656. *Synthetical Approaches to Alkaloids of the Sarpagine and Ajmaline Groups. Part I. The Preparation of Some Tetracyclic Intermediates.*

By J. D. Hobson, J. Raines, and R. J. Whiteoak.

1,2,3,4-Tetrahydro-10-oxo-1,3-propano-β-carboline (XVIII) and a number of its derivatives have been synthesised from (±)-tryptophan.

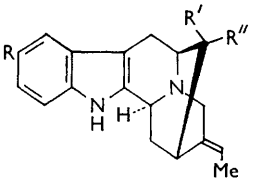
Several important members of the numerous "α" (yohimbine) class of indole alkaloids have been synthesised in recent years, including reserpine,[1] yohimbine,[2] (±)-dihydrocorynantheine,[3] and (±)-ajmalicine.[4] A small group of these bases, of which the best known are sarpagine (I)[5,6] and ajmaline (IV),[5,6,7] possess more highly condensed ring systems, representative of successive stages of a biogenetic pathway from a precursor closely related to corynantheine.[7,8] The relationship and absolute stereochemistry of members of this group have recently been firmly established by the elegant experiments of Taylor, Wenkert, and their colleagues.[6] Further confirmation is provided by the determination, by *X*-ray crystallography,[9] of the structure of akuammidine (II), previously interrelated[10] with normacusine-B (10-deoxysarpagine) (III),[11] thus defining the geometry of the ethylidene group in sarpagine and related alkaloids.[12] This paper records some of our preliminary work on a general synthetic approach to the pentacyclic ring system common to sarpagine (I) and its congeners, and to certain degradation products of ajmaline, *e.g.*, deoxyajmalal-A (Va) and -B (Vb),[6,7] and the ketone (VI).[13]

The tetracyclic ketone (XVIII), and the derivatives described below, were selected as potentially useful intermediates, in the expectation that further construction of the desired quinuclidine system would then be possible by several alternative routes.

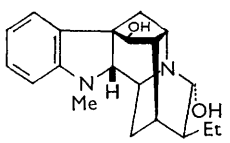
The ready formation of 1-substituted 1,2,3,4-tetrahydro-β-carbolines from tryptamine has resulted in general use of the latter as one of the starting materials in syntheses of the yohimbine type of alkaloid. A distinguishing feature, common to the sarpagine and

[1] Bader, Bickel, Frey, Kierstead, and Woodward, *Tetrahedron*, 1958, **2**, 1.
[2] van Tamelen, Shamma, Burgstahler, Wolinsky, Tamm, and Aldrich, *J. Amer. Chem. Soc.*, 1958, **80**, 5006.
[3] van Tamelen and Hester, *J. Amer. Chem. Soc.*, 1959, **81**, 3805.
[4] van Tamelen and Placeway, *J. Amer. Chem. Soc.*, 1961, **83**, 2594.
[5] For bibliography, see J. E. Saxton in "The Alkaloids," ed. Manske, Academic Press, Inc., New York, 1960, Vol. VII, p. 103.
[6] Bartlett, Sklar, Taylor, Schlittler, Amai, Beak, Bringi, and Wenkert, *J. Amer. Chem. Soc.*, 1962, **84**, 622.
[7] Woodward, *Angew. Chem.*, 1956, **68**, 13.
[8] Gossett, Le Men, and Janot, *Bull. Soc. chim. France*, 1961, 1033; Leete, Ghosal, and Edwards, *J. Amer. Chem. Soc.*, 1962, **84**, 1068, and references given there.
[9] Silvers and Tulinsky, *Tetrahedron Letters*, 1962, 339.
[10] Lévy, Le Men, and Janot, *Compt. rend.*, 1961, **253**, 131.
[11] Battersby and Yeowell, *Proc. Chem. Soc.*, 1961, 17.
[12] Janot, Le Men, Gosset, and Lévy, *Bull. Soc. chim. France*, 1962, 1079.
[13] Whiteoak, Ph.D. Thesis, Birmingham, 1961.

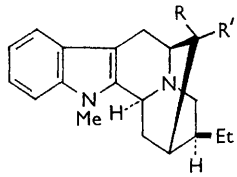
ajmaline structures, is the presence of a 1,3-disubstituted tetrahydro-β-carboline system, thus suggesting the use of the readily available (±)-tryptophan as a convenient starting point in this case.



(I) R = OH, R′ = H, R″ = CH_2·OH
(II) R = H, R′ = CO_2Me, R″ = CH_2·OH
(III) R = R′ = H, R″ = CH_2·OH



(IV)



(Va) R = CHO, R′ = H
(Vb) R = H, R′ = CHO
(VI) RR′ = O

In agreement with previous work,[14,15] exploratory attempts to effect cyclodehydration of *N*(*b*)-acetyl tryptophan ethyl ester to the 3,4-dihydro-β-carboline failed. Although successful in a recent case,[16] the use of the corresponding carboxylic acid in this type of reaction may result in decarboxylation and aromatisation,[14] and we preferred to turn our attention to the well-known condensation of tryptophan with aldehydes.[15,17]

From the condensation of (±)-tryptophan hydrochloride and β-ethoxycarbonylpropionaldehyde in aqueous-ethanolic solution, were isolated a γ-lactam (VII), and a sparingly soluble mixture of hydrochlorides, evidently consisting largely of the salt of a single isomer 1,2,3,3a,4,5-hexahydro-6-oxocanthine-2-carboxylic acid (VIII). This compound was obtained pure only after repeated recrystallisation, and its analytical figures and spectra were consistent with the δ-lactam structure. The ethyl ester (IX) could also clearly be formulated as an *N*-acylindole. Its ultraviolet spectrum closely resembled those of strychnone [18] and similar chromophores,[19] and its infrared spectrum showed a carbonyl band at 1710 cm.$^{-1}$ characteristic of an indole δ-lactam.[20] In model studies for the synthesis of eburnamonine, Bartlett and Taylor [20] have also observed that analogous cyclisations, involving either N(a) or N(b) of a tetrahydro-β-carboline, resulted in preferential formation of the 6-membered lactam.

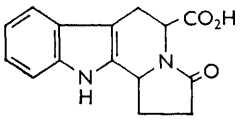
The δ-lactam ester (IX) was obtained in good yield, together with a small amount of the dicarboxylic ester (XI), by direct esterification of the mixture of hydrochlorides produced in the condensation. Thus, although both diastereoisomers were to be expected,[15] and may in fact have been present in this crude product,* it is conceivable that the esterification conditions were sufficiently vigorous to cause epimerisation at position 3a,[21] with equilibration to a more stable isomer. In the absence of any apparent tendency for epimerisation to occur in the presence of sodium ethoxide, this ester (IX) is assigned the 2,3a-*cis*-configuration.

These reactions provided the δ-lactam ester (IX) in reasonable quantities, but difficulties involved in the preparation and use of the acid-labile β-ethoxycarbonylpropionaldehyde, and the formation of the γ-lactam (VII) made improvements desirable. The latter compound could be converted into the δ-lactam ester (IX) in only poor yield by

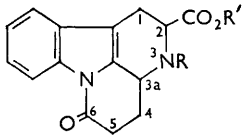
* The yield admits the possibility that a second, more soluble hydrochloride remained largely unisolated in the aqueous mother-liquors.

[14] Snyder and Werber, *J. Amer. Chem. Soc.*, 1950, **72**, 2962.
[15] Snyder, Hansch, Katz, Parmerter, and Spaeth, *J. Amer. Chem. Soc.*, 1948, **70**, 219.
[16] Tschesche, Jenssen, and Rangachari, *Ber.*, 1958, **91**, 1732.
[17] Cf., *inter alia*, Jacobs and Craig, *J. Biol. Chem.*, 1936, **113**, 759; Harvey and Robson, *J.*, 1938, 97; Harvey, Miller, and Robson, *J.*, 1941, 153.
[18] Woodward, Brehm, and Nelson, *J. Amer. Chem. Soc.*, 1947, **69**, 2250.
[19] *E.g.*, Prelog, Szpilfogel, and Battegay, *Helv. Chim. Acta*, 1947, **30**, 366.
[20] Bartlett and Taylor, *J. Amer. Chem. Soc.*, 1960, **82**, 5941.
[21] Cf., *inter alia*, Wenkert and Liu, *Experientia*, 1955, **11**, 302; Bader *et al.*, ref. 1.

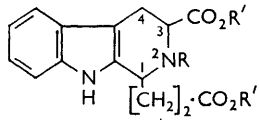
vigorous hydrolysis with concentrated acid, followed by esterification, and its formation represented an inefficient use of starting material for our ultimate purpose. It appeared that the use of more strongly acid conditions in the condensation, thereby completely converting N(b) into its conjugate acid, might discourage cyclisation in this direction.



(VII)



(VIII) R = R′ = H
(IX) R = H, R′ = Et
(X) R = Bz, R′ = Et



(XI) R = H, R′ = Et
(XII) R = Bz, R′ = Et
(XIII) R = Bz, R′ = H
(XIV) R = Bz, R′ = Me

These considerations, and the fact that tryptamine is known to condense readily with 2-oxoglutaric acid,[22] led to the use of the latter in reactions with (±)-tryptophan. Condensation took place rapidly in 4N-hydrochloric acid at 90°, and was accompanied by decarboxylation [22] and separation of the hydrochloride of the δ-lactam acid (VIII). As before, esterification without prior purification gave the ester (IX), isolated in 38% yield overall, based on tryptophan. Only minor amounts of the γ-lactam (VII) were obtained, resulting in a simplified isolation procedure.

For subsequent operations with the ester (IX), it was considered necessary to protect the basic centre, and, of the various derivatives prepared, the most convenient appeared to be the *N*-benzoyl compound (X). Attempts to convert the latter directly into the diethyl ester (XII) by ethanolysis with sodium ethoxide were not very successful. In ethanol solution, catalytic amounts of base evidently gave an equilibrium mixture containing only about 20% of the required diethyl ester, while greater concentrations of ethoxide led to partial Dieckmann condensation, giving the ethyl β-keto-ester (XV). Unfortunately, the latter was produced in only poor yield by this direct route and, in spite of attempted improvement by alteration of the conditions, it was necessary to proceed through the intervening stages described below.

The observation [23] that treatment of canthin-6-one with Raney nickel in boiling methanol resulted in reduction and cleavage of the δ-lactam, giving 1-(2-methoxycarbonylethyl)-β-carboline led to the application of these conditions to the δ-lactam (IX). In this case, however, the infrared spectrum and properties of the product indicated merely that reduction of the indole double bond had occurred.

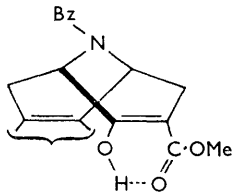
Conversion of the *N*-benzoyl-δ-lactam (X) into the dimethyl ester (XIV) was readily accomplished by alkaline hydrolysis, followed by treatment of the resulting dicarboxylic acid (XIII) with diazomethane. Sodium hydride in tetrahydrofuran proved to be the most effective of a variety of procedures investigated for the promotion of the Dieckmann condensation of the dimethyl ester (XIV), giving the methyl β-keto-ester (XVI) in high yield.

This product, and similar β-keto-esters encountered in this work, appeared to be completely enolic, having no carbonyl band in their infrared spectra at frequencies higher than 1670 cm.$^{-1}$. Their ultraviolet spectra showed broad absorption in the 245—280 mμ region, appearing as a shoulder to the intense peak at 225 mμ, due to the HO·C:C·CO_2R chromophore underlying the indole spectrum.* The methyl β-keto-ester, which was slowly soluble in aqueous sodium carbonate, failed to give an ethylene ketal under the

* Subtraction of the spectrum of the saturated parent compound (XIX; CH_2 replacing CO) from that of the methyl β-keto-ester (XVI) disclosed a band at 250 mμ (ε ~10,000) due to this chromophore.

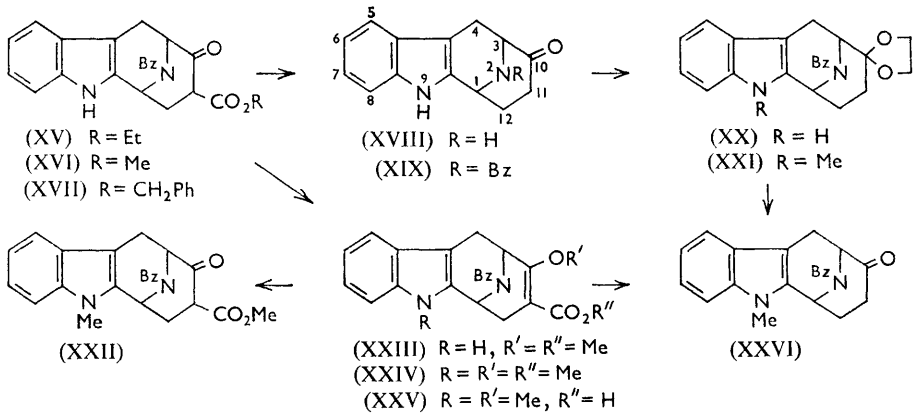
[22] Hahn and Hansel, *Ber.*, 1938, **71**, 2163.
[23] Haynes, Nelson, and Price, *Austral. J. Sci. Res.*, 1952, **5**, 387.

usual conditions or to show other carbonyl properties. A possible rationalisation for the unusual preponderance of the enolic tautomer is suggested by an examination of models. The presence of the indole double bond in one ring of the bridged bicyclic system appears to result in distortion of the other ring so as to favour the geometry required by the introduction of the second double bond, by enolisation to (XVIa).



(XVIa)

Direct hydrolysis and decarboxylation of the β-keto-ester (XVI) was accomplished with acid only under rather vigorous conditions, and was accompanied by loss of the *N*-benzoyl protecting group, giving the tetracyclic ketone (XVIII) in yields generally little better than 50%. Benzoylation of the latter ketone gave the *N*(*b*)-benzoyl ketone (XIX), which, however, was more efficiently prepared by alcoholysis of the methyl β-keto-ester (XVI) with benzyl alcohol, followed by hydrogenolysis of the benzyl ester (XVII) over palladised charcoal. Decarboxylation occurred spontaneously, giving the required ketone in high overall yield.



(XV) R = Et
(XVI) R = Me
(XVII) R = CH_2Ph

(XVIII) R = H
(XIX) R = Bz

(XX) R = H
(XXI) R = Me

(XXII)

(XXIII) R = H, R′ = R″ = Me
(XXIV) R = R′ = R″ = Me
(XXV) R = R′ = Me, R″ = H

(XXVI)

Attempts to prepare this intermediate directly from the dicarboxylic acid (XIII) by treatment with sodium acetate and acetic anhydride [24] gave unsatisfactory results (6% yield), presumably owing to competing δ-lactam formation.

Independent confirmation for the structure of the ketone (XIX) has been obtained by reduction to the parent compound (XIX; CH_2 replacing CO), which proved to be identical with a specimen obtained by application of the Fischer indole synthesis to 9-benzoyl-9-azabicyclo[3,3,1]nonan-2-one.[25]

Of the various synthetic objectives envisaged in this work, ajmaline and its structurally simpler degradation products possess an *N*(*a*)-methyl substituent. Furthermore, it was apparent that in some of the possible routes to the quinuclidine system present in these structures, the presence of a free indole NH group might prove a handicap. It was therefore considered desirable to have available the *N*(*a*)-methyl derivatives of the tetracyclic intermediates already described.

Methylation of the ketone (XIX) was achieved *via* the ethylene ketal (XX). Treatment of the latter with potassium amide in liquid ammonia followed by methyl iodide [26] gave the *N*(*a*)-methyl ketal (XXI), which was then smoothly hydrolysed with mineral acid to the ketone (XXVI). A more convenient route to this compound, by which the *N*(*a*)-methyl-β-keto-ester (XXII) also became accessible, was developed when it was appreciated that the pronounced enolic character of the β-keto-ester (XVI) rendered it

[24] *E.g.*, Uhle, McEwen, Schröter, Ching Yuan, and Baker, *J. Amer. Chem. Soc.*, 1960, **82**, 1200.
[25] Calvert, Ph.D. Thesis, Birmingham, 1962.
[26] Potts and Saxton, *J.*, 1954, 2641.

unusually susceptible to *O*-alkylation. Thus, treatment with diazomethane led to slow but virtually quantitative conversion into the enol ether (XXIII), thereby protecting the reactive grouping. In this case, in order to avoid possible ammonolysis of the ester, the method previously used for *N*-methylation was avoided, but the use of sodium hydride in 1,2-dimethoxyethane, followed by addition of methyl iodide or methyl toluene-*p*-sulphonate, proved to be equally effective. Alkaline hydrolysis of the *N*(*a*)-methyl enol ether (XXIV) to the corresponding acid (XXV), followed by hydrolysis and decarboxylation with mineral acid, gave the ketone (XXVI) obtained previously. On the other hand, direct hydrolysis of the enol ether (XXIV) with acid afforded the *N*(*a*)-methyl-β-keto-ester (XXII).

The use of these intermediates in *C*-alkylation studies, designed to introduce the features necessary for the completion of the desired quinuclidine ring system, is under investigation and will be reported in due course.

Experimental.

Ultraviolet spectra were determined for solutions in 95% ethanol with a Cary model 14 recording spectrophotometer. Infrared spectra were recorded on Perkin-Elmer Infracord and model 21 spectrophotometers.

Condensation of (±)-*Tryptophan with* β-*Ethoxycarbonylpropionaldehyde.*—A solution of β-ethoxycarbonylpropionaldehyde (13·5 g.) in ethanol (50 ml.) was added to a solution of (±)-tryptophan (15 g.) in N-hydrochloric acid (75 ml.), and the mixture was refluxed for 5 hr. Acidification of the cooled solution with 4N-hydrochloric acid (20 ml.) was followed by extraction with ether, first with two portions of 300 ml., and then continuously for 12 hr. The aqueous layer was separated, saturated with sodium chloride, and kept in the refrigerator for 2 days, whereupon the thick greenish precipitate was collected, washed with a little ice–water, and dried at 80° *in vacuo*. The crude product (10 g.) was generally esterified (see below) without further purification; six recrystallisations from water gave a pure specimen of 1,2,3,3a,4,5-*hexahydro*-6-*oxocanthine*-2-*carboxylic acid hydrochloride* (VIII) as colourless needles, m. p. 276—278° (decomp.), $\lambda_{max.}$ 239, 260, 291, and 299 mμ (ε 19,400, 9300, 4300, and 4400), $\nu_{max.}$ (in Nujol) broad bands centred at 1705 and 1675 cm.$^{-1}$ (Found: C, 58·9; H, 4·9; N, 8·8. $C_{15}H_{15}ClN_2O_3$ requires C, 58·7; H, 4·9; N, 9·1%).

The combined ether extracts were washed with saturated brine and then shaken with sodium hydrogen carbonate solution, the organic layer being discarded. Acidification with hydrochloric acid resulted in the separation of an oil, which crystallised. The product (3·3 g.) was washed with ice–water and dried by suction. Recrystallisation from aqueous ethanol gave 1,2,3,5,6,11b-*hexahydro*-3-*oxopyrrolo*[2,1-a]-β-*carboline*-5-*carboxylic acid* (VII) as prisms, m. p. 260—262° (decomp.), $\lambda_{max.}$ 225, 273, 279, and 290 mμ (ε 34,000, 7100, 7300, and 5800), $\nu_{max.}$ (in Nujol) 3340 (NH), 1710 (acid C:O), and 1635 cm.$^{-1}$ [N(b)·C:O] (Found: C, 66·4; H, 5·5; N, 10·2. $C_{15}H_{14}N_2O_3$ requires C, 66·7; H, 5·2; N, 10·4%).

Ethyl 1,2,3,3a,4,5-*hexahydro*-6-*oxocanthine*-2-*carboxylate* (IX).—A suspension of the finely powdered crude hydrochloride (8 g.), obtained as above, in dry ethanol (200 ml.) was saturated at 0° with dry hydrogen chloride, and the mixture was stirred for 15 hr. After refluxing for a further 3 hr., the solvent was removed *in vacuo* and the residue (6·5 g.) was freed from oily impurities (see below) with a little cold ethanol. Recrystallisation of a specimen from water gave the *ester hydrochloride* as hydrated prisms, m. p. 266° (decomp.) (Found: C, 57·7; H, 6·0; N, 7·9; loss on drying at 110° *in vacuo*, 5·0. $C_{17}H_{19}ClN_2O_3,H_2O$ requires C, 57·85; H, 6·0; N, 7·95; H_2O, 4·8%).

Addition of dilute aqueous ammonia to a suspension of the hydrochloride (6 g.) in water, followed by isolation with benzene and crystallisation from light petroleum (b. p. 60—80°), gave the δ-*lactam ester* (IX) (4·7 g.) as colourless prisms (becoming green), m. p. 98—100°, $\lambda_{max.}$ 241, 272, 294, and 300 mμ (ε 15,000, 8900, 4600, and 4500), $\nu_{max.}$ (in CCl_4) 1740 (ester CO), 1710 [N(a)·CO], and 1640 cm.$^{-1}$ (indole C:C) (Found: C, 68·4; H, 6·05; N, 9·6. $C_{17}H_{18}N_2O_3$ requires C, 68·5; H, 6·1; N, 9·4%).

The N(b)-*acetyl derivative*, obtained with acetic anhydride and pyridine, crystallised from ethanol as colourless plates, m. p. 169°, $\nu_{max.}$ (in CCl_4) 1740, 1710, 1660 [N(b)·C:O], and 1640 cm.$^{-1}$ (Found: C, 66·8; H, 6·15; N, 8·5. $C_{19}H_{20}N_2O_4$ requires C, 67·0; H, 5·9; N, 8·2%).

The N(b)-*benzoyl derivative* (X), obtained (90% yield) by treatment of the base with benzoyl

chloride in pyridine, crystallised from ethanol as colourless needles, m. p. 209° (Found: C, 71·5; H, 5·7; N, 6·6. $C_{24}H_{22}N_2O_4$ requires C, 71·6; H, 5·5; N, 7·0%).

The N(b)-*methyl derivative* was prepared (83% yield) by reductive methylation with formaldehyde and Raney nickel under conditions similar to those used for the methylation of tetrahydropapaverine.[27] It was obtained from light petroleum (b. p. 60—80°) as needles, m. p. 108—109° (Found: C, 69·4; H, 6·4; N, 8·9. $C_{18}H_{20}N_2O_3$ requires C, 69·2; H, 6·45; N, 9·0%).

The washings, containing that part of the products of esterification soluble in ethanol, were concentrated, diluted with acetone, and kept for several days; a small amount (0·8 g.) of the *hydrochloride* of the *diethyl ester* (XI) separated. Recrystallisation from ethanol–acetone gave needles, m. p. 183—184° (decomp.) (Found: C, 59·4; H, 6·9; N, 7·0. $C_{19}H_{25}ClN_2O_4$ requires C, 59·9; H, 6·6; N, 7·4%). Addition of dilute aqueous ammonia to an aqueous solution of the hydrochloride, followed by isolation with ether, gave the *base*, obtained from ethanol as prisms, m. p. 108—109°, $\nu_{max.}$ (in CCl_4) 3485, 3380 (NH), and 1735 cm.$^{-1}$ (ester C:O) (Found: C, 66·4; H, 6·85; N, 8·2. $C_{19}H_{24}N_2O_4$ requires C, 66·3; H, 7·0; N, 8·1%).

The N(b)-*benzoyl compound* (XII), obtained with benzoyl chloride in pyridine, crystallised from ethanol as prisms, m. p. 169—170° (Found: C, 69·5; H, 5·9; N, 6·0. $C_{26}H_{28}N_2O_5$ requires C, 69·6; H, 6·3; N, 6·25%).

Condensation of (±)-*Tryptophan with* 2-*Oxoglutaric Acid.*—A solution of (±)-tryptophan (20 g.) and 2-oxoglutaric acid (17 g.) in 4N-hydrochloric acid (200 ml.) was heated on a steam-bath for 2 hr. Evolution of carbon dioxide rapidly ensued, followed by the separation of a fluffy crystalline mass. After being kept overnight in the refrigerator, the product (15 g.) was collected and washed with ice–water followed by a little acetone. Recrystallisation of a specimen from water gave the hydrochloride, m. p. 276—278° (decomp.), of the δ-lactam acid (VIII), apparently identical (mixed m. p. and infrared spectra) with the product obtained previously. As before, esterification of the crude product gave the ethyl ester (IX) (11·2 g.), m. p. 98—100°. Continuous extraction of the mother-liquors with ether gave a small quantity of non-basic material, from which the γ-lactam (VII) (0·9 g.), m. p. 260—262° (decomp.), was isolated.

Hydrolysis of the γ-*Lactam* (VII).—The γ-lactam (8 g.) was refluxed with glacial acetic acid (30 ml.) and concentrated hydrochloric acid (70 ml.) for 4 hr. After cooling, the hydrochloride which separated was collected, washed with ice–water, and dried *in vacuo*. Esterification with ethanol and hydrogen chloride followed by isolation of the base gave the δ-lactam ester (IX) (2·8 g.), m. p. 98—100°, identical with the compound obtained as above.

Reactions of the N(b)-*Benzoyl*-δ-*lactam with Sodium Ethoxide.*—(*a*) The *N*(*b*)-benzoyl-δ-lactam (X) (1 g.), dissolved in anhydrous ethanol (30 ml.), was added to a solution of sodium ethoxide (from 20 mg. of sodium) in anhydrous ethanol (5 ml.) under nitrogen. After 24 hr. at room temperature, glacial acetic acid (0·5 ml.) was added, followed by ice and ether. The extract was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. Fractional crystallisation of the residue from ethanol gave unchanged starting material (0·3 g.), m. p. 209°, together with the diethyl ester (XII) (0·22 g.), m. p. 169—170°, identical with the compound previously obtained.

(*b*) A solution of the *N*(*b*)-benzoyl-δ-lactam (X) (1 g.) in dry benzene (50 ml.) was refluxed for 4 hr. with sodium ethoxide (0·5 g.) under nitrogen. Addition of ice and 4N-hydrochloric acid (3 ml.) was followed by extraction with ether. The extract was washed with aqueous sodium hydrogen carbonate, dried, and evaporated, and the residue crystallised from ethanol, giving the *ethyl* β-*keto-ester* (XV) as prisms (0·13 g.), m. p. 253—254°, $\nu_{max.}$ (in $CHCl_3$) 3470, 3300, 1660, and 1630 cm.$^{-1}$ (Found: C, 71·9; H, 5·5; N, 7·0. $C_{24}H_{22}N_2O_4$ requires C, 71·6; H, 5·5; N, 7·0%).

Reduction of the δ-*Lactam* (IX) *with Raney Nickel.*—A solution of the δ-lactam (IX) (0·5 g.) in anhydrous ethanol (100 ml.) was refluxed with Raney nickel (3 g.) for 4 hr. Evaporation of the filtered solution gave a gum which solidified under ether. The product (0·2 g.) was collected, washed with ether, and crystallised from light petroleum (b. p. 60—80°), giving colourless needles, m. p. 158—160°, of *ethyl* 1,2,3,3a,4,5,11b,11c-*octahydro*-6-*oxocanthine*-2-*carboxylate*, $\nu_{max.}$ (in CCl_4) 1740 (ester CO) and 1670 [N(a)·CO] (Found: C, 68·05; H, 7·0; N, 9·5. $C_{17}H_{20}N_2O_3$ requires C, 68·0; H, 6·7; N, 9·35%).

2-*Benzoyl*-3-*carboxy*-1-2′-*carboxyethyl*-1,2,3,4-*tetrahydro*-1-β-*carboline* (XIII).—The *N*(*b*)-benzoyl-δ-lactam (X) (15 g.) was refluxed with a solution of sodium hydroxide (9 g.) in water (75 ml.) and ethanol (60 ml.) for ½ hr. The solution was poured into a stirred mixture of ice

[27] Tarbell and Craig, *J. Amer. Chem. Soc.*, 1948, **70**, 2783.

(300 g.) and concentrated hydrochloric acid (30 ml.), and the product (13·9 g.) was collected and washed with ice–water. Crystallisation from methanol gave the *dicarboxylic acid* (XIII) as colourless cubes, m. p. 223—226° (decomp.) (Found: C, 67·4; H, 5·3; N, 6·8. $C_{22}H_{20}N_2O_5$ requires C, 67·35; H, 5·15; N, 7·15%).

A solution of this acid (25 g.) in methanol (100 ml.) was stirred overnight with a solution of diazomethane (7 g.) in ether (500 ml.). Evaporation followed by crystallisation from methanol gave the *dimethyl ester* (XIV) (24·6 g.), m. p. 172—173°, $\nu_{max.}$ (in $CHCl_3$) 3450, 3350, 1735, and 1640 cm.$^{-1}$ (Found: C, 68·4; H, 5·8; N, 6·5. $C_{24}H_{24}N_2O_5$ requires C, 68·6; H, 5·75; N, 6·7%).

Dieckmann Condensation of the Dimethyl Ester (XIV).—A solution of the dimethyl ester (XIV) (10 g.) in anhydrous tetrahydrofuran (50 ml.) was added to a suspension of sodium hydride (8 g. of a 50% oil dispersion) in anhydrous tetrahydrofuran (50 ml.) stirred under nitrogen. After 24 hr., the mixture was refluxed for 3 hr., cooled, and diluted with ether containing methanol (5 ml.) to destroy unchanged hydride. Addition of ice and 4N-hydrochloric acid was followed by extraction with ether and dichloromethane, and the combined organic layers were washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The residue, which crystallised under ether, was collected, washed with ether, and recrystallised from methanol, giving colourless prisms, m. p. 238—240°, of the *methyl 2-benzoyl-1,2,3,4-tetrahydro-10-oxo-1,3-propano-β-carboline-11-carboxylate* (XVI) (8·4 g.), $\lambda_{max.}$ 225, 245—280 (shoulder), and 290 mμ (ε 47,000, 16,000—10,000, and 7800), $\nu_{max.}$ (in $CHCl_3$) 3450 (NH), 1665 and 1625 cm.$^{-1}$ [conjugated chelate β-keto-ester, and N(b)·COPh] (Found, in material dried at 100° *in vacuo*: C, 70·9; H, 5·3; N, 7·1. $C_{23}H_{20}N_2O_4$ requires C, 71·1; H, 5·2; N, 7·2%).

The compound was slowly soluble in aqueous sodium carbonate, and gave an immediate purple colour with ethanolic ferric chloride; it did not form a 2,4-dinitrophenylhydrazone, and it was recovered unchanged after attempts to prepare a ketal by treatment with ethylene glycol in benzene in the presence of toluene-*p*-sulphonic acid.

1,2,3,4-Tetrahydro-1,3-propano-β-carbolin-10-one (XVIII).—Hydrochloric acid (60 ml.) was added to a hot solution of the β-keto-ester (XVI) (4 g.) in acetic acid (45 ml.), and the mixture was refluxed for 3 hr. More hydrochloric acid (50 ml.) was added, and after a further 2 hours' heating, the dark solution was concentrated *in vacuo* and rendered alkaline with concentrated sodium hydroxide solution. Isolation with dichloromethane gave the crude *ketone* (XVIII) (1·2 g.), obtained from ethyl acetate (charcoal) as colourless prisms, m. p. 197—199°, $\nu_{max.}$ (in $CHCl_3$) 3460, 3210 (NH), and 1710 cm.$^{-1}$ (C:O) (Found: C, 74·6; H, 6·3; N, 12·3. $C_{14}H_{14}N_2O$ requires C, 74·3; H, 6·2; N, 12·4%).

The N(b)-Benzoyl Ketone (XIX).—(*a*) A stirred solution of the ketone (XVIII) (0·5 g.) in chloroform (30 ml.) containing an excess of anhydrous sodium carbonate, was treated with benzoyl chloride (0·3 ml.). After 16 hr., the filtered solution was washed successively with dilute hydrochloric acid, dilute sodium hydroxide solution, and water. Evaporation of the solvent, followed by crystallisation of the residue from ethyl acetate, gave the *2-benzoyl derivative* (XIX) (0·59 g.) as prisms, m. p. 204—206°, $\nu_{max.}$ (in $CHCl_3$) 3450, 3280 (NH), 1715 (C:O), and 1625 cm.$^{-1}$ [N(b)·COPh] (Found: C, 76·5; H, 5·5; N, 8·5. $C_{21}H_{18}N_2O_2$ requires C, 76·3; H, 5·5; N, 8·5%).

(*b*) The methyl β-keto-ester (XVI) (9·5 g.) in benzyl alcohol (7·5 ml.) was heated in an oil-bath at 140—160° for 5 hr., while a slow stream of nitrogen was passed through the mixture. Dilution of the cooled solution with ether resulted in the eventual separation of the product, which was collected, washed with ether, and crystallised from ethanol. Colourless prisms (9·9 g.), m. p. 197—202° (Found: C, 75·2; H, 5·5; N, 5·7. $C_{29}H_{24}N_2O_4$ requires C, 75·0; H, 5·2; N, 6·05%), of the *benzyl β-keto-ester* (XVII), were obtained.

A solution of this ester (5 g.) in ethanol (150 ml.) containing 10% palladised charcoal (0·5 g.) was shaken for 3 hr. with hydrogen (4 atm.). Evaporation of the filtered solution and crystallisation of the residue from ethyl acetate gave the 2-benzoyl derivative (XIX) (3·3 g.), identical with the compound, m. p. 204—206°, described above.

Reaction of the Dicarboxylic Acid (XIII) *with Acetic Anhydride.*—A solution of the dicarboxylic acid (XIII) (1 g.) and anhydrous sodium acetate (50 mg.) in acetic anhydride (30 ml.) was heated on a steam-bath for 2 hr. After evaporation to dryness *in vacuo*, the dark residue was taken up in dichloromethane and shaken with aqueous sodium carbonate. The organic layer was separated, and removal of the solvent was followed by chromatography of the residue on deactivated alumina. Chloroform–benzene (1 : 1 v/v) eluted a small amount (50 mg.) of the *N(b)*-benzoyl ketone (XIX), m. p. 204—206°, identical with the samples obtained previously.

Formation of the Ketal (XX).—Ethylene glycol (10 ml.) and toluene-*p*-sulphonic acid (0·1 g.) were added to a solution of the *N*(*b*)-benzoyl ketone (XIX) (1 g.) in benzene (120 ml.), and two-thirds of the solvent is removed by slow distillation during 4 hr. The cooled solution was washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated. Crystallisation of the residue from ethyl acetate afforded the *ketal* (XX) (0·69 g.) as colourless cubes, m. p. 234—238° (Found: C, 73·6; H, 6·1; N, 7·2. $C_{23}H_{22}N_2O_3$ requires C, 73·8; H, 5·9; N, 7·5%).

Methylation of the Ketal (XX).—To a stirred solution of potassium amide (from 3·9 g. of potassium) in liquid ammonia (150 ml.) was added a solution of the ketal (XX) (7·5 g.) in anhydrous tetrahydrofuran (75 ml.) and ether (25 ml.). After 1 hr., methyl iodide (14·2 g.) was added, and after a further 2 hr. the remaining ammonia was evaporated and the mixture was refluxed for 2 hr. Evaporation of the solvent, followed by addition of ice–water and isolation with dichloromethane, gave the 9-*methyl-ketal* (XXI) (7·6 g.), crystallising from benzene as rosettes, m. p. 157—160° (Found: C, 73·6; H, 6·2; N, 7·0. $C_{24}H_{24}N_2O_3$ requires C, 74·2; H, 6·2; N, 7·2%).

O-*Methylation of the Methyl* β-*Keto-ester* (XVI).—An excess of ethereal diazomethane was added to a solution of the methyl β-keto-ester (XVI) (5 g.) in dichloromethane (70 ml.) and methanol (10 ml.), and the mixture was set aside for 30 hr. Evaporation of the solvent and crystallisation of the residue from methanol furnished the enol ether, *methyl 2-benzoyl-1,2,3,4-tetrahydro-10-methoxy-9-methyl-1,3-prop-1′-eno-β-carboline-11-carboxylate* (XXIII) (4·9 g.) as prisms, m. p. 236—238°, $\lambda_{max.}$ 225, 250—280 (shoulder), and 290 mμ (ε 50,000, 8500, and 6300), $\nu_{max.}$ (in Nujol) 3310 (NH), 1720 (conjugated ester C:O), and 1620 cm.$^{-1}$ (Found: C, 71·3; H, 5·7; N, 7·0. $C_{24}H_{22}N_2O_4$ requires C, 71·6; H, 5·5; N, 7·0%).

N(a)-*Methylation of the Enol Ether* (XXIII).—To a suspension of sodium hydride (0·98 g. of a 50% oil dispersion) in 1,2-dimethoxyethane (10 ml.), stirred under nitrogen, was added a solution of the enol ether (XXIII) (5 g.) in 1,2-dimethoxyethane (400 ml.). After refluxing for 1 hr., methyl iodide (3·6 g.) was added to the cooled mixture, which was then stirred for 15 hr. at room temperature. Addition of an equal volume of ether containing sufficient methanol to destroy unchanged hydride was followed by separation of the organic layer, which was washed with aqueous sodium carbonate and then with water. Evaporation of the solvent, and removal of mineral oil from the residue with light petroleum (b. p. 40—60°), gave a glass which crystallised under ether. Recrystallisation from methanol gave the N(a)-*methyl enol ether* (XXIV) (4·1 g.), m. p. 166—167°, $\nu_{max.}$ (in $CHCl_3$) 1720 and 1640 cm.$^{-1}$ (Found: C, 72·5; H, 5·7; N, 6·6. $C_{25}H_{24}N_2O_4$ requires C, 72·1; H, 5·8; N, 6·7%).

Acidification of the combined alkaline mother-liquors, followed by isolation of the liberated product with dichloromethane and crystallisation from methanol, gave the αβ-unsaturated β-*methoxy-acid* (XXV) (0·4 g.) as cubes, m. p. 216—218° (Found, in material dried at 100° *in vacuo*: C, 71·4; H, 5·5; N, 6·7. $C_{24}H_{22}N_2O_4$ requires C, 71·6; H, 5·5; N, 7·0%). Ethereal diazomethane reconverted this compound into the ester (XXIV), m. p. 166—167°.

The N(a)-*Methyl-ketone* (XXVI).—(*a*) *From the ketal* (XXI). A solution of the *N*(*a*)-methyl-ketal (XXI) (7 g.) in glacial acetic acid (15 ml.) was heated on a steam-bath for 2 hr. with 4N-hydrochloric acid (1 ml.). Most of the solvent was removed *in vacuo*, the solution was cooled and diluted with water, and the product was isolated with ether. Crystallisation from ethyl acetate gave the N(a)-*methyl-ketone* (XXVI) (5·1 g.) as prisms, m. p. 155—157°, $\nu_{max.}$ (in $CHCl_3$) 1715 (C:O) and 1630 cm.$^{-1}$ [N(b)·COPh] (Found: C, 77·0; H, 5·7; N, 8·4. $C_{22}H_{20}N_2O_2$ requires C, 76·7; H, 5·8; N, 8·1%).

(*b*) *From the enol ether* (XXIV). A suspension of the enol ether (XXIV) (2·5 g.) in methanol (20 ml.) and 4N-sodium hydroxide (10 ml.) was refluxed for ½ hr. The methanol was evaporated, the cooled solution was acidified with hydrochloric acid, and the liberated product (2·3 g.) was crystallised from methanol, giving the αβ-unsaturated β-methoxy-acid (XXV), m. p. 216—218°. A solution of this acid (2·3 g.) in acetic acid (20 ml.) and concentrated hydrochloric acid (5 ml.) was refluxed for 20 min. Dilution with water, followed by isolation of the product (1·8 g.) with ether and crystallisation from methyl acetate, gave the ketone (XXVI), m. p. 155—157°.

Preparation of the N(a)-*Methyl* β-*Keto-ester* (XXII).—A solution of the enol ether (XXIV) (3·5 g.) in dioxan (50 ml.) and 4N-hydrochloric acid (25 ml.) was heated on a steam-bath for 1 hr. The solution, diluted with water, was shaken with dichloromethane, and the extract was washed with aqueous sodium hydrogen carbonate. Evaporation of the dried extract, and crystallisation of the residue from ethyl acetate, gave the β-*keto-ester* (XXII) (2·8 g.), m. p.

173—175°, $\nu_{max.}$ (in $CHCl_3$) 1670 and 1630 cm.$^{-1}$ (Found: C, 71·7; H, 5·7; N, 7·1. $C_{24}H_{22}N_2O_4$ requires C, 71·6; H, 5·5; N, 7·0%).

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