[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Indole Alkaloids. A Study of the Dieckmann Condensation of 1-Carbethoxymethyl-2-(β-carbethoxyethyl)-1,2,3,4-tetrahydro-β-carboline. A Synthesis of 20-Carbethoxy-$\Delta^{15,16}$-yohimben-17-one

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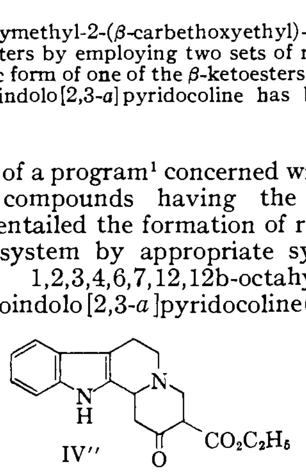
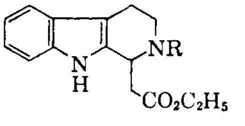
1-Carbethoxymethyl-2-(β-carbethoxyethyl)-1,2,3,4-tetrahydro-β-carboline has been converted into two different tetracyclic β-ketoesters by employing two sets of reaction conditions for the Dieckmann condensation. Both the enolic form and the ketonic form of one of the β-ketoesters have been isolated as crystalline solids. 3,4,6,7,12,12b-Hexahydro-3-carbethoxy-2-hydroxyindolo[2,3-*a*]pyridocoline has been converted into 20-carbethoxy-$\Delta^{15,16}$-yohimben-17-one by the Robinson reaction.

One phase of a program[1] concerned with the preparation of compounds having the yohimbane ring system entailed the formation of ring E of the pentacyclic system by appropriate synthetic operations on 1,2,3,4,6,7,12,12b-octahydro-3-carbethoxy-2-ketoindolo[2,3-*a*]pyridocoline(IV'').[2a,b]



IV''

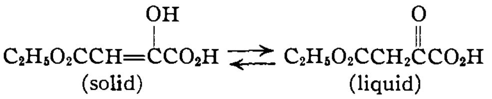
When this work was initiated, Groves and Swan[3] already had prepared but not isolated a tetracyclic β-ketoester by a Dieckmann condensation of 1-carbethoxymethyl-2-(β-carbethoxyethyl)-1,2,3,4-tetrahydro-β-carboline (II) during the course of a



I, R = H
Ia, hydrochloride of I
II, R = $-CH_2CH_2CO_2C_2H_5$
IIa, hydrochloride of II

synthesis of 1,2,3,4,6,7,12,12b-octahydro-2-ketoindolo[2,3-*a*]pyridocoline (V). Work on the same series of compounds in these laboratories has resulted in the isolation of *two* β-ketoesters, and chemical work necessary to ascertain the position of the carbethoxy group in each one has been in progress. However, this has been obviated by a recent publication by Prasad and Swan[4] in which their tetracyclic β-ketoester was shown by radiotracer technique to have the carbethoxy group in the 1-position (see i in footnote 2). In addition to the chemistry of the β-ketoesters, the present communication describes the isolation of both the enolic and ketonic forms of one of the β-ketoesters and the synthesis of a pentacyclic α,β-unsaturated ketone.[5]

Carbethoxypyruvic acid was prepared in 65% yield by partial alkaline saponification of the sodium salt of diethyl oxalacetate. After acidification, the free carboxylic acid was obtained as a mixture of an oil and crystalline solid which resisted separation by solvents. That the product was actually an equilibrium mixture of the enolic form (solid) and the ketonic form (liquid) is supported by the following observation. The equi-



$$\underset{\text{(solid)}}{C_2H_5O_2CCH{=}\overset{\overset{\displaystyle OH}{|}}{C}CO_2H} \rightleftharpoons \underset{\text{(liquid)}}{C_2H_5O_2CCH_2\overset{\overset{\displaystyle O}{\|}}{C}CO_2H}$$

librium mixture analyzed correctly for carbethoxypyruvic acid. After the solid (*ca.* 10%)[6] was separated from the oil by filtration without the benefit of a solvent, there rapidly appeared in the oil a new crop of crystals. Repeated filtrations always resulted in a new deposit of solid even when the mixture was allowed to stand for a prolonged period between filtrations. The separated solid, essentially free of oil, was readily recrystallized from acetone–benzene to give a pure sample of the enolic form.

When tryptamine hydrochloride was allowed to react with carbethoxypyruvic acid in refluxing ethanol, a 53% yield of 1-carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline hydrochloride (Ia) was obtained. The free base I, which was obtained by sodium bicarbonate neutralization of Ia but never isolated, was heated under reflux in an excess of ethyl acrylate to produce 1-carbethoxymethyl-2-(β-carbethoxyethyl)-1,2,3,4-tetrahydro-β-carboline (II), isolated in 77% yield as the hydrochloride (IIa).[7]

Compound II was dissolved in benzene and caused to undergo a Dieckmann reaction using sodium hydride as the condensing agent. The sodium enolate separated from the benzene as it was formed and the product was isolated as the hydrochloride in 86% yield. Fractional crystallization of this crude material, m.p. 154–158°

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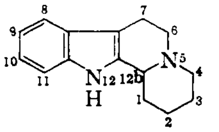
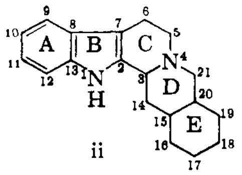
(1) Another approach has been reported from these laboratories; see R. T. Rapala, E. R. Lavagnino, E. R. Shepard and E. Farkas, THIS JOURNAL, **79**, 3770 (1957).

(2) (a) The nomenclature and numbering system employed here comply with that established in reference 3. 1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]pyridocoline is represented by i, yohimbane by ii;



i



ii

(b) the use of a prime or a double prime with a Roman numeral signifies that the β-ketoester is in the enolic form or ketonic form, respectively.

(3) L. H. Groves and G. A. Swan, *J. Chem. Soc.*, 650 (1952).

(4) K. B. Prasad and G. A. Swan, *ibid.*, 2045 (1958).

(5) Although a portion of the work described here is closely related to published material,[3,4] a brief exposition is deemed necessary for the maintenance of continuity.

(6) The infrared spectrum of the mixture showed that the amount of enolic form present was far greater than 10%, indicating that the solid is fairly soluble in the oil. A more detailed analysis of the infrared spectra of this series is presently in progress.

(7) Methyl methacrylate was found not to react with the secondary amine under similar conditions.

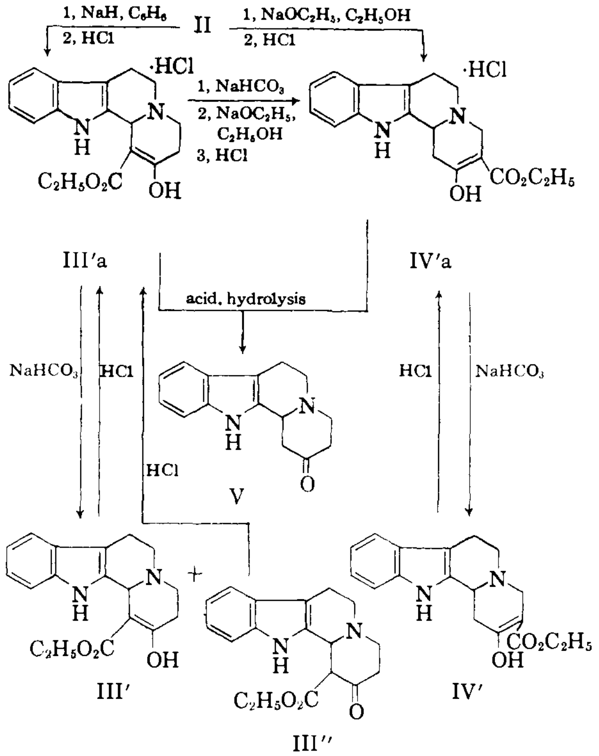


Fig. 1.

dec., from ethanol gave two enolic tetracyclic β-ketoester hydrochlorides, III'a (90%), m.p. 174–175° dec., and IV'a (10%), m.p. 232–233° dec. The presence of absorption maxima at 1661 and 1620 cm.$^{-1}$ for III'a and 1656 and 1618 cm.$^{-1}$ for IV'a along with the absence of any maxima between 1670 and 1750 cm.$^{-1}$ is consistent with previous observations of the characteristic infrared absorption which is exhibited by the conjugated chelate enolic form of β-ketoesters.[8] Acid treatment of both III'a and IV'a gave, by ester hydrolysis and decarboxylation, 1,2,3,4,6,7,12,12b-octahydro-2-ketoindolo[2,3-*a*]pyridocoline (V).

Since the Dieckmann reaction which led mainly to III'a was run under essentially non-equilibrating conditions, the possibility that III'a might be convertible into IV'a through the free base was considered.[9] The requirements for such a transformation would be: (1) the maintenance of an appreciable amount of homogeneity in the reaction mixture and (2) the greater thermodynamic stability of the enolate anion of the free base IV with respect to that of the enolate anion of the free base III. When III was allowed to react with sodium ethoxide in ethanol and the product isolated as the hydrochloride, IV'a was obtained in 21% yield. No III'a was recovered. Since the conditions of the above reaction are similar to an alternate method for performing the Dieckmann condensation, we investigated the possibility of obtaining IV'a directly from II using sodium ethoxide in ethanol as the condensing agent; IV'a was obtained exclusively in a yield of 31%. *Thus, by operating under two different sets of reaction conditions for the Dieckmann condensation, two different β-ketoesters have been realized.*[10]

Attention is next directed to the chemistry which evolved when the free bases of the β-ketoester hydrochlorides were isolated and characterized. When IV'a was neutralized with sodium bicarbonate, the free base IV', m.p. 164–165°, was obtained. The infrared spectrum of IV' in mineral oil showed double bond absorption maxima only at 1661 and 1623 cm.$^{-1}$, indicating this compound to be in the enolic form. When the spectrum of IV' in chloroform was recorded, broad absorption of low intensity appeared between 1700 and 1730 cm.$^{-1}$ indicating that IV exists to a small degree (less than 10%) in the ketonic form in solution; IV' was converted back to IV'a upon treatment with hydrogen chloride.

When III'a was neutralized with sodium bicarbonate and allowed to crystallize from petroleum ether, two different types of crystals were formed in approximately equal amounts. It was subsequently determined that the compound which crystallized as small cubes, m.p. 127–128.5°, was the enolic form of the free base (III'), and the compound which crystallized as rosettes, m.p. 116–117.5°, was the ketonic form of the free base (III''). A mixture of the two compounds melted at 125–128.5° after softening at 117°. The infrared spectrum of III' in mineral oil showed major double bond absorption maxima at 1634 and 1600 cm.$^{-1}$ and a minor maximum at 1712 cm.$^{-1}$. The appearance of a small amount of absorption above 1670 cm.$^{-1}$ suggested that this sample of the enolic compound was not completely free of the ketonic tautomer. The infrared spectrum of III'' in mineral oil showed double bond absorption maxima only at 1709 and 1695 cm.$^{-1}$, indicating that this was the pure ketonic compound. The spectrum of III' in chloroform was identical to that of III'' in chloroform. From the relative intensities of the appropriate absorption bands it was estimated that the equilibrium mixture consisted of 40% of III' and 60% of III''.[11] Both III' and III'' were converted back to III'a upon treatment with hydrogen chloride. *Thus, both the enolic form and the ketonic form of a β-ketoester have been isolated as separate crystalline entities.*

From the evidence so far presented, it was possible for us to assign tentatively the carbethoxy group in the III and IV series to the 1- and 3-positions, respectively, of the indolo[2,3-*a*]pyrido-

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[8] N. J. Leonard, H. S. Gutowsky, W. J. Middleton and E. M. Petersen, THIS JOURNAL, **74**, 4070 (1952).

[9] An example of such a transformation has been recorded by H. T. Openshaw and R. Robinson, *J. Chem. Soc.*, 941 (1937). 2-Carbethoxycyclohexanone was alkylated with ethyl β-chloropropionate to give 2-carbethoxy-2-(β-carbethoxyethyl)-cyclohexanone which was converted by sodium ethoxide and ethanol to the more stable 2-carbethoxy-(β-carbethoxyethyl)-cyclohexanone.

[10] (a) The isolation of a small amount of IV'a from the sodium hydride product may well be attributed to the promotion of partial equilibrating conditions caused by the ethanol which is formed during the condensation reaction. (b) A related occurrence has been reported by R. B. Woodward and R. H. Eastman, THIS JOURNAL, **68**, 2229 (1946). The Dieckmann cyclization of α,β'-dicarbomethoxymethyl ethyl sulfide resulted in 2-carbomethoxy-3-ketotetrahydrothiophene when sodium methoxide in dry ether at room temperature was employed, and 4-carbomethoxy-3-ketotetrahydrothiophene when sodium methoxide in dry toluene at 80–120° was employed.

[11] An attempt to obtain more critical data on the equilibrium concentrations is presently in progress. The main problem in such an endeavor is created by the difficulty of obtaining quantitative results when mineral oil is used as the spectral medium.

coline ring system.[12] This assignment has been confirmed by Prasad and Swan.[4] In a closer study of the Dieckmann reaction of II in which sodium ethoxide in benzene was employed as the condensation medium, they obtained two "β-ketoesters," m.p. 128–129° and 115–116°, both of which were shown by radiotracer methods to have the carbethoxy group in the 1-position. Although these authors made no attempt to explain the production of two compounds representing the same β-ketoester, the work reported in the present communication leaves little doubt that these are, in fact, the enolic and ketonic compounds, III′, m.p. 127–128.5°, and III″, m.p. 116–117.5°, respectively. The sequence of reactions is summarized in Fig. 1. The infrared data are summarized in Table I.

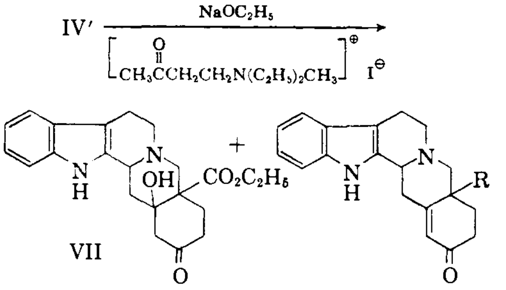
TABLE I

INFRARED DOUBLE-BOND ABSORPTION MAXIMA[a,b]

	Ester C=O	Ketone C=O	Chelated conjugated C=O	Conjugated C=C
III′a			1661	1620
IV′a			1656	1618
III′			1634	1600
IV′			1661	1623
V		1709		
III″	1695[c]	1709		
VI[b]	1741	1720	1660	1624

[a] Values are in cm.$^{-1}$. [b] All samples were run as a mineral oil mull except V which was run in chloroform and ethyl 1-ethyl-4-piperidone-3-carboxylate (VI) which is reported[8] to have been run as a pure liquid. [c] The low frequency of the ester absorption is attributed to hydrogen bonding by the indole –NH– (see Discussion).

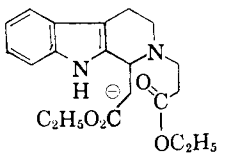
When IV′ was allowed to react with 4-diethylaminobutan-2-one methiodide and sodium ethoxide under the conditions of the Robinson reaction,[13] we obtained 20-carbethoxy-15-hydroxyyohimbone (VII) (13%) and 20-carbethoxy-$\Delta^{15,16}$-yohimben-17-one (VIII) (38.5%, isolated as the hydrochloride). Although one experiment, in which VIII was saponified with alkali and then heated in acid, gave material which was believed to be $\Delta^{15,16}$-yohimben-17-one (IX), m.p. 230° dec. (infrared carbonyl absorption at 1659 cm.$^{-1}$), further characterization of this compound was not possible because several subsequent experiments failed to give crystalline material. Several attempts to perform the Robinson reaction on the alternate β-ketoester III were unsuccessful. Because of poor yields at several stages, further exploitation of this sequence for the preparation of yohimbane compounds was deemed unprofitable.



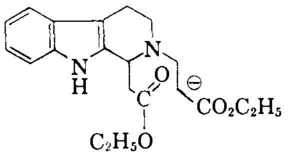
VII

VIII, R = $-CO_2C_2H_5$
IX, R = H

Discussion.—Although a Dieckmann condensation of an unsymmetrical diester might be expected to give two β-ketoesters, the case reported here is unusual in that each of the two β-ketoesters obtained from the unsymmetrical diester is formed under a distinct set of reaction conditions.[10] This situation can be explained readily if one considers the effect of kinetic and thermodynamic factors on the course of these reactions.[14] It is immediately obvious from previous discussion that the conversion of III to IV by means of sodium ethoxide in ethanol is an equilibrium process which proceeds by virtue of the greater thermodynamic stability of the enolate IV′. This can be attributed to the steric repulsion between the indole –NH– group and the carbethoxy group in III. It also follows that the formation of the less stable β-ketoester III from the diester II by means of sodium hydride in benzene must proceed by a process in which rate factors play the dominant role.[15] To account for this it is necessary to concede that of the two possible intermediate anions, IIb must be formed at a much faster rate than IIc, an occurrence which is explicable only if one assumes participation of the indole –NH– in the rate-determining step. Because of its relatively greater acidity, the indole –NH– will lose a proton to the base much more readily than will a carbon α to a carbethoxy group. The resulting anion can then initiate a series of electron shifts which end with the formation of III.

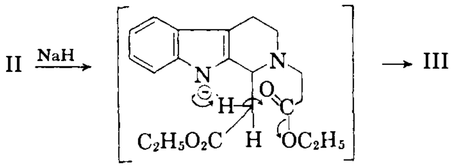


IIb



IIc

Although III was never isolated from the sodium ethoxide–ethanol condensation of II because of its ready equilibration to IV under the same conditions, it is quite likely that III is formed as an intermediate in this reaction by a mechanism identical to that just advanced for the sodium hydride condensation.



Another contrasting feature of the two β-ketoesters is the degree to which each exists in the ketonic form in chloroform solution. It is necessary to refer again to the steric interaction attend-

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(12) The rationale for this assignment will be discussed later in this communication, and the conclusions will be treated as supporting evidence.

(13) E. C. duFeu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.*, 53 (1937); A. V. Logan, E. N. Marvell, R. La Pore and D. C. Bush, THIS JOURNAL, **76**, 4127 (1954), and references therein.

(14) For a discussion of kinetic and thermodynamic control of reaction products, see E. J. Corey, *ibid.*, **76**, 175 (1954).

(15) If this were not the case, it would be expected that the reaction mixture would be comprised of at least 50% of IV.

ant in III as being the most important factor in the disposition of the keto–enol equilibrium in III (60% ketonic form) and IV (less than 10% ketonic form).[16] The carbethoxy group in the enol III′ cannot readily assume a position which is planar with the conjugated double bond. Consequently the resonance stabilization of the conjugated chelate form is reduced to such an extent that both the enolic and ketonic forms have comparable thermodynamic stability.

Because of insufficient data, a complete development of the stereochemistry is not possible at this time.[17] It is appropriate, however, to point out two salient features of the infrared data. The 1695 cm.$^{-1}$ maximum of III″ has been tentatively assigned to the ester carbonyl group, and its position at an abnormally low frequency has been attributed to hydrogen-bonding by the proximate acidic hydrogen of the indole ring.[18] Although the hydrogen bond constitutes part of a 7-membered cyclic system, molecular models indicate that the atomic arrangement necessary for a strong bond is present in at least one of the possible conformations of III″. It is unfortunate that the alternate ketonic compound IV″ is not available for direct comparison.

The second conspicuous abnormality appears in the infrared spectrum of the enol III′. The maxima at 1634 and 1600 cm.$^{-1}$ are lower than normal by approximately 26 and 20 cm.$^{-1}$, respectively. Although hydrogen-bonding again could be responsible for this discrepancy, the situation is complicated by the fact that the corresponding hydrochloride III′a shows normal absorption with maxima at 1661 and 1620 cm.$^{-1}$. We suggest that III′ and III′a might therefore have different conformations, but without additional evidence this point will not be pursued.

Acknowledgments.—The assistance of a number of people has been appreciated greatly: Mr. L. A. White who supplied ample quantities of several of the intermediates; Mr. W. L. Brown, Mr. G. Maciak, Mr. H. L. Hunter and Miss G. Beckmann who performed the analyses; and Dr. H. E. Boaz, Mr. D. O. Woolf, Mr. P. W. Landis, Miss M. Hofmann and Mrs. H. Arndt who recorded the physical measurements.

Experimental

Melting points were determined in soft glass capillary tubes and are uncorrected. The infrared measurements were made on a Baird double-beam automatic recording spectrophotometer using either chloroform or mineral oil as the spectral medium.

Carbethoxypyruvic Acid.—The sodium salt of diethyl oxalacetate (63 g., 0.3 mole) was dissolved in 600 ml. of water, and with efficient stirring 50 ml. of 6 *N* sodium hydroxide was added dropwise over a period of one hour. The mixture was allowed to stir at room temperature for three hours and then acidified at 0° by the addition of 105 ml. of 6 *N* hydrochloric acid. The acidic solution was extracted with eight 200-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo* at room temperature to give a mixture of solid and oil (enolic form and ketonic form). The yield of carbethoxypyruvic acid was 31.2 g. (65%).

Anal. Calcd. for $C_6H_8O_5$: C, 45.00; H, 5.04. Found: C, 45.18; H, 5.30.

Separation of the solid enol form by filtration and crystallization from acetone–benzene gave an analytical sample, m.p. 96–98° (lit.[3] m.p. 98–100°).

Anal. Found: C, 45.20; H, 5.28.

1-Carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline hydrochloride (Ia) was prepared by a modification of the method of Groves and Swan.[3] A solution of 29.5 g. (0.185 mole) of carbethoxypyruvic acid in 90 ml. of ethanol was added in three portions over a period of 24 hours to a refluxing solution of 27 g. (0.137 mole) of tryptamine hydrochloride in 400 ml. of ethanol. The mixture was allowed to reflux for an additional 24 hours, and then was refrigerated overnight. The product was collected on a funnel and washed with a minimum amount of cold ethanol. The yield of tricyclic ester hydrochloride, m.p. 239–241° dec., was 21.2 g. A second crop, m.p. 235–240° dec., brought the total yield to 23.9 g. (59%, based on tryptamine hydrochloride). Recrystallization from ethanol raised the melting point to 241–243° dec. (lit.[3] m.p. 240° dec.).

Anal. Calcd. for $C_{15}H_{18}N_2O_2 \cdot HCl$: C, 61.11; H, 6.50; N, 9.51. Found: C, 60.89; H, 6.73; N, 9.34.

1-Carbethoxymethyl-2-(β-carbethoxyethyl)-1,2,3,4-tetrahydro-β-carboline hydrochloride IIa was prepared by a modification of the method of Groves and Swan.[3] A mixture of 18.5 g. of 1-carbethoxymethyl-1,2,3,4-tetrahydro-β-carboline hydrochloride, 500 ml. of water, 25 ml. of ethanol, 6 g. of sodium bicarbonate and 500 ml. of ether was shaken in a separatory funnel until all of the solid material had dissolved. The layers were separated, and the aqueous layer was extracted with an additional 250 ml. of ether. The combined ether layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to an oil. The oil was dissolved in 100 ml. of ethyl acrylate, and the mixture was allowed to reflux for two days. The ethyl acrylate was removed *in vacuo* at 50°, and the residual oil was dissolved in 500 ml. of ether and saturated with hydrogen chloride at 0°. The resulting solid was collected on a filter, washed thoroughly with ether (slightly hygroscopic) and quickly dissolved in 60 ml. of methanol. Ether (200 ml.) then was added to the methanol solution and the product allowed to crystallize. The yield of the tricyclic diester hydrochloride, m.p. 152–155°, was 19.0 g. (77%). An analytical sample, m.p. 155–157° (lit.[3] m.p. 147–148°), was obtained by the addition of ether to a methanol solution of the above material.

Anal. Calcd. for $C_{20}H_{26}N_2O_4 \cdot HCl$: C, 60.83; H, 6.89; N, 7.10. Found: C, 60.74; H, 6.92; N, 7.28.

3,4,6,7,12,12b-Hexahydro-1-carbethoxy-2-hydroxyindolo[2,3-*a*]pyridocoline Hydrochloride (III′a).—A mixture of 19.0 g. of 1-carbethoxymethyl-2-(β-carbethoxyethyl)-1,2,3,4-tetrahydro-β-carboline hydrochloride, 4.6 g. of sodium bicarbonate and 750 ml. of water was extracted with 500 ml. of ether. The ether was dried over anhydrous magnesium sulfate and concentrated *in vacuo* at 50°. The resulting oil was combined with 60 ml. of dry benzene and 2.4 g. of sodium hydride and allowed to reflux for three hours. The mixture was cooled in an ice-bath, and several ml. of ethanol were added to decompose any unreacted sodium hydride. Acetic acid (250 ml. of 4%) was then added and the mixture was extracted with one 400-ml. and two 150-ml. portions of ether. The combined ether extracts were washed with 100 ml. of water, dried over anhydrous magnesium sulfate and concentrated to dryness *in vacuo*. The residue was dissolved in 400 ml. of ether and saturated with hydrogen chloride. The hydrochloride was collected on a funnel, washed thoroughly with ether (slightly hygroscopic) and

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[16] We recognize the possibility that the degree of ketonization might be influenced by the stereochemistry of the CD-ring juncture (for example, see R. B. Turner, W. R. Meador and R. E. Winkler, This Journal, **79**, 4122 (1957) and references therein). However, a rigorous assignment of a *cis* or *trans* ring juncture to any of these compounds is precluded by the facile inversion of the nitrogen atom common to rings C and D.

[17] The numerous conformations that can be drawn for several of the compounds in this series make such a treatment especially difficult.

[18] (a) The frequency of the second maximum, 1709 cm.$^{-1}$, is identical with that of the sole double bond maximum of the tetracyclic ketone V and is therefore assigned to the ketone carbonyl group. (b) In the case of *n*-butyl salicylate it has been shown that hydrogen-bonding is responsible for lowering the conjugated ester carbonyl frequency by 43 cm.$^{-1}$; R. S. Rasmussen and R. R. Brattain, This Journal, **71**, 1073 (1949).

dried *in vacuo* at room temperature. The yield of crude tetracyclic 1-carbethoxy-2-hydroxy hydrochloride, m.p. 154–158° dec., was 14.4 g. (86%). Crystallization from ethanol gave a sample, m.p. 166–168° dec., which analyzed correctly.

Anal. Calcd. for $C_{18}H_{20}N_2O_3 \cdot HCl$: C, 61.97; H, 6.07; N, 8.02; Cl, 10.16. Found: C, 61.89; H, 6.05; N, 8.18; Cl, 9.98.

The purest samples of III'a were obtained by the preparation of the hydrochloride from the free bases III' and III''; III' gave III'a, m.p. 174–175° dec., and III'' gave III'a, m.p. 173–174° dec. Fractional crystallization of 10 g. of the crude hydrochloride from ethanol gave 1 g. of the tetracyclic 3-carbethoxy-2-hydroxy hydrochloride, IV'a.

3,4,6,7,12,12b-Hexahydro-1-carbethoxy-2-hydroxyindolo[2,3-*a*]pyridocoline (III') and 1,2,3,4,6,7,12,12b-Octahydro-1-carbethoxy-2-ketoindolo[2,3-*a*]pyridocoline (III'').—3,4,6,7,12,12b-Hexahydro-1-carbethoxy-2-hydroxyindolo[2,3-*a*]pyridocoline hydrochloride was dissolved in water, neutralized with sodium bicarbonate and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, concentrated to dryness *in vacuo*, and the amorphous solid was crystallized from petroleum ether.

The enolic compound III' crystallized as cubes and had a m.p. 127–128.5°.

Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.15; H, 6.63; N, 9.00.

The ketonic compound III'' crystallized as rosettes and had a m.p. 116–117.5°.

Anal. Found: C, 69.10; H, 6.32; N, 8.87.

A mixture of III' and III'' melted at 125–128.5° after softening at 117°; III'' was found to be much more readily soluble in ether than was III'.

3,4,6,7,12,12b-Hexahydro-3-carbethoxy-2-hydroxyindolo[2,3-*a*]pyridocoline Hydrochloride (IV'a). A. From 3,4,6,7,12,12b-Hexahydro-1-carbethoxy-2-hydroxyindolo[2,3-*a*]pyridocoline Hydrochloride.—Pure tetracyclic 1-carbethoxy-2-hydroxy hydrochloride was converted to the free base (2.1 g.), combined with sodium ethoxide (from 0.28 g. of sodium hydride) in 30 ml. of dry ethanol, and the solution was heated under reflux for 5 hours. The mixture was allowed to cool, added to 100 ml. of water containing 0.9 ml. of glacial acetic acid and extracted with two 100-ml. portions of ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate and saturated with hydrogen chloride. The resulting oily solid was washed with ether and triturated with ethanol. The yield of the tetracyclic 3-carbethoxy-2-hydroxy hydrochloride, m.p. 225–227° dec., was 0.5 g. (21%). Crystallization from ethanol gave an analytical sample, m.p. 232–233° dec.

Anal. Calcd. for $C_{18}H_{20}N_2O_3 \cdot HCl$: C, 61.97; H, 6.07; N, 8.03; Cl, 10.16. Found: C, 61.94; H, 6.20; N, 8.03; Cl, 10.39.

B. From 1-Carbethoxymethyl-2-(β-carbethoxyethyl)-1,2,3,4-tetrahydro-β-carboline Hydrochloride.—The tricyclic diester hydrochloride (5.0 g.) was converted to the free base as described in the preparation of III'a, combined with sodium ethoxide (from 0.6 g. of sodium hydride) in 70 ml. of dry ethanol and the mixture was heated under reflux for 4 hours. After working up the reaction product as described in method A above there was obtained 1.2 g. of the tetracyclic 3-carbethoxy-2-hydroxy hydrochloride, m.p. 226–228° dec., representing a 31% yield.

3,4,6,7,12,12b-Hexahydro-3-carbethoxy-2-hydroxyindolo[2,3-*a*]pyridocoline (IV').—3,4,6,7,12,12b-Hexahydro-3-carbethoxy-2-hydroxyindolo[2,3-*a*]pyridocoline hydrochloride was dissolved in water, neutralized with sodium bicarbonate and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, concentrated to dryness *in vacuo*, and the oily residue was crystallized from benzene–petroleum ether. Recrystallization from benzene–petroleum ether gave an analytical sample, m.p. 164–165°.

Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.27; H, 6.53; N, 8.99.

1,2,3,4,6,7,12,12b-Octahydro-2-ketoindolo[2,3-*a*]pyridocoline (V).—A solution of 10 g. of 3,4,6,7,12,12b-hexahydro-1-carbethoxy-2-hydroxyindolo[2,3-*a*]pyridocoline hydrochloride in 200 ml. of 10% sulfuric acid was allowed to reflux under nitrogen for 10 hours. The mixture was added to an equal volume of ice and water, and 1.8 g. of an insoluble by-product was removed by filtration. The filtrate was made alkaline with 12 *N* sodium hydroxide and extracted with two 100-ml. portions of ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate and concentrated to dryness *in vacuo*. The yield of the tetracyclic ketone, m.p. 180–181°, was 4.4 g. (64%). An analytical sample was obtained by recrystallization from benzene, m.p. 181–182° (lit.[3] m.p. 180–180.5°).

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.95; H, 6.65; N, 11.57.

A similar hydrolysis of 3,4,6,7,12,12b-hexahydro-3-carbethoxy-2-hydroxyindolo[2,3-*a*]pyridocoline hydrochloride gave the same product as shown by the melting point, mixture melting point and infrared spectrum (carbonyl band at 1709 cm.$^{-1}$).

20-Carbethoxy-15-hydroxyyohimbone (VII) and 20-Carbethoxy-$\Delta^{15,16}$-yohimben-17-one (VIII) Hydrochloride.—To 2.2 g. of 3,4,6,7,12,12b-hexahydro-3-carbethoxy-2-hydroxyindolo[2,3-*a*]pyridocoline and sodium ethoxide (from 0.17 g. of sodium hydride) in 30 ml. of dry ethanol was added with stirring 2.0 g. of 1-diethylamino-3-butanone methiodide in 11 ml. of dry ethanol over a period of 25 minutes. The mixture then was allowed to reflux for 3.5 hours. Ether and water were added to the cooled mixture; the layers were separated; the ether solution was dried over anhydrous magnesium sulfate and then concentrated *in vacuo*. The residual oil (2.4 g.) was triturated with ethanol to give 0.4 g. (13%) of the pentacyclic hydroxyketoester, m.p. 196–198°. Recrystallization from ethanol raised the melting point to 201–202°. The infrared carbonyl bands of VII in chloroform at 1712 (ester), 1698 (ketone) and 1683 cm.$^{-1}$ (hydrogen-bonded ester) were poorly resolved.

Anal. Calcd. for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.11; H, 7.23; N, 7.92.

The hydrochloride melted at 244–245°. The infrared carbonyl bands of the hydrochloride in mineral oil were at 1700 (ketone) and 1683 cm.$^{-1}$ (hydrogen-bonded ester).

Anal. Calcd. for $C_{22}H_{26}N_2O_4 \cdot HCl$: C, 63.07; H, 6.50; N, 6.69. Found: C, 62.74; H, 6.31; N, 6.75.

The mother liquor from above was concentrated *in vacuo* to an oil which was dissolved in a small amount of acetone, combined with 2 volumes of ether and saturated with hydrogen chloride. The pentacyclic α,β-unsaturated γ-ketoester separated as the hydrochloride, 1.25 g. (38.5%). A sample recrystallized from ethanol melted at 235–236° with decomposition. Carbonyl bands in the infrared were at 1723 (ester) and 1681 cm.$^{-1}$ (conjugated ketone).

Anal. Calcd. for $C_{22}H_{24}N_2O_3 \cdot HCl$: C, 65.91; H, 6.29; N, 6.99. Found: C, 65.98; H, 6.44; N, 7.20.

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