a solution of 35.3 g (0.2 mol) of benzenesulfonyl chloride. The resulting mixture was stirred at room temperature under nitrogen for 16 hr and then stirred at reflux temperature for 4 hr. It was cooled and treated with water, and the layers were separated. The aqueous layer was extracted with methylene chloride and the combined organic layers were washed with water, and concentrated. Recrystallization of the residual solid from 250 ml of methanol gave 40.3 g (73%) of **28** as nearly white prisms, mp 117–118.5°.

Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.06; H, 4.76; N, 5.09; S, 11.65. Found: C, 60.75; H, 4.95; N, 5.16; S, 11.51.

1-Benzenesulfonyl-4-carbethoxymethylene-4-hydroxy-4,5,6,7-tetrahydroindole (26).—A mixture of 7.25 g (30 mmol) of **28**, 12.0 g (72 mmol) of ethyl bromoactate, 4.80 g (72 mg-atom) of zinc dust, and 69 ml of dry benzene was heated at reflux temperature for 45 min, cooled, and poured into ice water containing dilute sulfuric acid. The organic layer was washed with sodium bicarbonate solution, dried, and concentrated. Recrystallization of the residue from methanol–water afforded 10.1 g of **26** as white solid, mp 79–80.5°.

Anal. Calcd for $C_{18}H_{21}NO_5S$: C, 59.50; H, 5.82; S, 8.82. Found: C, 59.36; H, 5.78; S, 8.84.

1-Benzenesulfonyl-4-carbethoxymethylene-4,5,6,7-tetrahydroindole (27).—Upon prolonged storage the above-described sample of **26** was completely converted by spontaneous dehydration into **27**, which after recrystallization from ether–hexane had mp 89–92°: λ_{max} 293 mμ (ε 19,000), 275 (16,400), 268 (16,000); nmr δ 5.88 (vinyl), 4.12 (quartet, OCH_2CH_3), 2.84 (4-proton multiplet, C-5 and C-7 protons), 1.77 (2-proton multiplet, C-6 protons), 1.22 ppm (triplet, OCH_2CH_3).

Anal. Calcd for $C_{18}H_{19}NO_4S$ (345.41): C, 62.60; H, 5.55; N, 4.06; S, 9.27. Found: C, 62.40; H, 5.57; N, 4.08; S, 9.49.

If either **26** or **27** was heated with 10% palladium on charcoal in refluxing cumene, a low yield of an oily product was obtained. This oil had an uv spectrum typical for the corresponding fully aromatic indole [λ_{max} 292 mμ (ε 4200), 283 (4400), 252 (18,000)]. However, it was not possible to repeat this preparation on a usful scale and an analytical sample was not obtained.

1-Benzenesulfonyl-5-bromo-4-oxo-4,5,6,7-tetrahydroindole (29).—A solution of 550 mg (2 mmol) of **28** in 6 ml of tetrahydrofuran was treated with a solution of 752 mg (2 mmol) of phenyltrimethylammonium tribromide in 2 ml of tetrahydrofuran. After 30 min the mixture was filtered and the filtrate was concentrated under reduced pressure. A methylene chloride solution of the concentrate was washed with sodium bicarbonate and brine, dried, and concentrated. The residual syrup, upon trituration with ether, afforded 416 mg (59%) of **29** as white crystals, mp 85–88°. Recrystallization from tetrahydrofuran–hexane gave needles with mp 94–96°: λ_{max} 5.98 μ; nmr δ 8.2–7.7 (five protons, phenyl) ppm, 7.52 (d, 2 proton), 6.66 (d, 3 proton), 4.80 (dd, 4 proton), 3.18 (two-proton multiplet, 7 protons), 2.45 (DMSO + 6 protons).

Anal. Calcd for $C_{14}H_{12}BrNO_3S$: C, 47.46; H, 3.42; N, 3.96; Br, 22.56. Found: C, 47.86; H, 3.43; N, 3.99; Br, 22.06.

2-Amino-6-benzenesulfonyl-4,5-dihydro-6*H*-pyrrolo[3,2-*e*]benzothiazole (36).—A mixture of 708 mg (2 mmol) of **29**, 304 mg (4 mmol) of thiourea, 404 mg (4 mmol) of triethylamine, and 30 ml of ethanol was heated at reflux temperature for 18 hr (tlc showed no **29** present). It was then concentrated and the syrupy residue was treated with water. The light grey solid (600 mg) that separated was recrystallized from dimethyl sulfoxide–water. This procedure afforded white crystals of impure **34**, mp 203–205°.

Anal. Calcd for $C_{15}H_{13}N_3O_2S_2$: N, 9.98; S, 15.53; Br, 17.88. Found: N, 10.19; S, 15.55; Br, 19.38.

Attempted recrystallization from methanol afforded 317 mg of benzothiazole **36** (48% from **29**) as yellow needles, mp 215–219°.

Anal. Calcd for $C_{15}H_{13}N_3O_2S_2$: C, 54.37; H, 3.96; N, 12.69; S, 9.34. Found: C, 54.80; H, 3.99; N, 12.61; S, 19.62.

When this preparation was repeated with methanol as the solvent, **36** was isolated directly from the concentrate. A 63% yield of crystals with mp 215–219° was obtained after recrystallization from methanol.

1-Benzoyl-4-oxo-4,5,6,7-tetrahydroindole (30).—A mixture of 13.5 g (0.1 mol) of **5**, 11.2 g (0.1 mol) of potassium *tert*-butoxide, and 200 ml of dry benzene was stirred at reflux temperature for 1 hr. It was then cooled and treated gradually with 14.06 g (0.1 mol) of benzoyl chloride in 25 ml of benzene. The mixture was stirred for 2 hr and then treated with 200 ml of water and 150 ml of methylene chloride. The organic layer was washed with sodium bicarbonate solution, dried, and concentrated to a yellowish solid. This solid was washed with hexane and then recrystallized from acetone–hexane (charcoal). A yield of 14.98 g (63%) of **30** as colorless prisms, mp 120–123°, was obtained in two crops. Recrystallization from acetone gave mp 122–123°.

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.18; H, 5.51; N, 5.83.

1-Benzoyl-5-bromo-4-oxo-4,5,6,7-tetrahydroindole (31).—This compound was prepared by the procedure described for **29**. From 478 mg of **30** and 752 mg of phenyltrimethylammonium tribromide was obtained 433 mg (68%) of white crystals, mp 129–130°. The nmr spectrum showed two pyrrole protons at δ 6.92 and 6.58 ppm.

Anal. Calcd for $C_{15}H_{12}BrNO_2$: C, 56.62; H, 3.80; N, 4.40; Br, 25.11. Found: C, 57.05; H, 4.01; N, 4.59; Br, 24.62.

Larger scale preparations of **31** involved pyridinium bromide perbromide as the brominating agent in the same type of procedure. Yields were in the range of 71–83% on a 0.1-mol scale.

5-Bromo-4-oxo-4,5,6,7-tetrahydroindole (32).—A suspension of 636 mg (2 mmol) of **31** in 15 ml of methanol was treated with 2 mmol of 5 *N* NaOH. After 1 hr the resulting solution was neutralized with HCl and concentrated to dryness. A methylene chloride solution of the residue was washed with sodium bicarbonate solution, dried, and concentrated. Recrystallization of the white solid residue from methanol gave 351 mg (82%) of **32** as white prisms, mp 167–169°. Another recrystallization gave mp 170–173°.

Anal. Calcd for C_8H_8BrNO: C, 44.89; H, 3.77; N, 6.55; Br, 37.34. Found: C, 45.32; H, 3.91; N, 6.84; Br, 36.89.

6-Benzoyl-4,5-dihydro-2-dimethylamino-6*H*-pyrrolo[3,2-*e*]benzothiazole (37).—A mixture of 318 mg (1 mmol) of **31**, 104 mg (1 mmol) of 1,1-dimethylthiourea, 101 mg (1 mmol) of triethylamine, and 10 ml of tetrahydrofuran was warmed at reflux temperature for 20 hr and then filtered. The filtrate was concentrated to an oily residue which crystallized upon trituration with ether. Recrystallization from methanol afforded **37** as yellow needles, mp 117–120°.

Anal. Calcd for $C_{18}H_{17}N_3OS$: C, 66.86; H, 5.30; S, 9.92. Found: C, 66.48; N, 5.51; S, 9.49.

When this experiment was repeated on a 5.0-g scale, the yield of **37** was 3.8 g (75%).

4,5-Dihydro-2-methylamino-6*H*-pyrrolo[3,2-*e*]benzothiazole (38).—A suspension of 3.8 g (11.8 mmol) of **37** in 75 ml of methanol was treated with 11.8 mmol of 5 *N* NaOH. Within 10 min this yellow solid had dissolved and pale yellow crystals of product had formed. The product was washed well with methanol and

dried in air. A 2.15-g (80%) yield of crystals with mp 244–245° was obtained. Recrystallization from methanol afforded **38** as pale yellow needles, mp 246–248°.

Anal. Calcd for $C_{11}H_{11}N_3S$: C, 60.25; H, 5.98; N, 19.15; S, 14.62. Found: C, 59.98; H, 5.99; N, 19.02; S, 14.33.

1-Acetyl-4-oxo-4,5,6,7-tetrahydroindole (33).—A mixture of 10.3 g of **5**, 7.5 g of potassium acetate, and 75 ml of acetic anhydride was heated at reflux temperature for 16 hr and then concentrated. The residue was extracted with 150 ml of acetone. This extract was filtered and concentrated on a steam bath as hexane was added. When the first crystals appeared, the mixture was cooled. This procedure gave 12.1 g (90%) of **33** as white prisms, mp 85–93°. Recrystallization from acetone–hexane gave crystals with mp 98.5–99.5°: λ_{max} 5.75 μ ($COCH_3$), 6.00 μ (4-carbonyl), 275 mμ (ϵ 5200), 235 mμ (16,000).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.64; H, 5.50; N, 8.04.

Upon attempted recrystallization from methanol, **33** was hydrolyzed back to **5**, as indicated by identity of ir absorption spectra.

Dehydrogenation with Palladium on Charcoal.—A mixture of 10.0 g of the 4-oxo-4,5,6,7-tetrahydroindole or 6,7-dihydroindole, 2.5 g of 10% palladium on charcoal, and 50 ml of cumene was stirred at reflux temperature for 3 hr, cooled, and filtered. When a hydroxyindole was the product, the filtrate was extracted with 100 ml of 5% NaOH and this extract was layered with methylene chloride and carefully neutalized with acetic acid. The organic layer was washed with sodium bicarbonate, dried, and concentrated, and the residue was extracted with 500 mg of boiling *n*-hexane. White crystals of the product indole formed on cooling. Melting points and analytical data are given in Tables I and II.

Dehydrogenation with 5,6-Dichloro-2,3-dicyanobenzoquinone.—Equimolar portions of the 4-oxotetrahydroindole or 6,7-dihydroindole and 2,3-dichloro-5,6-dicyanobenzoquinone, each dissolved in the minimum volume of dioxane, were combined. After 1 hr the mixture was filtered to remove the hydroquinone and the filtrate was concentrated under reduced pressure. Residues were worked up as follows. For **39e** and **39f** the residual solids were extracted with boiling hexane and crystals formed upon cooling this extract. The products were recrystallized from hexane. For **35** the residue was extracted with dilute HCl and then the free base was literated by neutralization with NaOH. The best procedure for **13** was to dilute the dioxane filtrate with water until the product crystallized. Recrystallization was from ethanol. The yields, melting points, and analytical data for these compounds are given in Tables I and II.

4-Hydroxyindole.—A mixture of 1.35 g of **5**,[3] 0.50 g of 10% palladium on charcoal, and 75 ml of cumene was heated at reflux temperature for 4 hr and filtered, and the solid cake was washed with methylene chloride. The combined filtrate and wash was concentrated, and the residue was extracted with 10% sodium hydroxide solution containing a little sodium hydrosulfite. This extract was acidified with acetic acid and extracted with methylene chloride. The organic extract was dried and concentrated. The greenish residue was extracted with boiling cyclohexane. Upon cooling this extract gave 274 mg (21%) of a white solid: mp 101–102° (lit.[29] mp 98°); λ_{max} 222 mμ (ϵ 30,000), 264 (9700), 282 (5600), 292 (5400); one spot on tlc.

When the dehydrogenation of **5** was effected in mesitylene according to the procedure of Plieninger and Klinga,[25] a 48% yield of 4-hydroxyindole was obtained. It had mp 88–91° after recrystallization from water. The presence of a small amount of **5** was shown by tlc and its nmr spectrum.

1-Benzyl-4-hydroxyindole.—A mixture of 213 mg (0.79 mmol) of **18** and 25 mg (0.79 mmol) of sulfur was heated at 220–240° for 30 min, cooled, and extracted with methylene chloride. This extract was concentrated and the residue was purified by liquid–liquid partition chromatography on diatomaceous earth with a heptane–methanol system. The main peak absorbing at 300 mμ (sixth holdback volume) afforded 56 mg of a viscous, colorless oil upon concentration. This oil crystallized on standing. After washing with ether it had mp 90–92°.

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.55; H, 6.00; N, 6.30.

Registry No.—**4a,** 4674-52-6; **4b,** 4583-63-5; **5** oxime, 27866-27-9; **6a,** 4657-85-6; **6b,** 4657-86-7; **8,** 4657-73-2; **9a,** 4660-04-2; **9b,** 4657-71-0; **10a,** 4660-05-3; **10b,** 4657-72-1; **11,** 27866-35-9; **12,** 27866-36-0; **13,** 27866-37-1; **14,** 27866-38-2; **15,** 27866-39-3; **16,** 27866-40-6; **17,** 13671-74-4; **18,** 27866-42-8; **19,** 27866-43-9; **20,** 27866-44-0; **21,** 27866-45-1; **23,** 27866-46-2; **24,** 27866-47-3; **26,** 27866-48-4; **27,** 27866-49-5; **28,** 18518-46-2; **29,** 27866-51-9; **30,** 27866-52-0; **31,** 27866-53-1; **32,** 27866-54-2; **33,** 27866-55-3; **35,** 27866-56-4; **36,** 27928-70-7; **37,** 27866-57-5; **38,** 27866-58-6; **39a,** 4657-80-1; **39b,** 4657-81-2; **39c,** 4657-82-3; **39e,** 4624-36-6; **39f,** 4657-84-5; 1-benzyl-4-hydroxyindole, 27866-64-4.

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