the mixture was stirred for four more hours. Residual zinc was removed by filtration, and the methanol was removed under reduced pressure. The residue was diluted with water, brought to pH 10 with 10% sodium hydroxide solution, and extracted with ether. The combined extracts were dried over potassium carbonate and distilled. The first fraction, b.p. 140–144°, weighed 2 g. and appeared to be the pyrrolidine. A second fraction of 4.5 g. (45%), distilling at 149°, was the Δ^3-pyrroline. The infrared spectrum (pure liquid) had a band at 6.10 μ. The 60-Mc. n.m.r. spectrum in carbon tetrachloride (tetramethylsilane reference) showed a doublet centered at 8.92 p.p.m. with coupling constant of 7 c.p.s., assigned to the 2- and 5-methyls (*cf.* 1,2,5-trimethylpyrrole). A singlet at 8.48 p.p.m. is assigned to the 3- and 4-methyls, and a broad peak at 6.40 p.p.m. is due to the ring protons at the 2- and 5-positions.

The **perchlorate**, recrystallized from methanol and ether, melted at 172°.

Anal. Calcd. for $C_8H_{10}ClNO_4$: C, 42.58; H, 7.14; N, 6.20. Found: C, 42.60; H, 7.13; N, 6.46.

1-Methylpyrrole-2-carboxylic Acid.—Fifteen grams of 1-methylpyrrole-2-carboxaldehyde was d ssolved in a solution of 10 g. of sodium hydroxide in 300 ml. of water, and 20 g. of potassium permanganate was added in three portions to the stirred mixture. The temperature rose to 60–70° and was maintained there for 3–4 hr. The filtrate obtained by removal of the manganese dioxide was cooled to 5° and acidified to pH 2 with 5% hydrochloric acid. The product separated in white needles which were recrystallized from water, yielding 3.4 g. (20%) of pure material, m.p. 134–135° (lit.[29] m.p. 135°).

1,2-Dimethylpyrrole.—2-Methylpyrrole (8.19, 0.1 mole) was added dropwise to a stirred mixture of 4.7 g. (0.12 g.-atom) of potassium metal in 200 ml. of anhydrous ether, contained in a flask which was under a positive pressure of nitrogen and which had been previously dried over an open flame while purging with nitrogen. The mixture was refluxed overnight, cooled, and then 30 g. of methyl iodide was added. The resulting solution was refluxed for 4 hr., cooled, filtered, and the solvents were removed under reduced pressure. The residue was dissolved in ether, about 1 g. of potassium metal was added, and the mixture was refluxed for 4 hr. A chaser of 5 ml. of phenyl ether was added and the pyrrole was distilled. The colorless liquid, weighing 6.2 g. (65%), distilled at 74° (65 mm.), and its vapor chromatogram showed a single peak.

1,2,3,5-Tetramethylpyrrole.—The procedure was similar to that presented previously for the preparation of 1,2-dimethylpyrrole, but 1,2-dimethoxyethane was used as the solvent, and the second treatment with potassium was not needed. The product, which weighed 17 g. (67% based on 22 g. of 2,3,5-trimethylpyrrole), was a colorless liquid that distilled at 80–81° (16 mm.).

Anal. Calcd. for $C_8H_{13}N$: C, 77.99; H, 10.63; N, 11.37. Found: C, 78.11; H, 10.75; N, 11.57.

When more than a 20% excess of potassium was used, the product was contaminated by what appeared from n.m.r. data to be pentamethylpyrrole.

(29) E. Fischer, *Ber.*, **46**, 2510 (1913).

Arrested Deamination in the Fischer Indole Synthesis. The Synthesis of 1,2,3,3a,4,8b-Hexahydropyrrolo[3,4-*b*]indoles with Angular Substitution[1]

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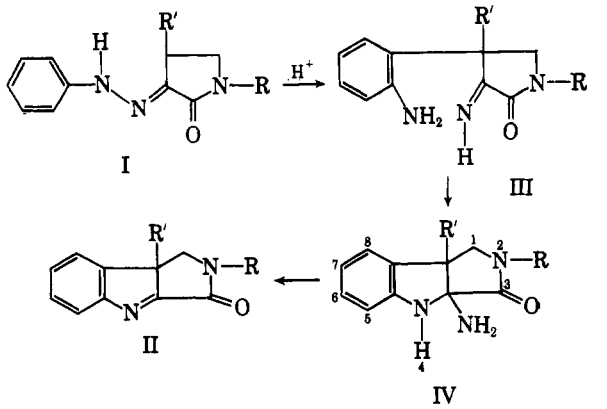
Phenylhydrazones of 1-substituted 4-benzyl-2,3-dioxopyrrolidines (I) rearrange in methanol–hydrochloric acid mixtures to yield 2-substituted 3a-amino-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-ones (IV). This type of transformation represents a normal Fischer indole synthesis arrested at the point at which ammonia is usually eliminated. The compounds IV were converted into a variety of other products containing the hexahydropyrrolo[3,4-*b*]indole ring system. Thus, it was possible to reduce the lactam carbonyl to a methylene group, to replace the angular 3a-amino function by hydrogen or hydroxyl, to acylate the 4-nitrogen, and to obtain products embodying two or more of such changes. It was shown that compounds of this series resemble alkaloids of the indoline type with respect to ultraviolet spectra and certain color tests.

Compounds in the pyrrolo[3,4-*b*]indole series have recently been made available by application of the Fischer indole synthesis to phenylhydrazones of 2,3-dioxopyrrolidines.[4] In order to make possible a more complete assessment of the potential biological activity of compounds containing this new heterocyclic ring system it was considered of interest to prepare members of the series of the type II, in which an angular substituent and an indolenine rather than an indole nucleus is present. Reduction of such compounds was expected to lead to structures of the type IX, related to the heterocyclic ring system of eserine, but with the position of the nitrogen changed in the outer pyrrolidine ring.

It was anticipated that the compounds II would result from the Fischer indole reaction of phenylhydrazones of 4-substituted 2,3-dioxopyrrolidines (I). When four phenylhydrazones of a series of recently obtained 1-substituted 4-benzyl-2,3-dioxopyrrolidines[5] (I, R′ = benzyl; R = methyl, isopropyl, cyclohexyl, or benzyl) were heated for a short time with methanolic hydrochloric acid, however, rearrangement products which



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(2) National Science Foundation Undergraduate Research Participant, 1961–1962.

(3) National Science Foundation Cooperative Predoctoral Fellow, 1959–1960. This paper is based principally on a thesis submitted by Richard J. Owellen in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Carnegie Institute of Technology, September, 1960.

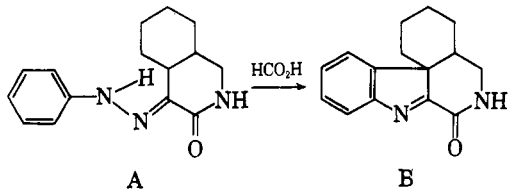
(4) P. L. Southwick and R. J. Owellen, *J. Org. Chem.*, **25**, 1133 (1960).

(5) P. L. Southwick and E. F. Barnas, *ibid.*, **27**, 98 (1962).

retained all three nitrogens of the starting materials were produced in yields of 40–90%. Thus indolenine derivatives II were not formed, but a family of compounds of more novel structure became available for chemical and biological investigation.

It was evident that the first phases of the mechanism of the Fischer indole synthesis had proceeded, since the rearrangement products readily underwent loss of ammonia when heated for thirty minutes with aqueous acetic acid or when heated for longer periods of time with sodium ethoxide. The easy removal of one nitrogen from these products by mild hydrolysis indicated that the N–N bond of the phenylhydrazones had been cleaved in the rearrangement itself, as expected in the Fischer reaction. This result suggested that the products might have the imine structure III, analogous to a product reported by Plieninger[6] to result from acid treatment of the phenylhydrazone of α-ketobutyrolactone. However, the spectroscopic data and the chemical behavior discussed below have led us to conclude that the compounds have the structure of 2-substituted 3a-amino-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-ones (IV, R′ = benzyl). It should be noted that somewhat analogous 1-acyl-2-aminoindolines have been described by Leuchs and his associates,[7] who obtained them by the action of ammonia on suitable 1-acyl-2-halo- or 1-acyl-2-acyloxyindolines.

The failure of the compounds IV to undergo conversion to the indolenines II can apparently be attributed to ring strain which would be associated with a structure such as II. An analogous Fischer indole reaction was carried out by Abramovitch and Muchowski[8a] on the phenylhydrazone A to yield a product tentatively



A B

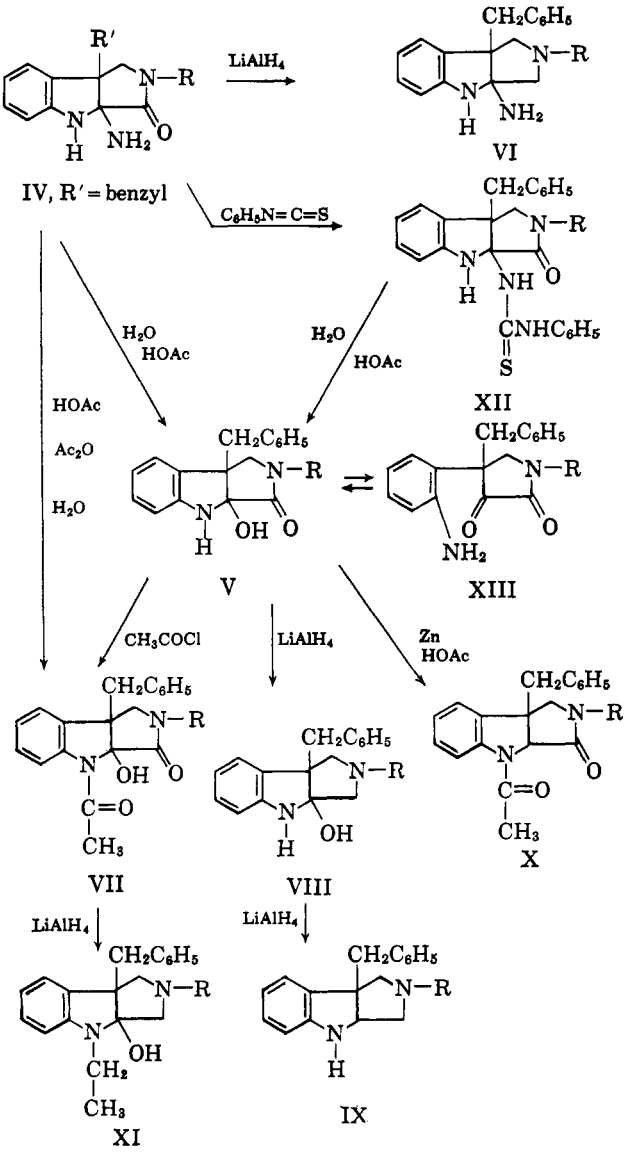
identified as the indolenine B. The difference between this result and our observations with phenylhydrazones of the type I would appear to reflect the difference in the size of the lactam ring. Our results suggest that the indolenine double bond is not readily accommodated in a fused ring system of the type II, in which two rings are five-numbered and rather rigid; whereas if the indolenine B has been obtained as indicated, it is clear that no comparable difficulty exists when the more flexible six-membered lactam (piperidone) ring is present.[8b,c]

(6) (a) H. Plieninger, *Ber.*, **83**, 273 (1950); (b) H. Plieninger and I. Nogradi, *ibid.*, **88**, 1965 (1955).

(7) (a) H. Leuchs, D. Philpott, P. Sander, A. Heller, and H. Köhler, *Ann.*, **461**, 27 (1928); (b) H. Leuchs, A. Heller, and A. Hoffmann, *Ber.*, **62**, 871 (1929).

(8) (a) R. A. Abramovitch and J. M. Muchowski, *Can. J. Chem.*, **38**, 557 (1960). (b) Other interesting effects which can be attributed to the strain which would accompany the presence of a tetrahedral and a trigonal carbon at the junction of two fused five-membered rings have been reported recently by Zaugg and his associates, who have discussed the literature pertaining to the strain energy of such a system. See H. E. Zaugg and R. W. DeNet, *J. Am. Chem. Soc.*, **84**, 4574 (1962), and references cited therein. (c) A referee has pointed out that the rapid ring opening of the presumed indolenine hydroperoxide from autoxidation of cyclopentanoindole [B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 2196 (1951)] also may illustrate the effects of strain in such systems.

CHART I



Starting from compounds of type IV, a variety of related structures were obtained, as indicated in Chart I. The numbered formulas in the chart designate structural types; individual compounds under discussion will be identified by appending to the number for the structural type a letter indicating the nature of the group R: b for benzyl, c for cyclohexyl, i for isopropyl, and m for methyl. Most of the reactions were first examined with the cyclohexyl derivative IVc, and then applied to one or more of the other compounds. In all compounds which were studied the group R′ was benzyl.

It will become apparent from the ensuing discussion that the interrelationships and properties of the varied reaction products support the assigned structure IV for the initial rearrangement products. It should be noted at the outset, however, that the uncyclized imine structure III for these compounds does not appear to be consistent with their failure to yield diazonium salts (IVc appeared to be converted largely to an N-nitroso compound), to give condensation products with salicylaldehyde, or to undergo hydrogenation in the presence of platinum or Raney nickel catalysts. Moreover, the ultraviolet data to be dis-

cussed and the lack of an infrared band assignable to an imino group[9] favor the choice of structure IV over structure III.

Also pertinent to the question of whether structure III or structure IV should represent the initial rearrangement products was the behavior of a phenylthiourea derivative obtained from one of the rearrangement products (IVc) with excess phenyl isothiocyanate. The hydrolysis of this substance, which occurred when it was merely heated for a short time in aqueous acetic acid, resulted in the loss of the entire phenylthioureido group; the hydrolysis products were phenylthiourea and the same compound (Vc) produced by mild hydrolysis of IVc itself. A product formed by reaction of the aromatic amino group of IIIc with phenyl isothiocyanate could yield phenylthiourea only by cleavage of the bond between nitrogen and the aromatic ring. Since such cleavage is not reasonable, the phenyl isothiocyanate must have reacted with a different nitrogen atom, and in the case of structure III, this would be the nitrogen of the imino group. Such a result would require that the imino group be reactive and the amino group be relatively inert toward phenyl isothiocyanate. No reason for such unexpected behavior is evident. Structure IV, on the other hand, would seem to accommodate the observations plausibly through direct conversion to a derivative of structure XIIc.

It would not have been surprising to find the products Vc, Vi, and Vm, obtained by hydrolysis of compounds of the types IV or XII with aqueous acetic acid, existing at least in part in an open form XIII. However, although some samples of Vc showed a barely discernible absorption at 5.68 μ, the infrared spectra of these compounds in chloroform never displayed the strong absorption at that wave length which is characteristic of the ketonic carbonyl of 2,3-dioxopyrrolidines.[10,11] The open form XIII can therefore have been present only in a very small concentration in these solutions, and the tricyclic fused ring formula V with the angular hydroxyl probably correctly represents the structure of the compounds. The infrared spectra in chloroform solution showed a shoulder at *ca.* 2.8 μ and a broad absorption at *ca.* 3.0 μ consistent with the O–H and N–H bonds of formula V.[12]

Lithium aluminum hydride reduction of the angular amino compounds IVc, IVi, and IVm removed the lactam (pyrrolidone) carbonyl group, but all of the nitrogen atoms were retained. The yields were in the range 47 to 61%. The infrared spectra revealed no evidence of a carbon–nitrogen double bond or other unsaturation. The composition and the additional spectroscopic evidence to be discussed subsequently favor formula VI for these basic compounds, with the fused ring system and angular amino group left undisturbed during the reductions.

Lithium aluminum hydride reduction also removed the pyrrolidone carbonyl group from the compounds Vc and Vm, but two reduction products were obtained in each case, one in which the angular hydroxyl group was retained (structure VIII) and a second in which that group had been removed (structure IX). Combined yields of both products were typically around 70%, but the relative amounts of VIII and IX obtained varied considerably between different runs. It was found that treatment of VIIIc with lithium aluminum hydride under the conditions of the original reduction converted a part of it into the desoxy compound IXc, but the conversion was never found to be complete. The infrared spectra of compounds VIIIc and VIIIm showed bands at 2.80 and 2.95 μ, indicating the presence of both O–H and N–H bonds, whereas IXc and IXm showed only the N–H absorption at 2.95 μ, The successful synthesis of the 1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indoles IXc and IXm represented the fulfillment of one of the original objectives of the investigation.

Compound Vc was also reduced with zinc and acetic acid, a procedure which has been applied to 2-hydroxyindolines by Volz and Wieland.[13] As in the case of the latter compounds, the hydroxyl group was removed. In the present instance, acetylation accompanied the reduction to yield a product of structure X. The compound showed no infrared bands corresponding to N–H or O–H absorption, and had very intense absorption at 5.94 μ,[14a] evidently representing both amide and pyrrolidone carbonyl groups. The same procedure also gave Xc from IVc.

Acetylation of either the angular amino compound IVc or the angular hydroxy compound Vc yielded a product of structure VIIc with an angular hydroxyl group and an acetylated indoline nitrogen. (The processing of the reaction mixtures would have allowed for hydrolytic removal of the angular nitrogen.) It was found that compound VIIc could be made directly from the phenylhydrazone Ic in 50% yield by adding acetic anhydride to acetic acid–hydrochloric acid solutions in which rearrangement of the phenylhydrazone was being carried out. The acetylated angular hydroxy compound VIIc showed broad hydroxyl absorption (3.04–3.13 μ) indicative of hydrogen bonding. Two well separated carbonyl bands were present (5.92 and 6.13 μ). The 6.13-μ band can no doubt be assigned to the N-acetyl group, and the shift to longer wave length as compared to the band for the N-acetyl group in compound X probably reflects hydrogen bonding with the angular hydroxyl.[14b]

Lithium aluminum hydride reduction of VIIc reduced both amide carbonyls to yield the N-ethyl derivative XIc, with the angular hydroxyl retained as in compounds VIIIc or VIIIm. The infrared spectrum of com-

(9) The phenylhydrazones all displayed very strong infrared bands at 6.20–6.24 μ which were much diminished in intensity in their rearrangement products. The remaining weaker absorption at 6.18–6.24 μ persisted in all members of the series of compounds, including the fully reduced structures IX. A band at this position is characteristic of indolines. See W. V. Philipsborn, H. Meyer, H. Schmid and P. Karrer, *Helv. Chim. Acta.*, **41**, 1257 (1958).

(10) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

(11) *Cf.* (a) W. L. Meyer and W. R. Vaughan, *ibid.*, **22**, 98, 1554, 1560 (1957); (b) W. R. Vaughan and I. S. Covey, *J. Am. Chem. Soc.*, **80**, 2197 (1958); (c) H. H. Wasserman and R. C. Koch, *Chem. Ind.* (London), 128 (1957); *J. Org. Chem.*, **27**, 35 (1962).

(12) In the case of compound Vm, crystallization from different solvents (95% ethanol or an *n*-hexane–benzene mixture) produced different crystalline forms which exhibited the same infrared spectrum in chloroform, but gave potassium bromide pellet spectra which differed slightly in the carbonyl region.

(13) H. Volz and T. Wieland, *Ann.*, **604**, 1 (1957).

(14) (a) This carbonyl absorption is at a wave length intermediate between that observed for N-acetylindoles (5.90 μ) and for some acetylated indoline alkaloids (6.01 μ). See B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **76**, 5603 (1954). (b) Witkop and Patrick found the carbonyl absorption of an N-acetylindoline derivative (demethylaspidospermine) shifted to 6.12 μ by hydrogen bonding with a hydroxyl group.

TABLE I

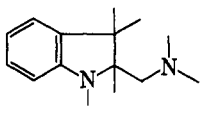
COLOR TESTS AND ULTRAVIOLET MAXIMA

Compound	H_2SO_4–$Ce(SO_4)_2$ colors[a] Immediate	After 20 min.	HNO_3 colors[b] Immediate	After 15 min.	Ultraviolet maxima: Neutral solution[c] λ, mμ	log ε	Acid solution[d] λ, mμ	log ε
Ic	...	...	Blue	Orange				
IVc	Pale crimson	Crimson	Pale yellow	Red-brown	241	3.78	235	3.79
					295	3.37	286	3.58
Vc	Crimson	Deep crimson	Pale crimson	Pale red-orange				
VIc	Bright orange	Orange-red	Pale yellow	Pale orange-brown	246	3.86	238	3.87
					301	3.43	294	3.40
VIIc	Pale wine-red	Pale red-brown	None	Pale yellow	252	4.11		
					277 i	3.42		
					287	3.30		
VIIIc	Bright orange	Orange-red	Pale yellow	Orange	246	3.89	241	3.90
					300	3.43	301	3.45
IXc	Orange-red	Orange-red	Yellow	Orange	246	3.85	246	3.86
					301	3.40	302	3.42
Xc	Pale pink	Pale yellow-brown	None	None	252	4.09		
					279	3.41		
					288	3.33		
XIc	Pale crimson	Pale crimson	Deep scarlet	Deep scarlet	258	4.08	252	4.08
					311	3.58	302	3.35

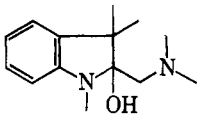
[a] The reagent[21] was a 1:1 mixture, by volume, of concentrated sulfuric acid and 1% ceric sulfate in 2 *N* sulfuric acid. [b] The reagent was concentrated nitric acid. [c] Ultraviolet spectra in 95% ethanol; i indicates inflection. [d] Solvent was 0.1 to 0.25 *N* hydrochloric acid in aqueous ethanol.

pound XIc showed only a single sharp band at 2.80 μ in the O–H or N–H region.

The members of this series of hexahydropyrrolo[3,4-*b*]indoles resemble such alkaloids as ajmaline,[15] tetraphyllicine,[16] and C-alkloid-Y[17] in that they incorporate the partial structures C or D. As a result, there were noted among these compounds some similarities to the properties of the alkaloids or their



C



D

derivatives which cannot be attributed just to the presence of the indoline structure alone. All of the members of the series show typical indoline ultraviolet spectra (Table I), with principal maxima near 250 mμ and secondary maxima near 300 mμ, but it is particularly significant that when the spectrum of a compound of the type IX (IXc) was measured in dilute acid solution there was almost no change, although the spectra of aromatic amines or simple indolines[18] are completely altered in appearance and greatly reduced in intensity in such acid solutions. In this respect, the behavior of IXc parallels that of deoxydihydroajmaline,[18] and it is evident that the indoline nitrogen is not being protonated in either case, probably, as pointed out by Hodson and Smith[18] with respect to deoxydihydroajmaline, because a more basic nonindoline nitrogen, only two carbons removed, has been protonated first. The compounds VIIIc and XIc also retained spectra of the indoline type in acid solution, although a small hypsochromic shift was observed.[19]

Compounds of the types IV and VI, like eserine, contain a basic nitrogen atom attached at the 2-position of the indoline portion of the structure. The ultraviolet spectra of these compounds are very similar to that of eserine,[18] both in neutral solution and in dilute acid solution, in which all of the spectra undergo a hypsochromic shift of 6 to 10 mμ. This spectroscopic resemblance to eserine constitutes additional substantial evidence that these compounds incorporate a 2-aminoindoline structure. The compounds VIIc and Xc showed ultraviolet spectra typical of N-acylindolines.[20]

Certain color tests which have proved useful in the classification of curare alkaloids,[17b,21] were found applicable to the synthetic hexahydropyrrolo[3,4-*b*]indoles obtained in the present investigation (see Table I). With ceric sulfate in sulfuric acid[21] all of the compounds tested developed characteristic colors, but the colors were rather pale in the case of the compounds VIIc, Xc, and XIc in which the indoline nitrogen was substituted. A stable orange color was obtained from compound IXc, as is true of indoline alkaloids having an unsubstituted indoline nitrogen.[17b] The test with concentrated nitric acid served to distinguish compounds with an acylated indoline nitrogen (VIIc and Xc gave little or no color) from the other members of the series. The most striking result with nitric acid was the deep scarlet color obtained from XIc which recalls the similar characteristic color reportedly obtained from C-alkaloid-Y.[17a] Like XIc, the alkaloid is believed to

(15) See (a) R. B. Woodward, *Angew. Chem.*, **68**, 13 (1956); (b) M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Amai, P. Peak, N. V. Bringi, and E. Wenkert, *J. Am. Chem. Soc.*, **84**, 622 (1962), and references cited therein.

(16) (a) C. Djerassi, M. Gorman, S. C. Pakraski, and R. B. Woodward, *ibid.*, **78**, 1259 (1956); (b) C. Djerassi, J. Fishman, M. Gorman, J. P. Kutney, and S. C. Pakraski, *ibid.*, **79**, 1217 (1957).

(17) (a) H. Fritz, T. Wieland, and E. Besch, *Ann.*, **611**, 268 (1958); (b) A. R. Battersby and H. F. Hodson, *Quart. Rev.* (London), **14**, 77 (1960).

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

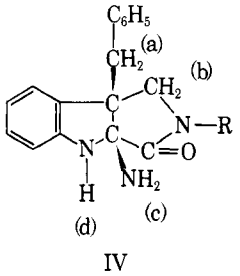
(19) Addition of sodium hydroxide did not further extend the bathochromic shift represented by the change in spectra upon changing the hydrochlorides of VIII and IX into the corresponding free bases, although certain alkaloids containing the 2-hydroxyindoline structure show a bathochromic shift in sodium hydroxide.[17] The reason for this difference is not clear, but it may be associated with such structural dissimilarities as the more rigid ring systems or the additional basic nitrogen in VIII and XI as compared to the alkaloids.

(20) *Cf.* J. Kebrle, H. Schmid, P. Waser, and P. Karrer, *Helv. Chim. Acta*, **36**, 102 (1953).

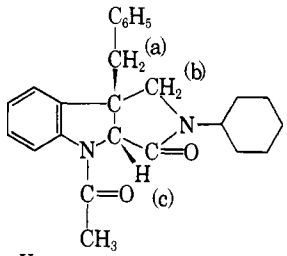
(21) H. Schmid, J. Kebrle, and P. Karrer, *ibid.*, **35**, 1864 (1952).

TABLE II

NUCLEAR MAGNETIC RESONANCE DATA



IV



Xc

Compound	Proton position	Line pattern	Line positions (c.p.s.) separation from TMS[a]	Chemical shift, τ-scale[b] Individual proton	Av.
IVb[c]	a	AB quartet	1 −161, 2 −174	7.17	7.00
			3 −186[d], 4 −199	6.82	
	b	AB quartet	1 −186[d], 2 −195	6.81	6.56
			3 −217, 4 −226	6.32	
	c	Broad peak (2 protons)	−122	...	7.97
	d	Broad peak (1 proton)	−303		4.95
IVc[e]	a	AB quartet	1 −162, 2 −175	7.17	6.97
			3 −189, 4 −202[d]	6.77	
	b	AB quartet	1 −193, 2 −202[d]	6.69	6.50
			3 −218, 4 −227	6.31	
	c	Broad peak[f]	*ca.* −119		*ca.* 8.02
	d	Broad peak (1 proton)	*ca.* −298		*ca.* 5.03
Xc[e,g]	a	Singlet (2 protons)	−180		7.00
	b	Singlet (2 protons)	−221		6.31
	c	Singlet (1 proton)	−281		5.31[h]
	d	Singlet (3 protons)	−141		7.65

[a] Determinations were made at 60 Mc. with a Varian high-resolution dual purpose instrument, Model V-4302. The solvent used was deuteriochloroform, with tetramethylsilane (TMS) as the internal reference. [b] Calculated chemical shifts for individual protons in pairs which give AB quartets (see Jackman, ref. 22a, pp. 89–90) are recorded in the left-hand column. In the right-hand (Av.) column absorptions appearing as singlets are given, as well as midpoints of AB quartets and approximate centers of broad unresolved absorptions. [c] In compound IVb the N-benzyl group gave rise to a barely resolved AB quartet with lines at −247, −262, −266, and −282 c.p.s.; midpoint 5.60 τ. [d] Strongest signal of the overlapping AB patterns; coincidence of lines indicated. [e] In the spectra of IVc and Xc the lines at *ca.* 6.30 τ were apparently superimposed over a broad unresolved absorption which is presumed, on the basis of its appearance and chemical shift, to be due to the proton on C-1 of the cyclohexyl group. [f] The absorption overlapped that arising from a portion of the spectrum of the cyclohexyl group. [g] A multiplet corresponding approximately to one proton was observed at *ca.* 1.88 τ on the downfield side of the main aromatic absorption of Xc. These signals may arise from the proton at position 5 of the ring system, which might be subjected to a long-range shielding effect by the acetyl carbonyl group at position 4 (*cf.* Jackman, ref. 22a, pp. 121–125). [h] The chemical shift of this proton is intermediate between those of similarly situated protons at the 2-position of the N-acetylindoline structures in spegazzinidine (doublet at 5.95 τ) and 3-dehydrospegazzinidine dimethyl ether (singlet at 4.89 τ). See C. Djerassi, *et al.*, *J. Am. Chem. Soc.* **84**, 3480 (1962). The downfield shift of this absorption in the spectra of compound Xc and 3-dehydrospegazzinidine dimethyl ether relative to its position in the spectrum of spegazzinidine reflects the effect of an α-carbonyl group, which in compound Xc may be partly offset by long-range shielding from the aromatic ring in the benzyl group (*cf.* Jackman, ref. 22a, pp. 18–19 and 51–52).

contain the partial structure D with an angular hydroxyl group and a substituted indoline nitrogen.

Nuclear magnetic resonance (n.m.r.) spectra of several numbers of this series were measured, and in the case of two types of compounds (IV and X) the signals from the various hydrogens were sufficiently well separated to permit an analysis of the significant part of the data (see Table II). In structures IV and X the angular benzyl methylene group and the only hydrogen-bearing carbons of the pyrrolidine rings are all separated from each other by a quaternary carbon, the atom at position 8b of the ring system. Hence there should be no vicinal spin–spin coupling affecting these hydrogens, and relatively simple line patterns might be anticipated. In the case of compound Xc, the spectrum from these portions of the structure was in fact, as simple as possible; there were single unresolved lines with appropriate intensity relationships for the benzyl methylene hydrogens at position a (see formulas given with Table II), for the pyrrolidine methylene hydrogens at position b, for the single pyrrolidine hydrogen at position c, and for the acetyl methyl hydrogens at position d. Evidently the individual hydrogens constituting the geminal pairs at positions a and b do not differ sufficiently from each other in chemical shift to give rise to resolved patterns of the AB type,[22a] despite the fact that these hydrogens are configurationally nonequivalent in this asymmetric structure.

On the other hand, the data indicate that each of the two pairs of geminal hydrogens at positions a and b in compounds IVb and IVc give rise to an AB quartet. These two quartets overlap to a slightly different extent in the spectra of the two compounds; as indicated in Table II, line 3 of the pattern from position a coincides with line 1 from position b in the spectrum of IVb, whereas line 4 of the pattern from position a coincides

(22) (a) See L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, pp. 89, 90. (b) private communication from Dr. Bernard L. Shapiro; the compound in question is that labeled VII in the communication by F. A. Hochstein, H. Els, W. D. Celmer, B. L. Shapiro, and R. B. Woodward, *J. Am. Chem. Soc.*, **82**, 3225 (1960); the geminal coupling constant was 9.8 ± 0.2 c.p.s.. (c) See L. M. Jackman, ref. 22a, Chap. 4.

with line 2 from position b in the spectrum of IVc. The amino proton at position d evidently gave rise to the broad and somewhat variable absorption seen at *ca.* 5.0 τ in the spectra of IVb and IVc, and the two protons of the angular amino group at position c appeared as a rather broad but well defined absorption at *ca.* 8.0 τ in the spectrum of IVb. The latter absorption was evident in the spectrum of IVc, also, but overlapped the absorption of the cyclohexane ring. The geminal coupling constants for the hydrogens at b in IVb and IVc were in the range of 9 to 10 c.p.s., close to a value observed for analogously situated geminal hydrogens in the γ-lactone portion of an oleandomycin degradation product[22b]; the spectra of five-membered lactams and lactones are apparently similar in this respect.

The indicated assignments of the lines of the n.m.r. spectra are supported by chemical shift data on related pyrrolidones which have been examined in this laboratory, and by similar data in the literature.[22c] That the spectra of compounds IVb and IVc are more complex than that of Xc may in part reflect the fact that with molecules in the relatively unstrained *cis* configuration at the junction of the two five-membered rings the angular benzyl group would be *cis* to the angular amino group in compounds IVb and IVc, so that the two protons of the geminal pair at position a, as well as those at position b, could be unequally influenced by the amino group.

One of the compounds in the pyrrolo[3,4-*b*]indole series prepared previously,[4] 2-cyclohexyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole, has shown some indications of weak activity in tests for central nervous system effects.[23] Several compounds obtained in the present investigation are undergoing biological screening, but no significant activity has been demonstrated as yet.

Experimental[24]

1-Isopropyl-4-benzyl-2,3-dioxopyrrolidine.—A suspension of 20 g. of 1-isopropyl-4-benzal-2,3-dioxopyrrolidine[5] in 250 ml. of 95% ethanol and 1 ml. of concentrated hydrochloric acid was hydrogenated over 120 mg. of Adams' platinum oxide catalyst in a Parr apparatus for 30 min. at *ca.* 5-atm. initial pressure while the pressure bottle was heated with an infrared lamp. (Recent experiments with other similar compounds indicate that a 10% palladium-on-calcium carbonate catalyst used in neutral ethanol at room temperature may give superior results in this type of hydrogenation.) The solution was filtered while still hot to remove the catalyst and an insoluble, white by-product, and evaporated to dryness under reduced pressure. The residual oil was crystallized from aqueous ethanol to give 10 g. (50%) of white needles. For analysis the compound was recrystallized three times from cyclohexane to give long colorless needles, m.p. 171–172.5°.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.38; H, 7.17; N, 6.06.

Infrared spectrum (μ): 2.80 w, 3.14 s, 3.32 s, 3.40 m, 3.48 m, 5.62 w, 5.98 s, 6.19 m, 6.66 m, 6.82 s, 6.97 m, 7.16 s, 7.21 s, 7.28 s, 7.45 m, 7.53 m, 7.83 s.

1-Substituted 4-Benzyl-2,3-dioxopyrrolidine Phenylhydrazones (I, R′ = Benzyl).—These compounds were prepared by suspending the 1-substituted 4-benzyl-2,3-dioxopyrrolidines[5] in 95% ethanol (5 ml./g.), adding phenylhydrazine (150 mole %) and glacial acetic acid (2 ml.), then heating the mixture at the boiling point for 10 to 20 min. Most of the starting material gradually dissolved and the solution turned yellow before the product began to precipitate. At the end of the heating period the mixture was cooled in an ice bath to complete precipitation of the product, which was collected by filtration, washed with cold 95% ethanol, and air-dried. Yields quoted are of the crystalline products as obtained in this way directly from the reaction mixtures. In a number of cases the products were pure enough to be used in the subsequent reaction without further purification. For analysis the compounds were recrystallized three times from 95% ethanol. Results with individual compounds are described in subsequent sections.

1-Methyl-4-benzyl-2,3-dioxopyrrolidine Phenylhydrazone.—The yield was 10 g. (95%) of pale yellow cubic crystals m.p. 163–165°, from 8 g. of 1-methyl-4-benzyl-2,3-dioxopyrrolidine. The analytical sample melted at 168–170° dec.

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.96; H, 6.63; N, 14.44.

Infrared spectrum: 2.97 m, 3.31 m, 3.39 m, 3.44 m, 5.88 s, 6.20 s, 6.68 s, 6.85 m, 6.96 s, 7.09 m, 7.62 m, 7.74 m, 7.94 s.

1-Isopropyl-4-benzyl-2,3-dioxopyrrolidine Phenylhydrazone.—The yield was 4 g. (48%) of long white needles, m.p. 205–206°. from 6 g. of 1-isopropyl-4-benzyl-2,3-dioxopyrrolidine.

Anal. Calcd. for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.32; H, 7.06; N, 12.92.

Infrared spectrum: 2.97 w, 3.32 m, 3.37 w, 3.42 w, 5.91 m, 5.97 m, 6.22 s, 6.60 m, 6.65 m, 6.70 m, 6.90 m, 6.97 s, 7.28 w, 7.74 m.

1,4-Dibenzyl-2,3-dioxopyrrolidine Phenylhydrazone.—The yield was 10 g. (75%) of fluffy white needles, m.p. 189–191°, from 10 g. of 1,4-dibenzyl-2,3-dioxopyrrolidine.

Anal. Calcd. for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.28; N, 11.37. Found: C, 77.38, 77.13; H, 6.24, 6.10; N, 11.50. (No reason for the low carbon value is apparent.)

Infrared spectrum: 2.98 w, 3.33 w, 3.43 w, 5.90 s, 6.20 s, 6.61 w, 6.68 m, 6.71 m, 6.92 m, 6.98 m, 7.36 w, 7.54 w, 7.76 w, 7.98 s.

1-Cyclohexyl-4-benzyl-2,3-dioxopyrrolidine Phenylhydrazone.—The yield was 24 g. (86%) of pale yellow or colorless prisms, m.p. 194–196° dec., from 20 g. of 1-cyclohexyl-4-benzyl-2,3-dioxopyrrolidine.

Anal. Calcd. for $C_{23}H_{27}N_3O$: C, 76.42; H, 7.53; N, 11.63. Found: C, 76.00; H, 7.72; N, 11.80.

Infrared spectrum: 2.99 w, 3.33 m, 3.41 m, 3.49 m, 5.95 s, 6.24 s, 6.62 m, 6.68 m, 6.73 m, 7.01 s, 7.77 m, 7.99 s.

The normal white phenylhydrazone melting at 194–196° dec. (1 g.) was isomerized to what may be a *syn–anti* isomer when it was refluxed for 2 hr. on the steam cone in a chloroform–benzene mixture (1:1 by volume), and the solution was evaporated to dryness. The residual oil crystallized slowly from a benzene–*n*-hexane mixture. There resulted 0.6 g. (60%) of bright orange needles that melted at 119–120° after three more recrystallizations from 95% ethanol. This material remained unchanged during 36-hr. refluxing in 95% ethanol.[25]

Anal. Calcd. for $C_{23}H_{27}N_3O$: C, 76.42; H, 7.53; N, 11.63. Found: C, 76.32; H, 7.44; N, 11.55.

Infrared spectrum: 3.09 w, 3.42 s, 3.51 m, 6.04 s, 6.28 s, 6.64 s, 6.74 m (sh), 6.91 s (sh), 7.02 s, 7.66 m, 7.78 m, 8.01 s.

2-Substituted 3a-Amino-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-ones (IV).—The 1-substituted 4-benzyl-2,3 dioxopyrrolidine phenylhydrazone (I) was suspended in a solution prepared from methanol (10 ml./g. of phenylhydrazone) and concentrated hydrochloric acid (1 ml./g. of phenylhydrazone). The mixture was heated on a steam cone until complete solution had occurred. After the solution had been cooled to room temperature rapidly in an ice bath, 10 to 20% aqueous sodium hydroxide was added slowly with cooling until the solution was strongly basic. ("Alkacid" test paper, Fisher Scientific Co.,

(23) The authors are indebted to Smith Kline and French Laboratories for biological screening. 2-Cyclohexyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]-indole produced some behavioral effects indicative of central nervous stimulation in rats at high dose levels, and was found partially effective in preventing one of the central effects of reserpine in the rat, the reserpine-induced ptosis. *Cf.* J. R. Gillette, J. V. Dingell, F. Sulser, R. Kuntzman, and B. B. Brodie, *Experientia*, **17**, 417 (1961), and references cited therein..

(24) Melting points are uncorrected. Microanalyses are by Drs. G. Weiler and F. B. Strauss, Oxford, England, and Geller Microanalytical Laboratories, Bardonia, N. Y. Ultraviolet spectra were determined with a Cary recording spectrophotometer; infrared spectra with a Perkin-Elmer Model 21 spectrophotometer. Intensities of infrared bands are recorded as strong, s (0–30% transmittance), medium, m (30–60% transmittance), and weak, w (60–90% transmittance); wave lengths (μ) are given for the 2.5- to 8.0-μ range in chloroform. Shoulders are indicated by (sh).

(25) R. A. Abramovitch, *Can. J. Chem.*, **36**, 354 (1958), reports the occurrence of *syn–anti* isomerization of the phenylhydrazone of 4-methyl-2,3-dioxopiperidine in the presence of zinc chloride or boron trifluoride, and the failure of the substance, unlike the isomer described here, to undergo the Fischer indole synthesis.

indicated a pH >12.) The product was extracted into chloroform and the solution was dried over magnesium sulfate. After filtration the chloroform solution was evaporated to dryness under reduced pressure, the residual oil was taken up in hot benzene or chloroform, and *n*-hexane was added to induce crystallization. Yields quoted are of the crystalline products as obtained in this way. (Alternatively, initial crystallization of IVc was induced by adding anhydrous ether to the residual oil.) The compounds were recrystallized from benzene–*n*-hexane mixtures with the exception of the 2-benzyl and 2-isopropyl compounds (IVb and IVi), with which chloroform–*n*-hexane mixtures were used. Benzene was avoided altogether in work with these compounds because it formed solvated crystals. Compound IVc crystallized well from mixtures of benzene and anhydrous ether. Results with individual compounds are listed.

3a-Amino-8b-benzyl-2-methyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (IVm).—The yield was 1.4 g. (70%) of colorless needles, m.p. 176–177°, from 2 g. of 1-methyl-4-benzyl-2,3-dioxopyrrolidine phenylhydrazone.

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.76; H, 6.37; N, 14.60.

Infrared spectrum: 2.97 w, 3.36 m, 3.43 w, 3.50 w, 5.92 s, 6.22 m, 6.70 m, 6.75 s, 6.83 s, 6.90 m, 6.96 m, 7.12 m, 7.17 m, 7.66 m, 8.02 m.

3a-Amino-8b-benzyl-2-isopropyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (IVi).—The yield was 1.5 g. (75%) of short white needles, m.p. 148.5–149°, from 2.0 g. of 1-isopropyl-4-benzyl-2,3-dioxopyrrolidine phenylhydrazone.

Anal. Calcd. for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.62; H, 7.05; N, 13.19.

Infrared spectrum: 2.95 m, 3.33 m, 3.44 w, 5.91 s, 6.17 m, 6.71 s, 6.80 s, 7.18 m, 7.28 m, 7.62 m.

3a-Amino-2,8b-dibenzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (IVb).—The yield was 2 g. (57%) of crude product, m.p. 90–100°, from 3.5 g. of 1,4-dibenzyl-2,3-dioxopyrrolidine phenylhydrazone. After two recrystallizations from acetic acid–water, two from benzene–*n*-hexane, and four more from benzene, white needles were obtained, m.p. 132–133°.

Anal. Calcd. for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.28; N, 11.63. Found: C, 78.30; H, 6.48; N, 11.25.

Infrared spectrum: 2.98 w, 3.33 w, 3.43 w, 5.90 s, 6.23 s, 6.61 w, 6.68 m, 6.71 m, 6.92 m, 6.98 m, 7.36 w, 7.54 w, 7.76 w, 7.98 s.

3a-Amino-8b-benzyl-2-cyclohexyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (IVc).—The yield was 18 g. (90%) of colorless prisms, m.p. 163–164°, from 20 g. of 1-cyclohexyl-4-benzyl-2,3-dioxopyrrolidine phenylhydrazone.

Anal. Calcd. for $C_{23}H_{27}N_3O$: C, 76.42; H, 7.53; N, 11.63. Found: C, 76.48; H, 7.31; N, 11.87.

Infrared spectrum: 3.01 w, 3.38 w, 3.43 m, 3.51 w, 5.97 s, 6.24 m, 6.76 m, 6.84 m, 6.91 m, 7.20 w, 7.79 w.

Starting with 1.0 g. of the orange isomer (m.p. 119–120°) of the normal phenylhydrazone, the same product was obtained in a yield of 0.4 g. (40%). The identity of the two products was shown by a mixture melting point determination.

2-Substituted 3a-Amino-8b-benzyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indoles (VI).—To a stirred solution of lithium aluminum hydride dissolved in ether (0.04 g./ml.) the solid 2-substituted 3a-amino-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]-indol-3(2*H*)-one (IV) was added in small portions. The lithium aluminum hydride was present in excess; 1 g. was used per gram of compound reduced. The mixture was refluxed for 2 hr. with stirring after the addition was complete. The excess hydride was destroyed by slow addition of a 20% aqueous solution of sodium potassium tartrate with continued stirring. The mixture was allowed to stir for 20 min. and was then filtered. The ether layer was separated and evaporated to dryness. The residual oily product was crystallized from *n*-hexane. Results with individual compounds are described.

3a-Amino-8b-benzyl-2-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (VIm).—The yield was 0.35 g. (61%) of white needles, m.p. 144–145°, from 0.6 g. of compound IVm. Three recrystallizations from cyclohexane failed to raise the melting point.

Anal. Calcd. for $C_{18}H_{21}N_3$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.29; H, 7.98; N, 14.55.

Infrared spectrum: 2.95 w, 3.42 m, 3.53 w, 3.62 m, 6.22 m, 6.73 s, 6.83 s, 7.18 m, 7.58 w, 7.98 m.

3a-Amino-8b-benzyl-2-isopropyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (VIi).—The yield was 0.45 g. (47%) of white needles, m.p. 118–119°, from 1.0 g. of compound IVi. Three more recrystallizations from *n*-hexane failed to raise the melting point.

Anal. Calcd. for $C_{20}H_{25}N_3$: C, 78.13; H, 8.20; N, 13.67. Found: C, 77.77; H, 8.46; N, 13.61.

Infrared spectrum: 2.91 w, 3.34 s, 3.56 m, 6.18 m, 6.70 s, 6.80 s, 7.10 m, 7.17 m, 7.32 m, 8.00 m.

3a-Amino-8b-benzyl-2-cyclohexyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (VIc).—The yield was 6.0 g. (62%) of colorless prisms from 10 g. of compound IVc. Three recrystallizations from *n*-hexane yielded a product of m.p. 107–108°. (Another crystalline form, m.p. 115–117°, was also encountered.)

Anal. Calcd. for $C_{23}H_{29}N_3$: C, 79.49; H, 8.41; N, 12.09. Found: C, 79.61; H, 8.44; N, 12.13.

Infrared spectrum: 2.96 w, 3.43 m, 3.51 m, 3.60 w, 6.24 m, 6.74 m, 6.84 m, 6.90 m, 7.18 w, 7.36–7.48 w.

2-Substituted 3a-Hydroxy-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-ones (V).—A mixture of the 2-substituted 3a-amino-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]-indol-3(2*H*)-one (IV) and 60% aqueous acetic acid (*ca.* 6 ml./g. of compound) was heated on a steam cone. Compounds Vc and Vm precipitated during a heating period of 30 to 90 min. The mixture was then cooled (to room temperature for Vc and Vm, to 0° for Vi) and the product was collected by filtration, washed with water, and air-dried. Yields quoted are of the initial crystalline product unless otherwise indicated.

2-Methyl-3a-hydroxy-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (Vm).—The yield was 1.2 g. (48%) of orange plates from 2.5 g. of compound IVc. After three recrystallizations from benzene–*n*-hexane or aqueous acetic acid, white plates were obtained, m.p. 205–207°.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 72.91; H, 6.17; N, 9.39.

Infrared spectrum: 3.00 w, 3.35 w, 3.43 w, 3.50 w, 5.91 s, 6.20 w, 6.69 w, 6.74 m. 6.82 m, 6.88 w, 7.12 w, 7.68 w.

A second form of the compound, m.p. 215–217°, was obtained by crystallization from 95% ethanol.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.36; H, 6.28; N, 9.29.

The 217° form melted at 207° when crystallized from benzene–*n*-hexane. The infrared spectra of the two forms were identical in chloroform, although the potassium bromide pellet spectrum of the 207° form showed a closely spaced splitting of the carbonyl band (5.83, 5.88, 5.94 μ) not found in the 217° form.

2-Isopropyl-3a-hydroxy-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (Vi).—The yield after two recrystallizations from absolute ethanol, was 0.8 g. (53%) of white needles, m.p. 197°, from 1.5 g. of compound IV heated for 2.5 hr.

Anal. Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 8.69; H, 6.88. Found: C, 74.71; H, 8.55; N, 7.01.

2-Cyclohexyl-3a-hydroxy-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (Vc).—The yield was 3.5 g. (70%) of pale yellow prisms, m.p. 163–166°, from 5.0 g. of compound IV. After three recrystallizations from aqueous acetic acid, colorless plates were obtained, m.p. 164–165°.

Anal. Calcd. for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 75.69; H, 7.32; N, 7.79.

Infrared spectrum: 2.80 w, 3.00 m, 3.34 m, 3.41 s, 3.49 m, 5.96 s, 6.19 m, 6.78 s, 6.81 s, 6.87 s, 7.30 w, 7.70 m, 7.95 m.

When IVc was refluxed with ethanolic sodium ethoxide, ammonia was evolved. The reaction mixture yielded Vc (29% yield) as the only crystalline product.

2-Substituted 8b-Benzyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indoles (IX) and 2-Substituted 8b-Benzyl-3a-hydroxy-1,2,3,-3a,4,8b-hexahydropyrrolo[3,4-*b*]indoles (VIII).—To a solution of lithium aluminum hydride (1 g./g. of compound to be reduced) in anhydrous ether (*ca.* 100 ml./g. of hydride) the 2-substituted 3a-hydroxy-8b-benzyl-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3-(2*H*)-one (V) to be reduced was added in solid form. The mixture was stirred and refluxed for 1–8 hr. then the excess hydride was destroyed by cautious addition of a 20% aqueous sodium potassium tartrate solution. The mixture was stirred for an additional 30 min., and the ether solution filtered and evaporated to dryness under reduced pressure. Results in the preparation of individual compounds are given.

8b-Benzyl-2-cyclohexyl-3a-hydroxy-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (VIIIc).—The reduction of 4 g. of compound Vc using a 1-hr. reaction period yielded an oil which was dissolved in hot *n*-hexane. When the solution was cooled to *ca.* 30° and allowed to stand, white needles, m.p. 126–130°, were deposited first. Recrystallization from cyclohexane afforded 0.95

g. (32%) of fluffy white needles, m.p. 129°. (Yields in different runs varied from 20 to 32%, and IXc once separated before VIIIc.) An analytical sample, m.p. 129–130°, was prepared by successive crystallizations from *n*-hexane and cyclohexane.

Anal. Calcd. for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.29; H, 7.75; N, 7.13, 8.16.

Infrared spectrum: 2.80 w, 2.95 w, 3.43 s, 3.51 m, 3.60 m, 6.21 m, 6.72 m, 6.82 m, 6.89 m, 7.15 m, 7.27 m, 7.46 m, 7.60 w.

8b-Benzyl-2-cyclohexyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (IXc). A. From Vc Directly.—The *n*-hexane solution from which the crystals of compound VIIIc had been deposited initially in the procedure described previously was concentrated by evaporation. A 1.15-g. quantity (40%) of compound IXc was deposited as colorless prisms, m.p. 96–99°. Yields of this product varied from 37 to 49% in different runs. Repeated recrystallization from *n*-hexane raised the m.p. to 98–100°.

Anal. Calcd. for $C_{23}H_{28}N_2$: C, 83.08; H, 8.49; N, 8.43. Found: C, 83.04; H, 8.23; N, 8.51.

Infrared spectrum: 2.95 w, 3.42 s, 3.51 m, 3.60 w, 6.22 m, 6.70 w, 6.76 m, 6.83 m, 6.90 m, 7.29 w, 7.57–7.68 w, 8.02 w.

B. From VIIIc.—Reduction of 0.65 g. of compound VIIIc by the same procedure used with Vc yielded, as the first crop of crystals from *n*-hexane, 0.15 g. (23%) of recovered starting material, and, as the second crop, 0.35 g. (56%) of compound IXc, m.p. 93–98°. Recrystallization from *n*-hexane gave colorless prisms, m.p. 98–110°. In another run 32% of VIIIc was recovered and 41% of IXc was obtained.

8b-Benzyl-3a-hydroxy-2-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (VIIIm).—An 8-hr. reaction period was used for the reduction of 5.5 g. of Vm. The crude product was dissolved in a boiling benzene–*n*-hexane mixture and the solution allowed to cool slowly to room temperature. Crystals of compound VIIIm separated over a period of several hours. After removal of the mother liquor by decantation the product (1.1 g., 22%, m.p. 128–129°) was recrystallized three times from benzene–*n*-hexane mixtures to give colorless prisms, m.p. 129–130°.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.14; H, 7.17; N, 10.00. Found: C, 76.55, 77.15; H, 7.05, 7.18; N, 10.35.

Infrared spectrum: 2.79 w, 2.92 w, 3.38 m, 3.48 m, 3.56 m, 6.18 m, 6.70 m, 6.80 m, 7.12 m, 7.42 w, 7.55 m, 7.96 m.

8b-Benzyl-2-methyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (IXm).—The mother liquor from which the crystals of compound VIIIm had separated, as described previously, was cooled for 36 hr. in a refrigerator. A second product (IXm) (2.3 g., 48%, m.p. 84–85°) separated and was recrystallized twice from benzene–*n*-hexane mixtures to yield long, colorless needles, m.p. 84.5–85.5°.

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.55; H, 7.58; N, 10.78.

Infrared spectrum: 2.90 w, 3.38 m, 3.49 m, 3.58 m, 6.21 m, 6.71 s, 6.81 s, 7.14 w, 7.38 w, 7.59 w, 7.97 m.

4-Acetyl-8b-benzyl-2-cyclohexyl-3a-hydroxy-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (VIIc). A.—To 5 g. of compound Vc was added 10 ml. of freshly distilled acetyl chloride, and the mixture was warmed on a steam cone until all of the excess acetyl chloride had evaporated. The flask was then cooled to room temperature and 25 ml. of cold water was added. The gummy product was stirred until it had completely solidified. The water layer was then decanted and the solid recrystallized from aqueous ethanol to give 3.2 g. (57%) of white needles, m.p. 195–198°. Two recrystallizations from a benzene–*n*-hexane mixture raised the m.p. to 199–200°.

Anal. Calcd. for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 74.67; H, 7.01; N, 6.90.

Infrared spectrum: 3.04–3.13 w, 3.42 m, 3.51 m, 5.92 s, 6.13 s, 6.27 m, 6.76 s, 6.84 m, 7.10 m, 7.30 s, 7.43 s, 7.56 m, 7.74 m.

B.—To a solution of 35 ml. of glacial acetic acid and 8 ml. of acetic anhydride saturated with dry hydrogen chloride was rapidly added 3.5 g. of 1-cyclohexyl-4-benzyl-2,3-dioxopyrrolidine phenylhydrazone. The mixture was swirled until the solution was complete, allowed to stand for 90 min. at room temperature, and then made strongly basic by addition of 20% aqueous sodium hydroxide with cooling. The product was extracted into benzene, and the benzene solution was dried over magnesium sulfate, then chromatographed on alumina. The product was eluted with acetone after the column had been washed with benzene, and was crystallized from an acetic acid–water mixture. Two grams (50%) of white needles was obtained, m.p. 197–198°. A mixture melting point with the product obtained by procedure A was not depressed.

8b-Benzyl-2-cyclohexyl-4-ethyl-3a-hydroxy-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-*b*]indole (XIc).—To a solution of 2 g. of lithium aluminum hydride in 50 ml. of anhydrous ether, 1.9 g. of compound VIIc was added in small portions. The mixture was stirred and refluxed for 1 hr., then 20% aqueous sodium potassium tartrate solution was added dropwise until the excess hydride was destroyed. The mixture was then stirred for 30 min. and filtered. The ether solution was evaporated to dryness under reduced pressure and the residual oil was crystallized from *n*-hexane. There resulted 0.7 g. (40%) of colorless prisms which, after two more recrystallizations from *n*-hexane, melted at 91.5–93°.

Anal. Calcd. for $C_{25}H_{32}N_2O$: C, 79.74; H, 8.57; N, 7.44. Found: C, 79.67; H, 8.63; N, 7.91.

Infrared spectrum: 2.80 m, 3.44 s, 3.51 s, 3.60 m, 6.23 s, 6.73 s, 6.84 s (sh), 6.90 s, 7.29 s, 7.42 s, 7.74 s.

4-Acetyl-8b-benzyl-2-cyclohexyl-1,3a,4,8b-tetrahydropyrrolo-[3,4-*b*]indol-3(2*H*)-one (Xc).—A solution of 1.0 g. of compound IVc in 50 ml. of 80% aqueous acetic acid was refluxed with 2 g. of zinc dust for 24 hr.[13] The solution was filtered to remove unchanged zinc, and diluted to 250 ml. with water. After standing 3 hr. the mixture was filtered to give 0.2 g. (19%) of product. Following three recrystallizations from cyclohexane or a benzene–*n*-pentane mixture white needles were obtained, m.p. 188–189°.

Anal. Calcd. for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.27; N, 7.21; N-acetyl, 9.79. Found: C, 77.07; H, 7.24; N, 7.35; N-Acetyl, 9.04.

Infrared spectrum: 3.43 m, 3.51 w, 5.94 s, 6.26 w, 6.77 m, 6.85 m, 6.89 m, 6.98 m, 7.18 s, 7.41 w, 7.72 m, 7.82 w.

8b-Benzyl-2-cyclohexyl-3a-N-phenylthioureido-1,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-3(2*H*)-one (XIIc).—To 3 g. of compound IVc was added 4.5 ml. of phenyl isothiocyanate, and the mixture was heated on a steam cone for *ca.* 7 min. The resulting oil became viscous when cooled and then crystallized. The crystals were collected on a filter and washed successively with *n*-pentane and 50% aqueous ethanol. Recrystallization from 70% aqueous ethanol yielded 3.5 g. (86%) of white crystals, m.p. 173–174°. Further recrystallizations from 70% aqueous ethanol raised the m.p. to 181–182°.

Anal. Calcd. for $C_{30}H_{32}N_4OS$: C, 72.55; H, 6.50; N, 11.28. Found: C, 72.25; H, 6.36; N, 11.25.

Infrared spectrum: 3.02 w, 3.35 w, 3.42 m, 3.51 w, 5.98 s, 6.15 m, 6.61–6.68 s, 6.73 s, 6.82 s, 6.89 m, 7.10 w, 7.19 w, 7.42 m, 7.68 m, 7.95 m.

Compound Vc was recovered unchanged when treated with phenyl isothiocyanate by the same procedure used with IVc.

Acetic Acid Hydrolysis of the Phenylthiourea Derivative XIIc.—Compound XIIc (1.5 g.) was heated on a steam cone for 1 hr. in 300 ml. of 75% (by volume) aqueous acetic acid. The solution was allowed to cool to room temperature slowly and then was evaporated under reduced pressure to remove the solvents. The last traces of acetic acid were removed from the residue by adding and evaporating three 100-ml. portions of benzene. During the third evaporation a white solid, m.p. 148–150°, precipitated. Recrystallization from hot water produced fine white needles, m.p. 152–153°. The infrared spectrum (Nujol mull) was identical with that of authentic phenylthiourea, and there was no mixture melting point depression.

The mother liquor from which the phenylthiourea had separated was concentrated to yield a brown oil. A white crystalline compound, m.p. 140–145°, precipitated when the oil was dissolved in *n*-heptane with a few drops of absolute ethanol added. Recrystallization from the same solvent mixture afforded white needles, m.p. 165–167°, which were shown to be compound Vc.

Reaction of Compound IVc with Nitrous Acid.—A solution containing 1 g. of compound IVc and 1.5 ml. of concentrated hydrochloric acid in 8 ml. of 95% ethanol was cooled to 5° and treated with 10 ml. of a cold 10% aqueous sodium nitrate solution. The mixture was allowed to stand in an ice bath for 5 min. and was then extracted with ether. The ether extract was washed with ice–water, dried over magnesium sulfate, and evaporated under reduced pressure without heating. The residue was recrystallized three times from a benzene–*n*-hexane mixture to yield 0.35 g. (32%) of a product which melted at 155–156° with extensive decomposition, corresponded in composition approximately to a mononitroso derivative of IVc, and gave a Liebermann's test.

Anal. Calcd. for $C_{23}H_{26}N_4O_2$: C, 70.74; H, 6.71; N, 14.35. Found: C, 71.34; H, 6.91; N, 14.32.

Infrared spectrum: 295–3.02 w, 3.43 m, 3.51 m, 5.90 s, 6.18 m, 6.23 m (sh), 6.70 w (sh), 6.80 (sh), 6.90–7.00 s, 7.50–7.57 s, 7.74 m, 7.84 s, 7.98 s.