with ethyl acetate. Ethyl acetate crystallization of the eluate residues gave crystalline material from the first four eluates. After these, only brown, noncrystalline materials were obtained. Fraction 1 (140 mg, 0.6%, mp 248–253°) corresponded by nmr to compound III. Fraction 2 (4.15 g, 17.3%, mp 228–232°) was shown by nmr to be a mixture of III and VIII (Ruschig's XIV). Fraction 3 (1.64 g, 6.8%, mp 252–255°) and fraction 4 (1.19 g, 5.0%), mp 253–255°) corresponded by infrared and nmr with Ruschig's XIV.

3β-Acetoxy-17α-hydroxy-17β-methyl-D-homopregn-5-en-17α-one-16α-carbonitrile (VIII).—A sample of Fraction 3 (from B, 200 mg) was acetylated in pyridine at room temperature with acetic anhydride. The product was crystallized from methanol–water to yield 160 mg of the 3-acetate of VIII: mp 202–205°; ν_{CHCl_3} 3480, 2245, 1730, 1708, 1255 cm^{-1}; $[\alpha]^{25}D$ −82.3° (1.05% in chloroform).

Anal. Calcd for $C_{24}H_{33}NO_4$ (399.5): C, 72.15; H, 8.33; N, 3.50. Found: C, 72.19; H, 8.29; N, 3.76.

Reaction of VIII with Base.—A sample (100 mg) of fraction 3 (above) was heated on the steam bath in a solution of 500 mg of KOH in 30 ml of methanol. After 10 min, the solution was cooled under an air stream and diluted with water. The product was separated, washed with water and dried in air to yield 90 mg: mp 259–261°; λ_{max}^{MeOH} 247 mμ (ε 10,500); ν_{KBr} 3450, 2215, 1680 cm^{-1}. The identity of the product with compound V was also shown by nmr.

Registry No.—VIa, 7745-50-8; VIb, 7745-51-9; VII, 7745-52-0; III, 2472-37-9; IIIa, 2324-73-4; IV, 7745-55-3; acetate of IV, 7782-06-1; 3-acetate of VIII, 7745-56-4; V, 2472-38-0; VIII, 7745-58-6; I, 1062-03-9; II, 2324-71-2; Va, 2324-74-5.

Acknowledgment.—The authors wish to thank Mr. C. E. Childs and staff for the combustion analyses and Dr. J. M. Vandenbelt and staff for the nmr, infrared, and ultraviolet measurements.

The Conversion of Tetrahydro-β-carbolines into 2-Acylindoles[1]

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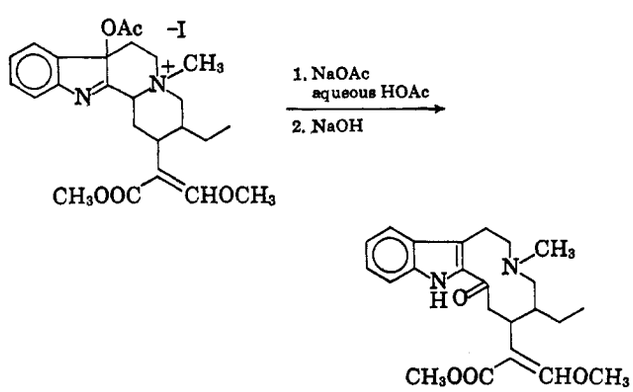
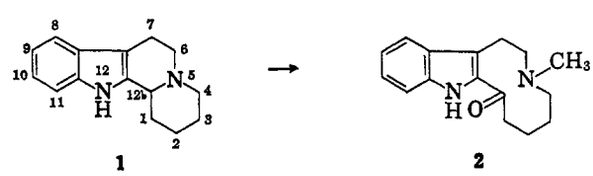
The 2-acylindole, 5-methyl-12b-keto-5,12b-*seco*-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**2**), has been synthesized. The mechanism of the previously reported C–D ring cleavage of dihydrocorynantheine is discussed. The 2-acylindole (**2**) has also been prepared by periodic acid oxidation of the tricyclic amine, 5-methyl-5,12b-*seco*-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**10**). The reaction of tricyclic ketone **2** with nucleophiles has been examined as a model for the suggested biogenesis of echitamine.

A previous report[4] from these laboratories has illustrated a new method for the C–D ring cleavage of dihydrocorynantheine derivatives.



It is the purpose of the present study to examine this process in more detail and explore new methods for effecting this transformation. We have also examined the reaction of the resulting 2-acylindoles with nucleophiles as a model for the synthesis of echitamine. To this end we have studied the conversion of the tetracyclic base, 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-quinolizine (**1**), into the tricyclic ketone (**2**), 5-methyl-12b-keto-5,12b-*seco*-1,2,3,4,6,7,12,12b-octahydroindole-[2,3-*a*]quinolizine, by two independent routes.

The required tetracyclic base was prepared from N-(indole-3-acetyl)piperidine[5,6] by a modification of Wenkert's procedure[6] employing mercuric acetate oxidation and cyclization of N-[2-(3-indolyl)-ethyl]piperidine (see the Experimental Section).



1 **2**

Treatment of the tetracyclic amine (**1**) with *t*-butyl hypochlorite gave the expected mixture of epimeric β-chloroindolenines[7] (**3**) which were alkylated with methyl iodide to form a mixture of β-chloroindolenine methiodides (**4**). Treatment of the methiodide mixture with sodium acetate in aqueous ethanol followed by basification with sodium hydroxide gave desired tricyclic ketone **2** in yields of 10–20% from tetracyclic amine (see Scheme I).

The structure of **2** was readily confirmed by spectral data. The ultraviolet spectrum in ether solution shows normal 2-acylindole[4] absorption [$\lambda_{max}^{Et_2O}$ 308 (ε 14,900)] which is changed to an indole spectrum by the addition of acetic acid. The ultraviolet spectrum in ethanol shows combination of indole and 2-acylindole chromophores. In aqueous ethanol the ultraviolet spectrum shows only indole absorption. This pronounced solvent effect is attributed to the ring-closed dipolar species (**5**) which is favored by polar media. A similar

(1) This work was supported by the National Institutes of Health (Grant HE 09521) and a Public Health Service career program award 1-K3-NB-28,105 from the National Institute of Neurological Diseases and Blindness.

(2) Alfred P. Sloan Research Fellow, 1965–1967.

(3) National Institutes of Health Predoctoral Fellow, 1965–1967.

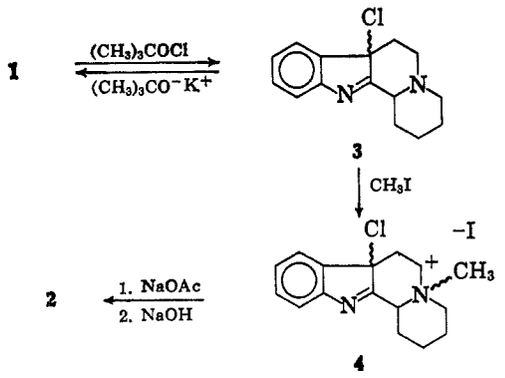
(4) L. J. Dolby and S. Sakai, *J. Am. Chem. Soc.*, **86**, 5362 (1964).

(5) R. C. Elderfield, B. F. Fischer, and J. Lagowski, *J. Org. Chem.*, **22**, 1376 (1957).

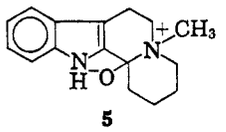
(6) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **84**, 4914 (1962).

(7) Interestingly, treatment of the chloroindolenine epimeric mixture with potassium *t*-butoxide results in the formation of tetracyclic amine **1**, presumably arising from nucleophilic attack on chlorine.

SCHEME I



phenomenon has been noted by others[8] with N-methyl-5-azacyclooctanone and other compounds where lone pair electrons are in a position to give direct charge



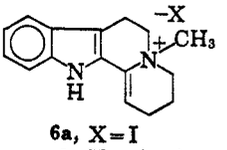
5

transfer interactions with an acceptor carbonyl group. The infrared spectrum shows strong absorption at 6.11 μ in accord with the tricyclic ketone structure. The N-methyl group in the nmr spectrum appears at 1.77 ppm, consistent with the signals exhibited for the N-methyl group in previously reported 2-acylindole compounds.[4] The mass spectrum is in agreement with the calculated molecular weight of 256 and is in good accord with the mass spectrum of dihydroburnamicine previously reported.[4]

The ring-cleavage reaction of the chloroindolenine methiodide mixture with acetate ion was followed by measuring the change in the ultraviolet spectrum. It was found that no change occurred when **4** was heated at 62° for 20 min in a 70% aqueous ethanol solution. However, when sodium acetate was added, an immediate increase in absorbance at 300–305 mμ was observed. The absorbance continued to increase for about 3 hr after which no change was observed. The addition of sodium hydroxide produced an immediate and complete bathochromic shift of 7 mμ with a slight absorbance increase. Work-up of the reaction mixture gave tricyclic ketone **1**. This preliminary result seems to indicate an acetate-catalyzed formation of a discrete intermediate which then undergoes rapid ring opening by hydroxide to give as the final product tricyclic ketone (**2**), but the only conclusive evidence would be the actual isolation and characterization of the suspected intermediate and its behavior with hydroxide ion.

Treatment of the chloroindolenine methiodide mixture (**4**) with sodium acetate followed by fractional crystallization of the reaction mixture gave an iodide salt, mp 189–190°, which had ultraviolet absorption at λ_{max}^{EtOH} 304 mμ (ϵ 20,000) and which analyzed correctly for the $\Delta^{12b(1)}$-tetracyclic methiodide (**6a**). The $\Delta^{12b(1)}$-tetracyclic methopicrate (**6b**) was isolated and characterized from a similar reaction by converting the entire reaction mixture into the picrate form (Dowex 2-X4 sodium picrate ion-exchange resin).

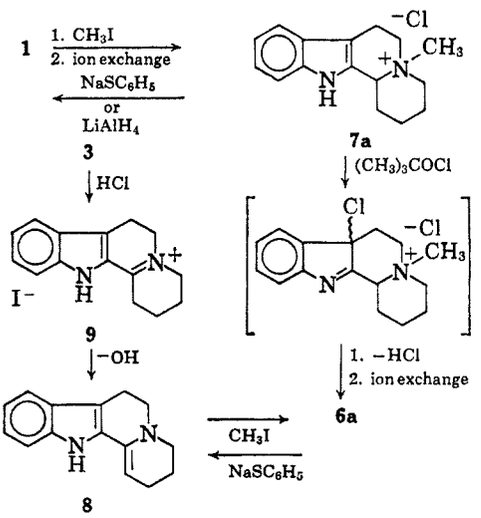
The structure of the $\Delta^{12b(1)}$-tetracyclic methiodide (**6a**) has been completely confirmed by two independent



6a, X = I
b, X = picrate

syntheses and a degradation reaction. Interestingly enough, treatment of the tetracyclic amine methochloride (**7**) with 1 equiv of *t*-butyl hypochlorite followed by conversion into the iodide form gave a salt[9] which was completely identical in every respect with the $\Delta^{12b(1)}$-tetracyclic methiodide (**6a**) obtained from the ring-cleavage reaction mixture. The $\Delta^{12b(1)}$-tetracyclic methiodide (**6a**) could also be synthesized *via* the relatively unstable $\Delta^{12b(1)}$-tetracyclic amine[10] (**8**) which was readily prepared by treating the $\Delta^{12b(5)}$-tetracyclic immonium salt (**9**) derived from the chloroindolenine (**3**) with base. Methylation of the $\Delta^{12b(1)}$-tetracyclic amine (**8**) gave a mixture of methiodides which could be separated by fractional crystallization to give the $\Delta^{12b(1)}$-tetracyclic methiodide (**6a**). The $\Delta^{12b(1)}$-tetracyclic methiodide could be demethylated with sodium thiophenoxide using the procedure of Shamma, Deno, and Kemar[11] to afford the $\Delta^{12b(1)}$-tetracyclic amine (**8**), which was identical with the material obtained by base treatment of the $\Delta^{12b(5)}$-tetracyclic immonium salt (**9**). These reactions are summarized in Scheme II. The structure of the compound isolated

SCHEME II



from the reaction of acetate ion and the chloroindolenine methiodide epimeric mixture is thus firmly established as **6a**. It should be mentioned that the yield of this salt could not be ascertained directly because of material losses during the tedious fractional crystalliza-

(8) N. J. Leonard, R. C. Fox, and M. Oki, *J. Am. Chem. Soc.*, **76**, 5708 (1954). For a good review, see S. F. Mason in "Physical Methods in Heterocyclic Chemistry," Vol. II, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, p 14.

(9) It appears that this chlorination reaction gives the chloroindolenine methochloride which eliminates hydrogen chloride giving the $\Delta^{12b(1)}$-tetracyclic methiodide (**6a**) after ion exchange.

(10) R. N. Schut and T. J. Leipzig, *J. Heterocyclic Chem.*, **3**, 101 (1966). There has also been published a synthesis of the 3-dehydro base derived from yohimbane: H. Zinnes, R. A. Comes, and J. Shavel, Jr., *J. Org. Chem.*, **30**, 105 (1965).

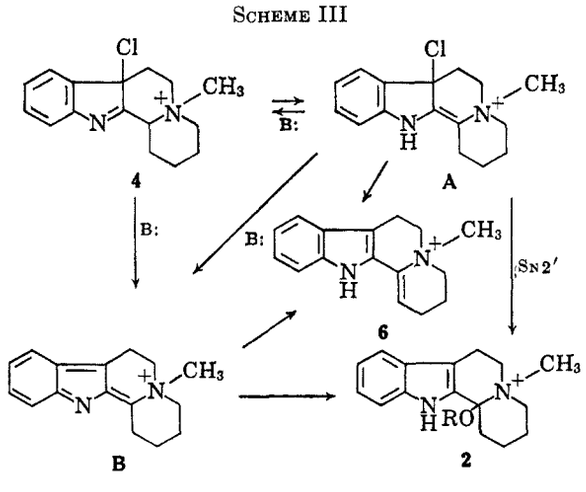
(11) M. Shamma, N. C. Deno, and J. F. Kemar, *Tetrahedron Letters*, 1375 (1966).

tion procedure. However, since the ultraviolet spectrum of the pure $\Delta^{12b(1)}$-tetracyclic salt (**6a**) was available, the amount present in the reaction mixture can be estimated from the absorbance in the ultraviolet spectrum at 303 mμ. This yield determined in this manner was approximately 50%.

It seemed possible that the $\Delta^{12b(1)}$-tetracyclic methiodide (**6a**) which is formed in the reaction of acetate with the chloroindolenine methiodide (**4**) could be an intermediate in the formation of the tricyclic ketone (**2**). The behavior of the suspected intermediate with sodium hydroxide in aqueous ethanol was now investigated. In several experiments under different conditions no tricyclic ketone **2** could be detected when the $\Delta^{12b(1)}$-tetracyclic methiodide (**6a**) was treated with sodium hydroxide. In each case a parallel experiment was performed with the chloroindolenine methiodide (**4**) which underwent expected ring cleavage to give tricyclic ketone **2** in yields up to 50%. The only other isolable compound produced in these reactions was the $\Delta^{12b(1)}$-tetracyclic salt (**6a**) which was isolated in one experiment and shown to be identical with authentic material. The yields of the $\Delta^{12b(1)}$-tetracyclic methiodide from base cleavage of the chloroindolenine methiodide were determined by measuring the ultraviolet spectrum after the tricyclic ketone had been removed by extraction. The yield of $\Delta^{12b(1)}$-tetracyclic methiodide was usually slightly higher than the yield of tricyclic ketone.

Two facts emerge from these studies: the conversion of the chloroindolenine methiodide to the tricyclic ketone is base induced and the $\Delta^{12b(1)}$-tetracyclic salt (**6a**) is not an intermediate. A reasonable mechanistic proposal is outlined in Scheme III.

SCHEME III



This proposal thus fits into the general mechanistic scheme put forward by Taylor.[12] The 2-alkylidene-2H-indole intermediate (B) is not required by any of the available data, but it is an attractive intermediate when compared to the alternative pathways. The alternative SN2′ reaction of the 2-alkylideneindoline (A) species must involve nucleophilic attack at a tertiary carbon and the allylic rearrangement of the 2-alkylideneindoline intermediate *via* a carbonium ion is unlikely because the carbonium ion would be a doubly charged species with adjacent positive charges in one of the possible resonance structures.

It was felt that it would be interesting and worthwhile to separate the chloroindolenines (**3**) into *cis* and *trans* components (*cis* and *trans* refers in this case to the spatial arrangement of the chlorine atom and the C-12b methine proton), and then examine the ring cleavage reaction of each of the derived chloroindolenine methiodides. It seemed possible that the different chloroindolenine methiodide epimers might give different yields of tricyclic ketone.

Thin layer chromatography revealed the chloroindolenine mixture (**3**) as two spots of about equal intensity. It was observed by ultraviolet spectroscopy that the slower moving compound rearranged more rapidly to the $\Delta^{12b(5)}$-tetracyclic immonium salt (**9**) than its epimer with acid. This observation was confirmed by treating a mixture (~50:50) of chloroindolenines with less than 1 equiv of aqueous acid for a brief period and then examining the reaction mixture by tlc. As expected the slower moving compound had greatly decreased in intensity while the faster moving spot had changed only slightly. In contrast, treatment of both epimers with methanolic potassium hydroxide yielded the corresponding imido ethers which could be converted to the oxindoles with aqueous acid.[13]

The two epimeric chloroindolenines were separated by column chromatography over pretreated silica gel. The yield of pure epimeric chloroindolenines obtained in this way was 86% from tetracyclic amine. Both are crystalline compounds which slowly decompose at room temperature but which could be satisfactorily stored under nitrogen at 0° for extended periods, with slight decomposition.

On the basis of spectral evidence the faster moving epimer was assigned the *trans* structure (**3a**) with *trans*-fused conformer **i** probably predominating and the slower moving epimer was assigned the *cis* structure (**3b**) probably also in conformer **i**. Both epimers show, in addition to intense absorption at 6.28 μ (C=N), strong Bohlmann bands[14] at 3.49, 3.54, and 3.62 μ which correspond to those at 3.50, 3.56, and 3.62 μ for the tetracyclic amine (**1**) which is well known to exist predominantly in the *trans*-decalin conformation (**i**). The nmr spectrum of the faster moving epimer showed no methylene or methine absorption below 3.4 ppm, again in agreement with the predominance of the *trans*-decalin conformation (**i**) since it is known[15] that an equatorial C-12b methine proton should appear at much lower fields (4.5 ppm) in the nmr spectrum. The nmr spectrum of the slower moving material is dramatically different. The C-12b methine proton appears at 3.87 ppm as a distinct quartet (J_{trans} = 12.5 cps; J_{cis} = 3 cps). This deshielding is ascribed to the close proximity of the chlorine atom and the C-12b proton in the *cis* epimer (**3b**). The chlorine atom has a 1,3-diaxial relationship (conformation **3bi**) with the C-12b proton, and such deshielding is anticipated from the inductive effect of the chlorine atom and the diamagnetic anisotropy of the carbon–

(12) W. I. Taylor, *Proc. Chem. Soc.*, 247 (1962); see also G. Büchi and R. E. Manning, *J. Am. Chem. Soc.*, **88**, 2532 (1966).

(13) N. Finch and W. I. Taylor, *ibid.*, **84**, 3871 (1962).

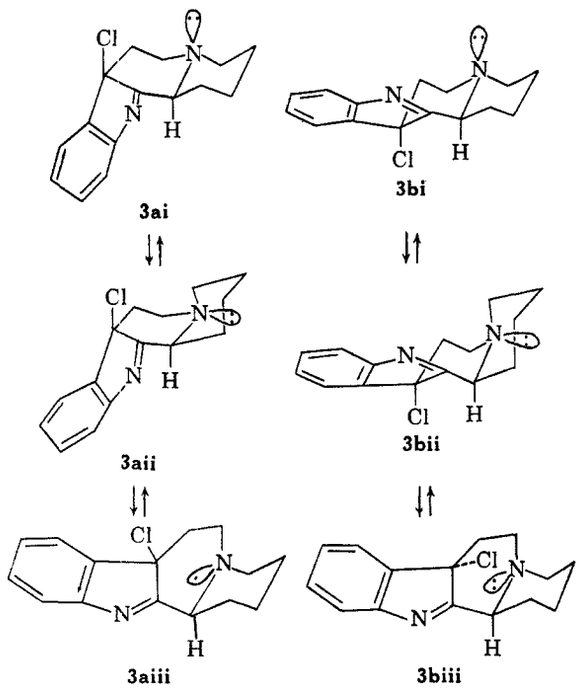
(14) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); E. Wenkert and D. K. Roychaudhuri, *ibid.*, **78**, 6417 (1956); W. E. Rosen, *Tetrahedron Letters*, No. 14, 481 (1961).

(15) E. Wenkert, B. Wickberg, and C. L. Leicht, *J. Am. Chem. Soc.*, **83**, 5037 (1961).

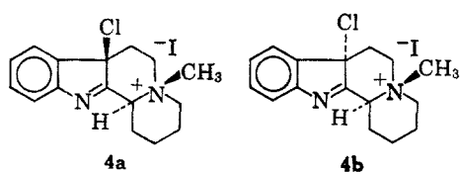
chlorine bond. Accordingly, the faster moving chloroindolenine is assigned the *trans* structure (**3a**).

Both *cis*- and *trans*-chloroindolenines (**3a** and **3b**) gave crystalline methiodides with methyl iodide but the rates of formation were quite different. The *cis*-chloroindolenine gave a quantitative yield of methiodide **4b** after 4 days. On the other hand the *trans*-chloroindolenine gave only a 76% yield of methiodide **4a** after 2 weeks. This difference may be attributable to the 1,4-pseudo-diaxial relationship of the chlorine atom and Nb lone pair in conformer **3ai**; *i.e.*, the chlorine atom interferes with the approach of methyl iodide (see Scheme IV). On the basis of nmr evidence it is

SCHEME IV



assumed that methylation occurs primarily with the most stable conformers (*i.e.*, **3ai** and **3bi**) giving the epimeric methiodides shown (**4a** and **4b**). The signal



exhibited for the N-methyl group appears at 3.38 ppm in both methiodides, in agreement with previous studies[16] which have demonstrated that a *trans*-N-methylquinolizidinium system gives rise to a peak at 3.3–3.4 ppm, whereas a *cis* system shows a peak near 3.5 ppm.

Sodium borohydride reduction of each of the chloroindolenine methiodides gave the same tetracyclic methiodide as was obtained from methylation of the tetracyclic amine. This appears to confirm the fact that both ring junctures are *trans* in the chloroindolenine methiodides. It is possible, however, that epimerization occurs during reduction giving exclusively *trans* methiodide.

Both methiodides appear to be quite sensitive to air and heat especially the *cis* epimer (**4b**) which cannot be recrystallized. Both epimers decompose to a red, glassy gum (291, 355 mμ) on standing in solution or in the solid state in the presence of air. This decomposition is very rapid in refluxing methanol in the presence of air.

Both chloroindolenine methiodides (**4a** and **4b**) give both tricyclic ketone **2** and $\Delta^{12b(1)}$-tetracyclic methiodide **6a** when treated with sodium acetate–sodium hydroxide or sodium hydroxide directly. The yields are somewhat higher with the more stable *trans* isomer (**4a**). These results are summarized in Table I.

TABLE I

Chloroindolenine methiodide	Conditions	% tricyclic ketone[a]	% $\Delta^{12b(1)}$-tetracyclic methiodide
Recrystallized "mixture"[b]	NaOH/aqueous EtOH (4 hr at reflux)	40–50	12[c]
Recrystallized "mixture"[b]	NaOH/aqueous EtOH (4 hr at 62°)	40	50
trans epimer **4a**	NaOH/aqueous EtOH (4 hr at 62°)	40	48
cis epimer **4b**	NaOH/aqueous EtOH (4 hr at 62°)	28	36
trans epimer **4a**	1. NaOAc/aqueous EtOH 2. NaOH (12 hr at 62°)	55	45
cis epimer **4b**	1. NaOAc/aqueous EtOH 2. NaOH (12 hr at 62°)	22	21

[a] Determined by isolation which in most cases gave very clean material. [b] Since the *cis* epimer is so unstable and cannot be recrystallized satisfactorily, this is probably enriched in *trans* epimer **4a**. [c] Pure material obtained by ion exchange and fractional crystallization.

The "recrystallized chloroindolenine methiodide" refers to that obtained from methylation of the chloroindolenine epimeric mixture. Presumably during recrystallization the less stable *cis* epimer (**4b**) decomposes and mainly *trans* epimer **4a** is obtained. Satisfactory analytical data have been obtained for this material.

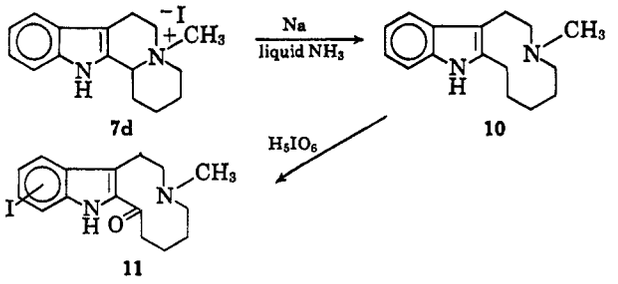
The second method we have examined for the conversion of the tetracyclic base (**1**) to the tricyclic ketone (**2**) involves the recently developed periodic acid oxidation of indoles.[17] This approach involves cleavage of the C–D ring juncture by a Birch reduction.[18] Treatment of tricyclic amine **10** under slightly modified conditions usually gave a mixture of tricyclic ketone **2** and iodotricyclic ketone **11** in yields of 10–20% based on tetracyclic amine **1**. The iodotricyclic ketone could be quantitatively hydrogenolyzed to tricyclic ketone. The oxidation reaction was very erratic and yields of both materials were variant depending on reaction conditions. In one reaction only iodotricyclic ketone was formed (see Scheme V). The two ketones could be readily distinguished by thin layer chromatography (see the Experimental Section) and could be separated by crystallization or column chromatography. It is interesting to note that lithium aluminum hydride reduction of the tetracyclic methiodide (**7b**) effects demethylation and not ring cleavage to tricyclic amine

(16) M. Shamma and J. M. Richey, *J. Am. Chem. Soc.*, **85**, 2507 (1963); see also T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962).

(17) L. J. Dolby and D. L. Booth, *J. Am. Chem. Soc.*, **88**, 1049 (1966).

(18) L. J. Dolby and D. L. Booth, *J. Org. Chem.*, **30**, 1550 (1965).

SCHEME V



10 as was previously observed[18] for the corresponding 2-hydroxytetracyclic methiodide.

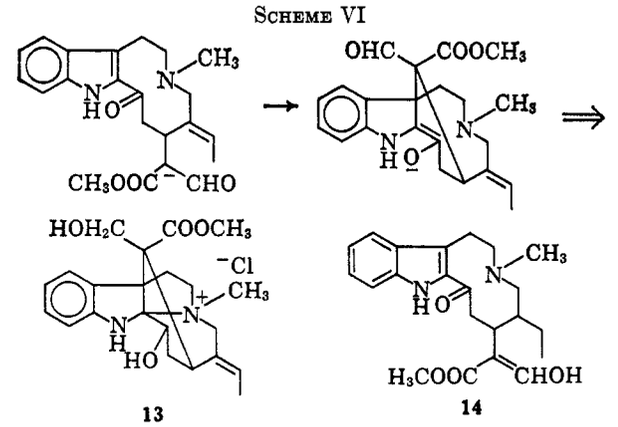
It was felt that possibly the low yields in the periodate oxidation of the tricyclic amine (**10**) could be due to interference in some way by the basic Nb nitrogen. Accordingly, the tricyclic base was converted into the methiodide and oxidized with periodic acid. The crude product could be demethylated with sodium thiophenoxide to afford the tricyclic ketone (**2**), but the over-all yield by this route was not significantly different from that obtained by direct oxidation of the tricyclic amine.

The tricyclic amine (**10**) underwent an interesting but not unexpected reaction with *t*-butyl hypochlorite. The initially formed chlorindolenine underwent tautomerization and rapid ring closure followed by attack of a second mole of *t*-butyl hypochlorite giving rise to a mixture of the chlorindolenine salt (**4**) and the $\Delta^{12b(1)}$-tetracyclic methochloride (**6c**), the latter being formed by loss of hydrogen chloride from the chloroindolenine-methochloride as mentioned earlier.[9]

With substantial quantities of the tricyclic ketone on hand, it became of interest of examine the action of nucleophiles on this 2-acylindole system. Such a reaction is a key step in one biogenetic scheme for echitamine[19] (**13**).

We had previously examined the acid- and base-catalyzed reactions of the 2-acylindole alkaloid (**14**) derived from dihydrocorynantheine and we could find no indication of the desired cyclization reaction.[20] (see Scheme VI). However, this lack of reactivity

SCHEME VI



could be the result of an unfavorable conformer distribution and it seemed desirable to examine a bimolecular reaction. The tricyclic ketone (**2**) was treated with diethyl malonate anion and cyanide ion under several different conditions with no evidence of any reaction. In most cases the tricyclic ketone was quantitatively recovered.

(19) G. F. Smith, *Chem. Ind.* (London), 1120 (1961).

(20) Unpublished results of Dr. R. H. Iwamoto.

Experimental Section

General.—Melting points and boiling points are uncorrected. Anhydrous potassium carbonate was used as the drying agent. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Woelm alumina was used for column chormatography unless otherwise specified and silica gel G (according to Stahl) was used for thin layer chromatography. R_f values and spot colors reported herein refer to a 98% ethyl acetate–2% triethylamine solvent system using a 3% ceric sulfate–10% sulfuric acid solution (heat) to develop the spots. Infrared spectra were measured with a Beckman IR5-A infrared spectrophotometer and ultraviolet spectra were recorded on either a Perkin-Elmer Model 202 spectrophotometer or a Cary Model 11 spectrophotometer. A Varian Associates A-60 instrument was used to record the nmr spectra. Deuteriochloroform and formamide (organic salts) were used as solvents and tetramethylsilane was the internal standard.

N-(Indole-3-acetyl)piperidine.—This was prepared according to the method of Wenkert,[6] although we were able to obtain the amide as a crystalline solid. Methyl 3-indolylacetate (23.0 g) was refluxed with anhydrous piperidine (100 ml) for 24 hr. After concentration, the crude product was dissolved in chloroform, washed with 10% hydrochloric acid and sodium bicarbonate solution, dried, and concentrated to give 20 g (71%) of a yellow solid, mp 101–104°. Crystallization from ether–petroleum ether (bp 30–60°) gave pure amide as colorless needles, mp 105–106°.

Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 73.84; H, 7.62; N, 11.79.

This amide was also prepared according to the method of Elderfield[5] using 3-indolylacetyl chloride but the synthesis *via* methyl 3-indolylacetate was preferred.

N-[2-(3-indolyl)ethyl]piperidine.—This was prepared from N-(indole-3-acetyl)piperidine as previously described.[5]

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (1).—A mixture of 4.0 g of N-[2-(3-indolyl)ethyl]piperidine, 50 g of mercuric acetate, and 200 ml of 5% aqueous acetic acid was stirred under nitrogen at 75–85° for 12 hr. Then about 10 g of granulated zinc was added to the reaction mixture and it was filtered with some difficulty. The filtrate was then treated with 30 g of zinc dust and heated at 65–85° with stirring for 12 hr. After filtration the mixture was made basic with concentrated ammonium hydroxide and extracted with chloroform. Drying and concentration gave 3.1 g of yellow solid. Chromatography on activity III neutral Woelm alumina gave 1.7 g (42%) of off-white solid, eluted with benzene. Crystallization from benzene–petroleum ether gave the tetracyclic base as tiny, colorless crystals: mp 153–154° (lit.[6] mp 152–153°), R_f 0.70 (blue-green on orange).

7a-Chloro-1,2,3,4,6,7,7a,12b-octahydroindolo[2,3-*a*]quinolizine (**3**).[21]—To 14.1 g (0.0624 mole) of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**) in 250 ml of methylene chloride cooled in an ice–salt bath under nitrogen was added over the period of 1 hr, 238 ml of 0.262 *M* *t*-butyl hypochlorite[22] (0.0624 mole) in carbon tetrachloride. After addition was complete the solution was stirred for 30 min with no external cooling. The yellow solution was washed with water, dried, and concentrated at or below 25° to give 18.2 g of a viscous, amber oil which crystallized slowly on standing. Tlc showed two distinct spots in about equal amounts: R_f 0.56 (light brown) and R_f 0.77 (yellow on brown). These are ascribed to the two possible epimeric chloroindolenines.[23] The yield of pure chloroindolenines after chromatography (see separate entry) was 86%.

Potassium *t*-Butoxide Conversion of Chloroindolenine 3 to Tetracyclic Amine 1.—A solution of 0.22 g (0.85 mmole) of chloroindolenine 3 (epimeric mixture) and 1.0 g (9 mmole) of

(21) This compound is named as a substitution product of 7aH-indolo[2,3-*a*]quinolizine; see N. Finch, C. W. Germenden, I. Hsu, and W. I. Taylor, *J. Am. Chem. Soc.*, **85**, 1520 (1963).

(22) H. M. Teeter and E. W. Bell, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 125.

(23) It was found that the presence or absence of triethylamine did not affect the reaction. Usually triethylamine is used in these chlorinations; see N. Finch and W. I. Taylor, *J. Am. Chem. Soc.*, **84**, 3871 (1962), and H. Zinnes and J. Shavel, Jr., *J. Org. Chem.*, **31**, 1765 (1966).

potassium *t*-butoxide in 25 ml of *t*-butyl alcohol was refluxed under nitrogen for 15 min. The dark mixture was poured into 5% aqueous sodium hydroxide and extracted with ether. Washing, drying, and concentration left 0.195 g of a dark amber gum. Filtration through activity III neutral alumina with benzene elution, gave 0.11 g (57%) of crystalline tetracyclic amine **1** identified by infrared and tlc comparison with authentic material.

5-Methyl-7a-chloro-1,2,3,4,6,7,7a,12b-octahydroindolo[2,3-*a*]-quinolizinium Iodide (4).—The crude epimeric mixture (18.2 g) of 7a-chloro-1,2,3,4,6,7,7a,12b-octahydroindolo[2,3-*a*]quinolizines (**3**) and 225 g of methyl iodide in 1000 ml of dry benzene was allowed to stand at 5–10° for 3 days. The resulting precipitate was collected (21.2 g, 85% from tetracyclic amine) in two crops. Several crystallizations from methanol–ether gave after substantial material loss colorless crystals, mp 165–166° dec, or 145–147° dec.

Anal. Calcd for $C_{16}H_{20}ClIN_2$: C, 47.71; H, 4.97; N, 6.96. Found: C, 47.68; H, 5.01; N, 6.79.

5-Methyl-12b-keto-5,12b-*seco*-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (2).—A solution of 10.0 g (0.0248 mole) of the crude 5-methyl-7a-chloro-1,2,3,4,6,7,7a,12b-octahydroindolo[2,3-*a*]quinolizinium iodide (**4**) and 10 g of sodium acetate in 300 ml of 70% aqueous methanol was refluxed under nitrogen for 3.5 hr. The mixture was brought to pH 9 with sodium hydroxide and stirred at 25° under a benzene layer for 14 hr. The benzene layer was separated and the aqueous layer was further extracted with benzene. The combined organic layers were washed with water. Drying and concentration afforded 2.1 g (33%) of yellow solid. Crystallization from ether gave pure tricyclic ketone **2**, mp 138–139°. The infrared showed 2.86 (NH) and 6.11 μ (C=O); ultraviolet showed $\lambda_{max}^{Et_2O}$ 308 mμ (ϵ 14,900); λ_{max}^{EtOH} 285 sh mμ (ϵ 6700), 293 (8100), 312 (11,000). The nmr spectrum showed a sharp signal at 1.77 ppm attributed to the N-methyl group.

Anal. Calcd for $C_{16}H_{20}N_2O$: C 74.97; H, 7.86; N, 10.93. Found: C, 75.20; H, 8.21; N, 10.89.

5-Methyl-2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizinium Iodide (6a) from Chloroindolenine Methiodide 4.—A solution of 7.8 g of crude chloroindolenine methiodide **4** and 10 g of sodium acetate in 250 ml of methanol was refluxed for 5 hr under nitrogen. The excess sodium acetate could be removed by the addition of ether to the hot solution. After many such crystallizations there began to form tiny yellow prisms, mp 185°. Several additional crystallizations from methanol–ether gave pure $\Delta^{12b(1)}$-tetracyclic methiodide **6a**: mp 189–191° dec. The ultraviolet spectrum showed λ_{max}^{EtOH} 303 mμ (ϵ 20,100), 238 mμ (ϵ 14,700).

Anal. Calcd for $C_{16}H_{19}IN_2$: C, 52.47; H, 5.23; I, 34.65; N, 7.65. Found: C, 52.16; H, 5.47; I, 34.54; N, 7.76.

5-Methyl-2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizinium Picrate (6b).—A solution of 0.57 g of chloroindolenine methiodide **4** and 0.8 g of barium acetate in 15 ml of 50% aqueous ethanol was warmed on a steam bath for 2 hr. The resulting solution was passed through a Dowex 2-X4 ion-exchange column (resin volume, 33 ml) in the sodium picrate form prepared by treating the standard chloride form with a 5% sodium picrate solution (33 g of picric acid and 5.25 g of sodium hydroxide) in 50% aqueous ethanol. Fractional crystallization of the resulting mixture of picrate salts from methanol–ether finally yielded a few milligrams of yellow needles, mp 210–211°. The ultraviolet spectrum shows the expected absorption at 306 and 357 mμ.

Anal. Calcd for $C_{22}H_{21}N_5O_7$: C, 56.53; H, 4.53; N, 14.98. Found: C, 56.32; H, 4.23; N, 14.44.

5-Methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizinium Iodide (7b).—A solution of 1.0 g of tetracyclic amine **1**, 10 ml of methyl iodide, and 20 ml of dry benzene was stirred at 25° for 2 hr. The yellow solid which formed (1.6 g 100%) was collected. Two crystallizations from methanol–ether gave colorless crystals, mp 224–226°. The nmr spectrum ($HCONH_2$) showed the N-methyl group as a sharp signal at 3.38 ppm.

Anal. Calcd for $C_{16}H_{21}IN_2$: C, 52.18; H, 5.75; N, 7.61. Found: C, 52.02; H, 5.84; N, 7.27.

5-Methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizinium Chloride (7a).—This was prepared by ion exchange over Dowex 2-X4 in the chloride form (1 g of tetracyclic methiodide 7b, 15-ml resin volume, 5% solution in 80% aqueous ethanol). Crystallization of the crude methochloride from isopropyl alcohol–ether gave white powder, mp 220–224° dec.

5-Methyl-2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizinium Iodide (6a) from Tetracyclic Methochloride 7a.—To 2.8 g (0.0101 mole) of tetracyclic methochloride **7a** in 50 ml of methanol at 0° was added dropwise 100 ml of 0.101 *M* *t*-butyl hypochlorite in methylene chloride over a 1-hr period with stirring. After addition, stirring was continued for 1 hr at 25°. Concentration of the reaction mixture gave crude, foamy material. This crude chloride salt was converted to the iodide form by ion-exchange (Dowex 2-X4). Crystallization of the crude iodide salt from methanol–ether several times gave light orange needles, mp 180°. This material was identical in every respect [infrared (KBr), ultraviolet, nmr, and mixture melting point] to $\Delta^{12(1)}$-tetracyclic methiodide **6a** obtained from the reaction of sodium acetate with chloroindolenine methiodide **4**.

Anal. Calcd for $C_{16}H_{19}IN_2$: C, 52.45; H, 5.23; I, 34.65; N, 7.65. Found: C, 52.18; H, 5.28; I, 34.48; N, 7.71.

12H-1,2,3,4,6,7-Hexahydroindolo[2,3-*a*]quinolizinium Iodide (9).—This 12b-dehydro salt was inadvertently obtained when a sample of chloroindolenine **3** was heated on a steam bath during solvent removal.[24] Exposure to methyl iodide and crystallization from methanol–ether gave pure $\Delta^{12b(5)}$-tetracyclic immonium iodide **9**, as dark red needles, mp 228–229°. It showed the expected ultraviolet absorption at 281, 290, and 350 mμ.

Anal. Calc for $C_{15}H_{17}IN_2$: C, 51.15; H, 4.85; N, 7.95. Found: C, 50.96; H, 4.93; N, 7.80.

2,3,4,6,7,12-Hexahydroindolo[2,3-*a*]quinolizine (8).—A solution of 2.9 g of $\Delta^{12b(5)}$-tetracyclic immonium iodide **9** in 125 ml of 50% aqueous ethanol was made strongly basic with sodium hydroxide solution and extracted with ether. Drying and concentration gave 1.9 g of dark red solid. This material was filtered through activity III neutral alumina to give 1.75 g (70%) of crystalline material eluted with benzene. Repeated crystallization from ether, with material losses, afforded pure 12b-dehydro base **8**, mp 140° dec. Solutions of this enamine were quite sensitive to air and heat and rapidly turned dark purple. Spectral data were consistent with those reported.[10]

Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.10; N, 12.49. Found: C, 80.25; H, 7.21; N, 12.43.

Demethylation of $\Delta^{12b(1)}$-Tetracyclic Methochloride 6c with Sodium Thiophenoxide.—The $\Delta^{12b(1)}$-tetracyclic methiodide **6a** was converted into the chloride form by stirring for 9 hr with a 50-fold excess of freshly prepared silver chloride in methanol.

To a solution of 0.075 g of (0.273 mmole) $\Delta^{12b(1)}$-tetracyclic methochloride **6c** in 10 ml of ethanol was added a solution of 0.1 g (0.76 mmole) of sodium thiophenoxide in 10 ml of ethanol. After stirring for 30 min the sodium chloride which precipitated was removed by filtration. The filtrate was taken to dryness and the resulting residue was refluxed under nitrogen with 50 ml of methyl ethyl ketone for 40 hr. After solvent removal, water and chloroform were added to the residue. The chloroform layer was concentrated and 10% hydrochloric acid was added to the residue. After repeated ether extraction of the acid layer the acid solution was made basic with dilute, aqueous sodium hydroxide and extracted with chloroform. After drying, concentration of the final chloroform extract gave 0.055 g of crude material. Filtration through activity IV basic alumina gave, with benzene elution, 0.033 g (54%) of pure (tlc), crystalline material which was identical with 12b-dehydro amine **8** prepared above.

Methylation of $\Delta^{12b(1)}$-Tetracyclic Amine 8.—A solution of 0.062 g (0.277 mmole) of **8** and 5 ml of methyl iodide in 20 ml of benzene was stirred at 25° for 24 hr under nitrogen. The resulting solid was collected and washed with benzene. Crystallization from methanol–ether gave 0.032 g (32%) of light brown crystals, mp 175–179° dec. This material was identical (infrared and ultraviolet) with the $\Delta^{12b(1)}$-tetracyclic methiodide obtained from the sodium acetate reaction of chloroindolenine methiodide **4**.

Comparison of $\Delta^{12b(1)}$-Tetracyclic Methiodide 6a and Chloroindolenine Methiodide 4 with Sodium Hydroxide.—A solution of 0.032 g (0.08 mmole) of recrystallized chloroindolenine methiodide **4** (probably mostly *trans* isomer) in 10 ml of 50% aqueous ethanol was refluxed under nitrogen with 25 drops of 10% aqueous sodium hydroxide for 4 hr. Benzene extraction of the reaction mixture gave 0.011 g (50%) of yellow-white solid which was shown to be pure tricyclic ketone **2** by tlc.

In an identical experiment 0.03 g (0.082 mmole) of $\Delta^{12b(1)}$-tetracyclic methiodide **6** gave 0.003 g of yellow, glassy material. The ultraviolet spectrum did not show typical tricyclic ketone **2** absorption. Tlc showed several small spots one of which had

(24) For the usual synthesis of 3-dehydro salts with hydrogen chloride, see W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **10**, 1414 (1956).

about the same R_f value as tricyclic ketone **2** but gave a slightly different color test. The ultraviolet spectrum of the aqueous layer showed absorption at 304 mμ indicative of starting material.

Isolation of $\Delta^{12b(1)}$-Tetracyclic Methiodide 6a from Alkali Treatment of Chloroindolenine Methiodide 4.—A solution of 0.307 g (7.62 mmoles) of recrystallized chloroindolenine methiodide **4** was refluxed with 10 ml of 10% aqueous sodium hydroxide in 15 ml of 50% aqueous ethanol for 4 hr under nitrogen. Benzene extraction gave 0.114 g (50%) of crude tricyclic ketone **2**. The aqueous basic layer was neutralized with hydrochloric acid and taken to dryness. The residue was taken up in 80% aqueous ethanol and converted to the chloride form by ion exchange (Dowex 2-X4). The solution of chloride salts was concentrated to dryness and taken up in ethanol. The insoluble sodium chloride was removed by filtration and the filtrate was passed through an ion-exchange resin in the iodide form (Dowex 2-X4). The solution of iodide salts was taken to dryness and the resulting residue was crystallized from methanol–ether to afford 0.033 g (12%) of $\Delta^{12b(1)}$-tetracyclic methiodide **6a**, as prisms, which was identical (infrared) with that obtained previously.

A similar reaction showed the presence of 50% of $\Delta^{12b(1)}$-tetracyclic methiodide **6a** (40% tricyclic ketone **2**) by ultraviolet spectroscopy. The aqueous, basic layer, after removal of tricyclic ketone **2**, was diluted to exactly 100 ml. The ultraviolet spectrum of appropriate aliquots was then examined. Since the extinction coefficient of pure $\Delta^{12b(1)}$-tetracyclic methiodide **6a** is known and the absorbance at 304 mμ can be measured directly, the concentration can be readily determined using Beer's law.

Separation of *cis*- and *trans*-Chloroindolenines 3.—The crude epimeric chloroindolenines **3** (5.2 g) obtained from 5.15 g (0.0228 mole) of tetracyclic amine **1** were chromatographed on 200 g of silica gel G (according to Stahl). The silica gel was first made into a slurry with 250 ml of water and then baked in an oven at 110° for about 12 hr. The solid silica gel was then ground and baked again for about 6 hr. After grinding again, the silica gel was suspended in the eluting solvent, 98% ethyl acetate–2% triethylamine, and poured through a large Büchner funnel (no paper) to remove large particles. The slurry of silica gel was then packed in a long column. Initial elution gave a few milligrams of crude gum. Further elution with ethyl acetate–triethylamine (98:2) gave 1.25 g (fractions 8–10) of a single, pure chloroindolenine epimer (upper spot on tlc) as a yellow oil which became a nearly colorless solid on standing. Further elution gave 2.50 g (fractions 11–21) of both chlorindolenines which by tlc showed varying composition of both epimers. Continued elution with ethyl acetate–triethylamine gave 1.12 g (fractions 22–29) of the pure slower moving chloroindolenine as a yellow oil which crystallized immediately on removal of the solvent. The total yield of pure chloroindolenines was 4.87 g (82%). The intermediate fractions of various enrichments (by tlc) were rechromatographed to afford additional pure material.

Both epimeric chloroindolenines were stored under nitrogen at 0° but the decomposition reactions still slowly occurred. Important spectral data of each chloroindolenine are discussed in the text.

***trans*-Chloroindolenine Methiodide 4a.**—A solution of 1.25 g (4.8 mmoles) of *trans*-chloroindolenine **3a** (faster moving spot) and 10 ml of methyl iodide in 25 ml of dry benzene was stirred at 0–5° for 3 hr. A precipitate forms after about 2 hr. The mixture was allowed to stand for 4 days at 5–10°. The collected precipitate was washed with benzene and dried *in vacuo* at 25° to give 1.25 g (65%) of nearly white powder, mp 124° dec. After a second week there was collected an additional 0.216 g (11%) of *trans*-chloroindolenine methiodide.

***cis*-Chloroindolenine Methiodide 4b.**—A solution of 1.03 g (3.95 mmoles) of *cis*-chloroindolenine **3b** (slower moving spot) was stirred at 0–5° for 3 hr with 10 ml of methyl iodide in 25 ml of dry benzene. A precipitate forms after about 30 min. After standing for 4 days at 5–10° the precipitate was washed with benzene and dried *in vacuo* (no heat) to give 1.58 g (99%) of light tan powder, mp 118–120° dec. Both *cis*- and *trans*-chloroindolenine methiodides were stored at 0° under nitrogen.

Comparison of *trans*- and *cis*-Chloroindolenine Methiodies with Sodium Hydroxide.—A solution of 0.134 g (0.333 mmole) of *trans*-chloroindolenine methiodide **4** and 5 ml of 10% aqueous sodium hydroxide in 15 ml of 50% aqueous ethanol was heated at 62° under nitrogen in a glass-stoppered flask with stirring for 4 hr. The aqueous layer was extracted with benzene and ether. This organic layer gave, after water washing and drying, on concentration 0.034 g (40%) of tricyclic ketone **2**. Examination of the aqueous basic layer by ultraviolet showed the presence of 48% $\Delta^{12b(1)}$-tetracyclic methiodide **6a**.

A solution of 0.133 g (0.330 mmole) of *cis*-chloroindolenine methiodide **4b** was similarly treated with aqueous, ethanolic sodium hydroxide. There was found to be present 0.024 g (28%) of tricyclic ketone **2** and 36.5% of **6a** as determined by methods just described.

Reduction of *cis*- and *trans*-Chloroindolenine Methiodides 4 with Sodium Borohydride.—In separate reactions 0.2 g (0.5 mmole) of each chloroindolenine methiodide **4** in 4 ml of methanol was stirred at 25° with 0.05 g (1.3 mmoles) of sodium borohydride. After a few minutes the mixture was filtered and the filtrate was induced to crystallize by the addition of ether. In each case white, flocculent material (inorganic salts) was decanted. Each chloroindolenine methiodide gave tiny needles or prisms, mp 220°, which were identical (infrared and nmr) with each other and identical with tetracyclic methiodide **7b** obtained from direct methylation of tetracyclic amine **1**.

5-Methyl-5,12b-*seco*-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (10).—To 6.0 g (0.0163 mole) of tetracyclic methiodide **7b** in 20 ml of dry ethanol in a three-necked flask equipped with drying tube, Dry Ice condenser, ammonia inlet tube, and magnetic stirring bar was distilled 250 ml of ammonia, which had been previously distilled to remove traces of iron. To the mixture (maintained at −40° with isopropyl alcohol–Dry Ice) was added 10 g (0.435 g-atom) of sodium and the resulting dark blue solution was stirred for 30 min. The blue color was quenched with ammonium chloride and the addition of ethanol for convenience. The ammonia was allowed to evaporate overnight. The solids were thoroughly extracted with chloroform which was washed with sodium hydroxide and water. Concentration of the dried chloroform solution gave 2.15 g of an amber oil which, after chromatography on activity III neutral alumina with benzene elution, gave 1.7 g (44%) of a light yellow syrup (R_f 0.80) which slowly crystallized on standing. Crystallization from hexane gave pure material, mp 98–99° (lit.[25] mp 95–97°).

Demethylation of Tetracyclic Methiodide 7b with Lithium Aluminum Hydride.—To 2.0 g (5.44 mmoles) of tetracyclic methiodide **7b** in 250 ml of dry N-methylmorpholine at 0° was added 8.0 g (210 mmoles) of lithium aluminum hydride. The mixture was stirred at 25° for 10 hr then refluxed for 10 hr. The excess hydride was cautiously destroyed by the addition of water then sodium hydroxide. The salts were collected and extracted with chloroform. The chloroform layer was washed with water, dried, and concentrated to give 1.2 g of crude oil. Filtration through activity III neutral alumina with benzene elution gave 0.84 g of (68%) of yellow solid. Crystallization from ether–petroleum ether (bp 30–60°) gave pure tetracyclic amine **1**, mp 151–152.5°, which was completely identical (infrared and nmr) with material obtained previously.

Demethylation of Tetracyclic Methochloride 7a with Sodium Thiophenoxide.—To 0.2 g (0.725 mmole) of tetracyclic methochloride in 20 ml of ethanol was added 0.27 g (2.04 mmoles) of sodium thiophenoxide in 20 ml of ethanol. The sodium chloride was removed and the filtrate was taken to dryness. After refluxing the residue under nitrogen with 100 ml of methyl ethyl ketone for 39 hr the usual work-up gave 0.125 g (76%) of crude solid. Comparisons with authentic material (tlc) showed it to be tetracyclic amine **1**.

Tricyclic Ketone 2 from 5-Methyl-5,12b-*seco*-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (10).—To a solution of 0.845 g (3.7 mmoles) of periodic acid in 10 ml of 50% aqueous methanol under nitrogen at 25° was added dropwise, a solution of 0.29 g (1.2 moles) of tricyclic amine **10** with stirring. The mixture was refluxed for 1 hr after which time thiosulfate was added followed by dilute, aqueous sodium hydroxide. Chloroform extraction gave 0.21 g of crude material which was chromatographed on activity III neutral alumina. Benzene elution gave 0.033 g (11%) of recovered tricyclic amine while benzene–chloroform (3:1) elution gave 0.075 g (28% based on unrecovered starting material) of solid which gave the same color reaction on tlc but which had a slightly smaller R_f value than tricyclic ketone **2**. Crystallization from ether and ether–petroleum ether (bp 30–60°) gave iodotricyclic ketone **11**, mp 203–206°.

Anal. Calcd for $C_{16}H_{19}IN_2O$: C, 50.55; H, 4.87; I, 33.17; N, 7.32. Found: C, 49.28; H, 4.89; I, 32.54; N, 7.20.

(25) D. Herbst, R. Rees, G. A. Hughes, and H. Smith. *J. Med. Chem.*, **9**, 864 (1966).

In general, other conditions (24 hr, 25°) gave mixtures of the two ketones which could be separated by column chromatography or fractional crystallization, or more conveniently, directly hydrogenolyzed as described below.

Iodotricyclic ketone 11 (0.03 g) was stirred in 5 ml of ethanol with 2 drops of triethylamine and 10% palladium on carbon (0.03 g) at 25° in the presence of hydrogen (1 atm) for 15 hr. The mixture was filtered and the filtrate was concentrated to dryness. The residue was suspended in dilute sodium hydroxide and extracted with ether. Drying and concentration gave pure tricyclic ketone 2 (0.02 g, ~100%) which showed no trace of iodotricyclic ketone 11 by tlc.

5,5-Dimethyl-5,12b-*seco*-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-*a*]quinolizinium Iodide (12).—A solution of 0.2 g (0.827 mmole) of tricyclic amine 10 and 5 ml of methyl iodide in 20 ml of benzene was stirred at 0° for 1 hr then allowed to stand at 5–10° for 2.5 days. The precipitate was collected (~100%), washed well with benzene, and converted into the chloride form as described below. Iodide 12 had mp 154–157° after several crystallizations from methanol–ether (needles).

Tricyclic Ketone 2 from 5,5-Dimethyl-5,12b-*seco*-1,2,3,4,6,7,-12,12b-octahydroindolo[2,3-*a*]quinolizinium Iodide (12).—Tricyclic methiodide 12 (0.3 g, 0.8 mmole) was converted into the corresponding chloride by stirring it with 2 g of freshly prepared silver chloride in 60 ml of methanol for 25 hr at 25°. Filtration and concentration gave crude yellow oil (0.21 g) which was taken up in 5 ml of methanol and added dropwise to periodic acid (0.35 g, twofold excess) in 2 ml of 50% aqueous methanol. The mixture was stirred for 30 min at 25°. After the addition of aqueous thiosulfate, chloroform extraction gave a mixture of salts which were converted into the chloride form by ion exchange (Dowex 2-X4). The resulting residue was taken up in 25 ml of ethanol and stirred with 0.3 g of sodium thiophenoxide in 25 ml of ethanol for 30 min at 25°. The precipitate (sodium chloride) was removed and the filtrate was taken to dryness. The residue was refluxed for 40 hr under nitrogen with 110 ml of methyl ethyl ketone. Usual work-up (see earlier demethylation procedures) gave 0.17 g of dark amber residue. Chromatography on activity III basic alumina gave on benzene elution 0.04 g (20%) of recovered tricyclic amine 10. Further elution with benzene–chloroform (1:4) gave 0.075 g (30–40% based on unrecovered tricyclic amine 10) of a mixture of tricyclic ketone 2 and iodotricyclic ketone 11 (tlc).

Treatment of Tricyclic Ketone 2 with Diethyl Malonate Anion.—To 0.011 g (0.0005 g-atom) of sodium dissolved in 1 ml of dry ethanol was added 0.08 g (0.5 mmole) of diethyl malonate with stirring under nitrogen. After a few minutes 0.013 g (0.05 mmole) of tricyclic ketone 2 in 2 ml of ethanol was added. Examination of aliquots by ultraviolet spectroscopy over 8 hr showed only starting material. The mixture was treated with aqueous sodium hydroxide and extracted with chloroform. The chloroform layer was extracted with 10% hydrochloric acid which was then made basic with 10% sodium hydroxide and chloroform extracted. Drying and concentration of this chloroform extract gave 0.01 g (77%) of recovered tricyclic ketone 2 identified by spectral and tlc comparisons with starting material.

To 0.008 g (0.33 mmole) of sodium hydride in 1 ml of dry ethanol was added with stirring under nitrogen 0.10 g (0.62 mmole) of diethyl malonate. After a few minutes 0.079 g (0.31 mmole) of tricyclic ketone 2 was added. The mixture was stirred at 70–80° for 8 hr. Usual work-up gave 0.06 g (76%) of tricyclic ketone 2.

Treatment of Tricyclic Ketone 2 with Potassium Cyanide.—A solution of 0.023 g (0.09 mmole) of tricyclic ketone 2 and 0.006 g (0.9 mmole) of potassium cyanide in 15 ml of ethanol was stirred under nitrogen at 25° for 17 hr. Dilution of the reaction mixture with sodium hydroxide solution and ether extraction gave 0.023 g (100%) of tricyclic ketone 2 identified by spectral and tlc comparisons with authentic material. Refluxing this mixture in 2 ml of ethanol for 24 hr gave a 48% recovery of starting material. Reaction mixture aliquots were examined by ultraviolet and tlc but no reaction could be detected.

Registry No.—N-(Indole-3-acetyl)piperidine, 7774-14-3; **1**, 4802-79-3; **2**, 7774-20-1; *cis* **3**, 7774-16-5; *trans* **3**, 7774-17-6; **4a**, 7774-19-8; **4b**, 7774-18-7; **6a**, 7774-21-2; **6b**, 7774-22-3; **7a**, 7774-23-4; **7b**, 7784-64-7; **8**, 5912-12-9; **9**, 7774-24-5; **10**, 7262-67-1; **12**, 7774-27-8.

Proton Spin Coupling in 1-Indanone[1]

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The alicyclic protons of 1-indanone represent an ideal system for the test of theory on magnitudes and signs of $^2J_{HH}$ and $^3J_{HH}$ values because the alicyclic ring is unstrained, unsubstituted, and rigid and the proton spectrum is well resolved. The corresponding A_2B_2 spectrum was completely analyzed. The two $^2J_{HH}$ values are of the same sign, and their sign is opposite that of the $^3J_{HH}$ values, in accordance with theory. Long-range coupling in 1-indanones is discussed, and the methods of preparing deuterated 1-indanones and their intermediates are described.

The determination of relative signs of proton–proton spin coupling constants has been of considerable interest during the last years.[2] It is generally accepted that in systems in which protons are bonded to ethane-like CC fragments, the coupling constants between vicinal protons ($^3J_{HH}$) have a sign opposite those between geminal protons ($^2J_{HH}$). The proofs of this were based either on the results of double-resonance experiments or on the analysis of spectra mostly of the ABC or ABX type. A_2B_2 spectra (from CH_2CH_2 groupings) have the advantage over ABX or ABC spectra (from CH_2CHR groupings) that effects of substituents on carbon atoms, which do affect both $^3J_{HH}$ and $^2J_{HH}$, are absent, and thus the conclusions regarding the relative signs are on a firmer basis. A further desirable requirement is that the CH_2CH_2 grouping be rigid,[3] so that uncertainties about the actual magnitude of $^3J_{HH}$ owing to motional averaging[4] do not arise.

Both of these requirements were met in the studies described in the first two reports on the subject in A_2B_2 systems: on metacyclophane[3] and on two 1,1,2,2-tetrasubstituted cyclobutanes.[5] Since in both cases the protons in the CH_2 group are nonequivalent, an ambiguity remains in the assignment of the J values

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(2) For an introduction to the subject, *cf.* (a) A. A. Bothner-By in "Advances in Magnetic Resonance," J. S. Waugh, Ed., Academic Press Inc., New York, N. Y.. 1965, p 195; (b) M. Barfield and D. M. Grant, ref 2a; (c) N. S. Bhacca and D. H. Williams, "Applications of N.M.R. Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 149; (d) R. C. Fahey, G. C. Graham, and R. L. Piccioni, *J. Am. Chem. Soc.*, **88**, 193 (1966).

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