THE SYNTHESIS OF CRYPTOPLEURINE AND RELATED PHENANTHROQUINOLIZIDINES[1]

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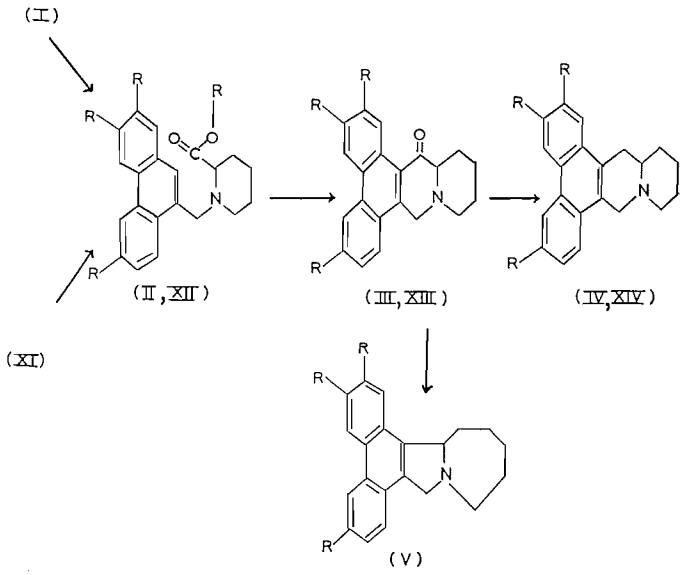
ABSTRACT

The synthesis of the alkaloid cryptopleurine has been accomplished by a sequence involving as the key step the cyclization of amino acid XII. It was established that the approach is applicable to the synthesis of simpler phenanthroquinolizidines such as IV. The biogenesis of the alkaloid is briefly discussed.

INTRODUCTION

The structure of the unusual alkaloid cryptopleurine (1) was deduced by Fridrichsons and Mathieson (2) by an X-ray investigation and its chemistry examined by Gellert (3). The remarkable physiological properties of this alkaloid have been described by de La Lande (1). Recently Bradsher and Berger (4) reported on a synthesis of cryptopleurine through the application of the general method already developed by Bradsher and Beavers (5, 6) for the synthesis of polycondensed quinolizines. In an independent investigation which was completed at the time Bradsher's report appeared, we accomplished the synthesis of cryptopleurine by a different route involving a series of well-characterized intermediates. Our approach differs from that of Bradsher's in that only reduced quinolizines are involved as intermediates (Chart I).



II, III, IV, V, R = H.
XII, XIII, XIV, R = CH_3O—.

CHART I.

In a model experiment, the synthesis of the phenanthroquinolizidone III was attempted through cyclization of the amino acid II, which was readily obtained from 9-chloromethylphenanthrene and methyl pipecolate followed by acid hydrolysis; this amino acid (II)

[1]*Manuscript received November 14, 1957.*
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was heated to 100° in polyphosphoric acid whereupon smooth ring closure to the desired amino ketone (III) occurred in 50% yield. Optimum conditions for this conversion were studied and are given in the experimental section. Evidence for structure III is based on elemental analysis, the infrared absorption spectrum which includes a strong band at 1664 cm.$^{-1}$ characteristic of an aromatic ketone, and the ultraviolet spectrum (curve B, Fig. 1) which shows the characteristic secondary peak of 9-phenanthryl ketones at 320 mμ (7,8). Reduction of the ketone (III) by the Huang-Minlon (9) procedure afforded

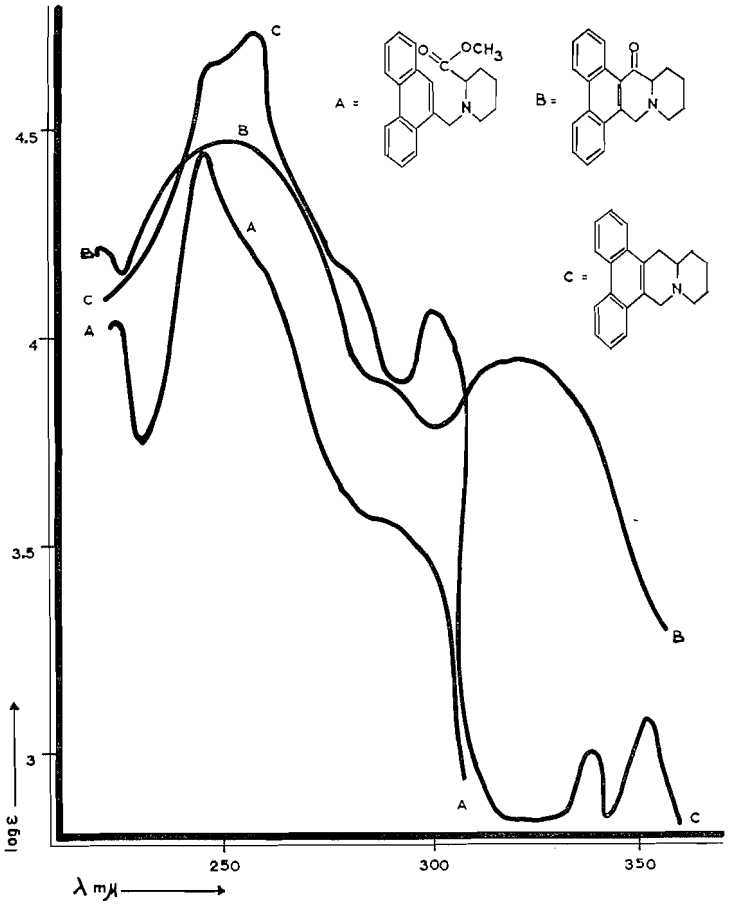

FIG. 1.

the desired phenanthroquinolizidine (IV) in high yield. Its ultraviolet absorption spectrum (curve C, Fig. 1) shows only the characteristic absorption bands of the phenanthrene nucleus, as expected. It is pertinent to note that Clemmensen reduction of the ketone (III) also produced a crystalline base in high yield of identical composition, but different from the one obtained by Wolff-Kishner reduction. Structure V is assigned to this product on the basis of the previous observations of Leonard and Wildman (10) on the reductive rearrangement of 1-quinolizidones.

With these results on hand, the synthesis of cryptopleurine itself could be considered, and a sequence of reactions also adopted by Bradsher (4) for the preparation of 9-bromomethyl-2,3,6-trimethoxyphenanthrene was carried out. Details of this synthesis are given in the experimental section and differ from Bradsher's synthesis in that only the

pure crystalline 9-chloromethyl derivative was used as a key intermediate. Reaction of the latter with methyl pipecolate followed by hydrolysis gave the amino acid (XII), which underwent smooth ring closure to 1-cryptopleurinone (XIII) when heated in polyphosphoric acid. The ultraviolet spectrum of the latter was recorded and as can be seen in Fig. 2 (curve E), the principal maxima exhibit a bathochromic shift with respect to the phenanthrene series and although the spectrum is similar to the one reported for

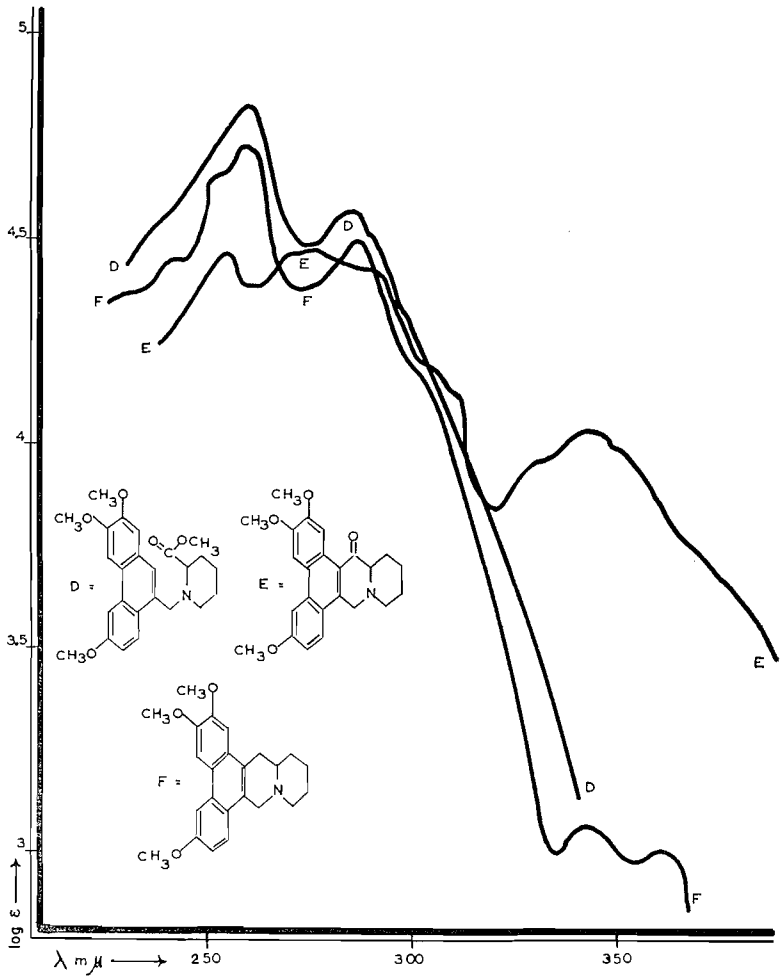

FIG. 2.

cryptopleurine, the peak at 345 mμ is of much greater intensity. Wolff-Kishner reduction of this ketone (XIII) gave rise to a mixture of phenolic compounds from which after treatment with diazomethane a small amount of crystalline material was obtained. The identity of the latter with cryptopleurine was ascertained by mixed melting point determination and by comparison of the infrared spectrum with an authentic specimen kindly provided by Dr. Bradsher. It should be noted that the spectrum was virtually superimposable on that of cryptopleurine except for the presence of a low-intensity band at 1700 cm.$^{-1}$ which is absent in the authentic specimen. It is most probable that this minor difference can be attributed to the presence of trace amounts of unchanged starting material in our sample or to deterioration of the latter on storage. The instability of

cryptopleurine has been commented upon before by Gellert (3). The small amount of material available precluded further purification or the preparation of the stable methiodide.

Additional proof of the identity of our material with cryptopleurine was obtained by comparison of the respective ultraviolet spectra, which proved to be identical in every respect (curve F, Fig. 2).

In view of Bradsher's recent report (4), no effort was made to improve the yield at the final stage of reduction although there can be little doubt that other procedures could be more successful.

The structure of cryptopleurine being of a novel type, it is of interest to attempt uncovering its biogenetical links with other classes of alkaloids. Robinson (11) suggested that the alkaloid originates from two tyrosine and one lysine unit. However, no mechanism was offered in support of this idea and we would like to suggest the scheme outlined in Chart II.

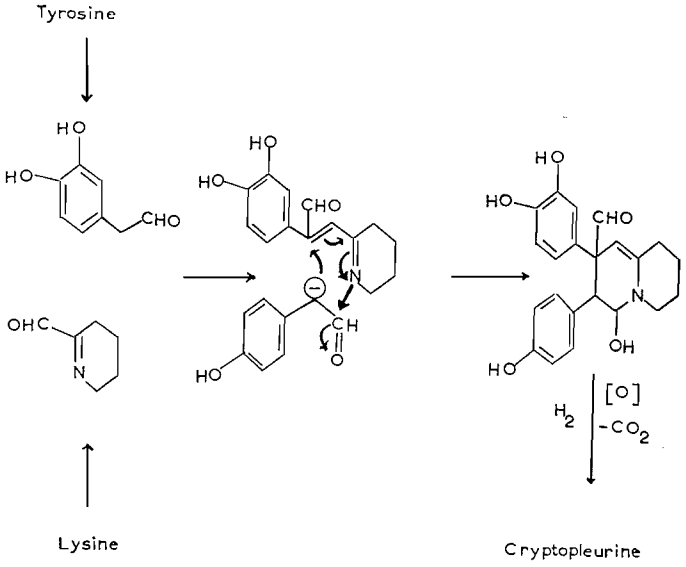

CHART II.

EXPERIMENTAL*

The spectra were determined with a Beckman spectrophotometer, Model DU, in 95% ethanol. Melting points are uncorrected and were obtained with a hot-stage microscope.

The pipecolic acid methyl ester was prepared by esterification of picolinic acid followed by hydrogenation in the presence of platinum oxide according to the procedure described by Tilford and co-workers (12).

The chloromethylphenanthrene was obtained by chloromethylation of phenanthrene as reported by Badger and co-workers (13).

Methyl N-(9-Phenanthrylmethyl)-pipecolate (1)

To a solution of 7 g. of methyl pipecolate in 150 ml. of methyl alcohol, containing 1.4 g. of potassium carbonate (freshly fused), 8.6 g. of 9-chloromethylphenanthrene was added at once. The mixture was then heated at 60°–70° and stirred for 12 hours. The suspension was evaporated almost to dryness and poured into water, and then extracted

**Microanalyses by Midwest Microlaboratories Inc., Indianapolis, Indiana, and Messrs. B. Girard and B. Mercier of our laboratories.*

with ether. The ethereal solution was washed with water, dried with sodium sulphate, and evaporated to a small volume. Treatment with dry hydrogen chloride gave a precipitate which after crystallization from acetone–ethyl acetate weighed 5 g., m.p. 177°–178°. λ_{max}: 255, 260, 289 mμ; log ε: 4.45, 4.40, 3.98 (curve A, Fig. 1). Calc. for $C_{22}H_{23}NO_2$. $HCl.H_2O$: C, 68.21; H, 6.70; N, 3.61. Found: C, 68.60; H, 6,92; N, 4.07.

Hydrolysis to the amino acid was accomplished by refluxing 5.5 g. of the ester (1) for 2 hours in 100 ml. of concentrated hydrochloric acid. After evaporation to half volume and cooling, 5.3 g. of crystalline material (II) was collected, m.p. 195°–200°. Calc. for $C_{21}H_{21}NO_2.HCl$: N, 3.9. Found: N, 3.8.

Phenanthro-(9,10;2,3)-1-quinolizidone (III)

To a solution of 10 g. of phosphorus pentoxide in 10 g. of sirupy phosphoric acid, 3 g. of the acid II was added at once. The mixture was heated to 100° for 6 hours with rapid stirring. After cooling the mixture was poured into ice-water, made alkaline with 50% sodium hydroxide solution, and extracted with chloroform.

The chloroform solution was washed with water, dried, and evaporated. The residue (III), weighing 1.4 g., crystallized from chloroform–methanol in light yellow prisms, m.p. 168°–169°. Calc. for $C_{21}H_{19}NO$: C, 83.74; H, 6.38; N, 4.64. Found: C, 83.46; H, 6.43; N, 4.62. The infrared spectrum showed (nujol mull) a strong band at 1664 $cm.^{-1}$. λ_{max}: 250, 260, 285, 320 mμ; log ε: 4.47, 4.42, 3.95, 3.95 (see Fig. 1, curve B).

Phenanthro-(9,10;2,3)-quinolizidine (IV)

To a solution of 0.6 g. of potassium hydroxide in 7 ml. ethylene glycol and 1 ml. hydrazine hydrate 0.5 g. of the ketone III was added. After refluxing for 1 hour (9), water was distilled, and distillation continued until the temperature of the vapors reached 195°; the mixture was then heated to 200° for 6 hours. The mixture was poured into water and extracted with ether. After evaporation of the solvent, the solid material was dissolved in hot ethanol and allowed to stand overnight: 0.3 g. of white needles was obtained, m.p. 169°–170° (sublimes at 155°). Calc. for $C_{21}H_{21}N$: C, 87.82; H, 7.31; N, 4.87. Found: C, 87.68; H, 7.52; N, 4.76. λ_{max}: 255, 260, 289, 330, 353 mμ; log ε: 4.48, 4.42, 3.90, 3.03, 3.07 (see Fig. 1, curve C).

3,4-Phenanthro-1-azabicyclo[0,3,5]decane (V)

To a refluxing solution of 0.4 g. of ketone III in 50 ml. of hydrochloric acid and water (3:1), 2.5 g. of zinc amalgam was added in small portions over a period of 4 hours. Every hour, 5 ml. of concentrated hydrochloric acid was added. After cooling, the solution was made alkaline and extracted with chloroform. The chloroform solution was evaporated and the residue dissolved in benzene. After filtration through a small column of basic alumina, the solution was evaporated to dryness. The solid material so obtained by crystallization from methanol gave 0.25 g. of white needles melting at 164°. Calc. for $C_{21}H_{21}N$: C, 87.82; H, 7.31; N, 4.87. Found: C, 87.46; H, 8.19; N, 5.05.

6-Nitro-3,4,4'-trimethoxy-α-phenylcinnamic Acid (VI)

Upon heating under reflux for 24 hours 58 g. of 6-nitroveratraldehyde (14) with 60 g. of homoanisic acid (15) in 300 ml. of acetic anhydride containing 5 g. of potassium acetate, 50 g. of crude product was obtained. After several crystallizations from acetic acid the m.p. was constant at 183°–184° (reported 185°–186°) (yield 38 g.).

2,3,6-Trimethoxyphenanthrene-9-carboxylic Acid (VII)

The preceding compound (37 g.) was dissolved in 112 ml. of 14% aqueous ammonia, and the resulting solution added at once to a hot solution of 228 g. of ferrous sulphate in

1 l. of 14% aqueous ammonia; the temperature was then maintained at 90° for a further 30 minutes. After cooling, careful neutralization of the mixture gave 30 g. of the corresponding amino acid. After several crystallizations from dilute ethanol, 25 g. of silky yellow crystals were obtained, m.p. 203°–204° (reported 206°–207°). Calc. for $C_{18}H_{19}NO_5$: N, 4.25%. Found: N, 4.23%.

This amino acid (23 g.) was suspended in 1400 ml. of water followed by the addition of 100 ml. of concentrated hydrochloric acid and 400 ml. dioxane. The mixture was cooled to 3°–5° and a solution of 9 g. of sodium nitrite in 100 ml. of water was added dropwise over a period of 2 hours, the temperature being kept below 5°. The clear, dark brown solution was then stirred for an additional 90 minutes.

After this time, 20 g. of activated copper bronze was added and stirring continued at room temperature for 24 hours. Evaporation *in vacuo* to half volume gave an amorphous precipitate which was collected by filtration and dissolved in chloroform. Evaporation of the solvent and crystallization of the residue from acetic acid afforded 12 g. of white crystalline material, m.p. 219°–220° (reported 222°). λ_{max}: 260, 280, 285 mμ; log ϵ: 4.58, 4.36, 4.33.

2,3,6-Trimethoxyphenanthrene-9-carboxylic Acid Methyl Ester (VIII)

The preceding acid (11.5 g.) (VIII) was heated under reflux for 2 hours in 250 ml. of methanol containing 15 ml. of sulphuric acid. The solution was then poured on ice and extracted with chloroform. Evaporation *in vacuo* left 10 g. of crude solid material. Chromatography on neutral alumina afforded in the petroleum ether eluate 5.4 g. of white crystals which crystallized from ethyl acetate – isopropyl alcohol, m.p. 156°–157°.* Calc. for $C_{19}H_{18}O_5$: C, 66.87; H, 5.52. Found: C, 66.76; H, 5.43. Extraction of the alumina with hot methanol gave 2 g. of white crystalline material, m.p. 85°–86°, which was not examined further.

2,3,6-Trimethoxy-9-phenanthrenemethanol (IX)

A solution of 5 g. of VIII in tetrahydrofuran was added dropwise with cooling to a suspension of 2.5 g. of lithium aluminum hydride in 100 ml. of ether. The mixture was then heated under reflux for 90 minutes, the excess of hydride decomposed with ethyl acetate, and the mixture poured into water and extracted with chloroform–ether. Evaporation of the solvent gave 4.5 g. of white solid mass. Crystallization from ethanol gave 4 g. of white silky needles, m.p. 186° (reported 185°–187°).

2,3,6-Trimethoxy-9-chloromethylphenanthrene (X)

To a solution of 3.7 g. of IX in 170 ml. of anhydrous chloroform containing 2.2 ml. of pyridine was added dropwise 2.96 ml. of thionyl chloride at ice temperature. The reaction was brought to completion by heating at 40°–60° while stirring for 60 minutes. The mixture was then poured on ice, and the chloroform layer separated, washed with dilute bicarbonate solution, then with water, and dried. The residue obtained by evaporation of the solvent was crystallized from benzene and weighed 3.45 g., m.p. 150°–151°. Calc. for $C_{18}H_{17}O_3Cl$: C, 68.35; H, 5.35; Cl, 11.08. Found: C, 68.11; H, 5.56; Cl, 11.30.

Methyl 2,3,6-Trimethoxy-N-9-phenanthrylmethyl-pipecolate (XI)

A mixture of 3 g. of X and 6 g. of methyl pipecolate as free base† in 100 ml. of anhydrous toluene was heated under reflux with stirring for 20 hours.

The residue obtained after evaporation of the solvent was poured into water and the

**The ethyl ester of III prepared in an analogous way was crystallized from ethanol and melted at 137° (reported 136.5°–137°).*

†The base was prepared by treatment of the hydrochloride with sodium methoxide at room temperature for 12 hours and vacuum distillation, b.p. 88°/16 mm.

pH adjusted to 9 with alkali followed by extraction with chloroform. After it was washed with water, the solution was dried and evaporated to dryness to yield a solid which was dissolved in a small volume of ether. Treatment of this solution with dry hydrogen chloride gave a precipitate which crystallized from acetone – ethyl acetate. The weight of the hydrochloride was 4.7 g., m.p. 165°–167°. λ_{max}: 250, 260, 285 mμ; log ε: 4.67, 4.80, 4.55 (see Fig. 2, curve D). Calc. for $C_{25}H_{29}O_5N.HCl.\frac{1}{2}H_2O$: C, 64.10; H, 6.41; N, 3.00. Found: C, 63.49; H, 6.84; N, 3.03.

2,3,6-Trimethoxyphenanthro-(9,10;2,3)-1-quinolizidone (XIII)

The above ester (XI) was hydrolyzed by heating for 90 minutes in 80 ml. of hydrochloric acid. After cooling a microcrystalline material was collected and dried, and without further purification, 2.4 g. of this amino acid (XII) was added to a mixture of 10 g. of phosphorus pentoxide and 10 g. of phosphoric acid and the solution heated for $3\frac{1}{2}$ hours. After cooling, the violet mixture was slowly poured on ice, and after 50% potassium hydroxide solution had been added to pH 9, the mixture was extracted with chloroform.

The solution was washed with water, dried, and evaporated *in vacuo* under nitrogen to give 1 g. of a slightly yellow solid which crystallized from acetone–methanol as yellow prisms, m.p. 154.5°–155°. λ_{max}: 255, 270, 290, 310, 345 mμ; log ε: 4.42, 4.51, 4.40, 4.02, 4.01 (see Fig. 2, curve E). Calc. for $C_{24}H_{25}O_4N$: C, 73.66; H, 6.39. Found: C, 73.87; H, 6.84.

2,3,6-Trimethoxyphenanthro-(9,10;2,3)-quinolizidine (XIV)

The reduction of 0.45 g. of XIII was effected as described above in the case of IV except that the reaction was carried out under nitrogen. The crude reaction product was chromatographed on basic alumina but no pure substance could be obtained from the various eluates. A ferric chloride test was strongly positive for all of the main fractions; a 0.25 g. portion of the brown waxy material was therefore treated in methanol–ether with a large excess of diazomethane and allowed to stand overnight.

Evaporation of the solvent *in vacuo* gave an oil which was dissolved in ether and extracted with dilute hydrochloric acid. Neutralization of the acidic solution gave a precipitate which was extracted with ether. After evaporation of the solvent, the residue was dissolved in a small volume of acetone and allowed to stand at −10°. The solution slowly deposited 5 mg. of light yellow needles which after several recrystallizations had m.p. 199°–201° (reported 197°–198° (3), 199°–200° (4)). Mixture with an authentic specimen of cryptopleurine gave no depression of the melting point. λ_{max}: 258, 286, 345, 358 mμ; log ε, 4.70, 4.47, 3.12, 2.97.

The infrared spectrum was recorded with a Baird double-beam instrument using the KBr pellet technique. The spectrum was identical to that of cryptopleurine except for the presence of a low-intensity band at 1700 $cm.^{-1}$.

ACKNOWLEDGMENTS

We express our gratitude to Dr. C. K. Bradsher for supplying an authentic specimen of cryptopleurine and to Dr. H. Hooper of Bristol Laboratories Inc. for the infrared determinations. We also express our thanks to the National Research Council of Canada for a fellowship to one of us (P.M.) and for financial assistance.

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