methanol, m.p. 99–100°. This material was identical with that prepared from the 7-keto compound and with dihydrodeaminocolchinol methyl ether.[2]

5-Amino-1,2,3,9-tetramethoxydibenzo[a,c][1,3]cycloheptadiene (Isocolchinol Methyl Ether) (II).—A solution of 845 mg. (2.46 mmoles) of 1,2,3,9-tetramethoxydibenzo[a,c][1,3]cycloheptadiene-5-one oxime in 20 ml. of glacial acetic acid and 3 ml. of 60% aqueous perchloric acid was hydrogenated at 25° and atmospheric pressure in the presence of 440 mg. of 5% palladized carbon. When hydrogenation ceased after the absorption of slightly more than 200 mole % of hydrogen, the mixture was filtered and made alkaline with 10 *N* potassium hydroxide after adding 50 ml. of water. Chloroform (six 50-ml. portions) was used to extract the aqueous solution and the residue from evaporation of the combined chloroform extracts was distilled at 90° (0.1 mm.) onto a cold finger. Crystallization of the distillate from methylcyclohexane gave 770 mg. (95% yield) of isocolchinol methyl ether, m.p. 113–115°.

Anal. Calcd. for $C_{19}H_{23}O_4N$: C, 69.3; H, 7.0; N, 4.3. Found: C, 69.4; H, 7.0; N, 4.1.

By heating the amine (100 mg.) on the steam-bath for 5 min. with 0.4 ml. of acetic anhydride and adding 20 ml. of water, 110 mg. of crystalline **N-acetylisocolchinol methyl ether** was obtained, m.p. 213–214°, unchanged on recrystallization from benzene.

Anal. Calcd. for $C_{21}H_{25}O_5N$: C, 67.9; H, 6.8. Found: C, 68.2; H, 7.0.

BERKELEY, CALIFORNIA

[CONTRIBUTION FROM CHEMISTRY LABORATORY, UNIVERSITY OF NEW BRUNSWICK]

Synthesis of Dimethylapoerysopine and an Approach to the Total Synthesis of the Unrearranged Erythrina Bases

BY K. WIESNER, Z. VALENTA, A. J. MANSON AND F. W. STONNER

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Apoerysopine dimethyl ether II (R = CH_3) was synthesized and found identical with the methylation product of authentic apoerysopine. The reaction of 1,2-dialkyl-3,4-dihydroisoquinolinium bromides with Grignard reagents is described. By the use of this reaction the lactam diester XXXIII, which offers good possibilities for the elaboration of various erythrina alkaloids, was prepared.

Introduction

Carmack, MacKusick and Prelog[1] have proposed the structure II (R = H) for apoerysopine, which can be obtained by (*e.g.*) treatment of the alkaloid erythraline with refluxing hydrobromic acid. For erythraline itself the above authors proposed the structure I. It was the purpose of this investigation to confirm these proposals by an unambiguous synthesis of the structure II (R = CH_3) and identification of the synthetic product with dimethylapoerysopine obtained by methylation of apoerysopine. It was also intended to develop methods for the total synthesis of compounds of the general structure I.

The first part of this program has now been completed and has been reported in a preliminary communication.[2] In a preliminary communication[3] we have reported a general approach to the synthesis of compounds of the type XXX and we now describe the preparation of compound XXXIII. This or an analogous compound seems not only to be a suitable intermediate for the preparation of the erythrina skeleton, but might be useful in a total synthesis of the various erythrina alkaloids since the introduction of the necessary functional groups and double bonds would probably offer no insuperable difficulty. The synthesis by another method of a compound possessing the erythrina carbon and nitrogen skeleton has been subsequently reported by Belleau[4]; this compound could not however be connected with any derivative of the natural alkaloids.

Discussion of Results

The synthesis of dimethylapoerysopine was begun with the preparation of 2-carboxy-4,5-dimethoxy-2′-nitrobiphenyl (III). This compound was obtained by the Ullmann reaction between methyl 6-bromoveratrate and *o*-nitrobromobenzene. The reaction products were saponified and the compound III separated from the symmetrical 4,5,-4′,5′-tetramethoxy-2,2′-dicarboxy-biphenyl IV by a countercurrent distribution using three funnels. The acid III was then converted by an Arndt–Eistert reaction[5] into the homologous ester V. Hydrogenation of V with Raney nickel gave the corresponding aminoester with consumption of the theoretical volume of hydrogen. On heating this aminoester in an atmosphere of nitrogen to 200°, the lactam VI was quantitatively obtained. Lithium aluminum hydride reduction of this compound gave the secondary amine VII. The ultraviolet spectrum of VII taken in alcoholic hydrochloric acid is parallel with the spectrum of dimethylapoerysopine prepared by methylation of apoerysopine with diazomethane (Fig. 1). The fact that no rearrangement has taken place in the course of the Ullmann reaction was demonstrated by hydrogenation of compound III in alkaline solution with Raney nickel and oxidation of the crude product with potassium permanganate. A good yield of *m*-hemipic acid VIII was obtained and characterized as the methylimide.

In a model experiment 2-aminobiphenyl was chloroacetylated and the product was fused with aluminum chloride; a good yield of the 7-phenyloxindole IX resulted. This compound was smoothly reduced to 7-phenyldihydroindole by lithium aluminum hydride. The chloroacetyl derivative of VII was prepared in an analogous manner but treatment of this compound under a variety of conditions with aluminum chloride followed by treatment with diazomethane gave small amounts of starting material as the only detectable product.

(1) M. Carmack, B. C. MacKusick and V. Prelog, *Helv. Chim. Acta*, **34**, 1601 (1951).

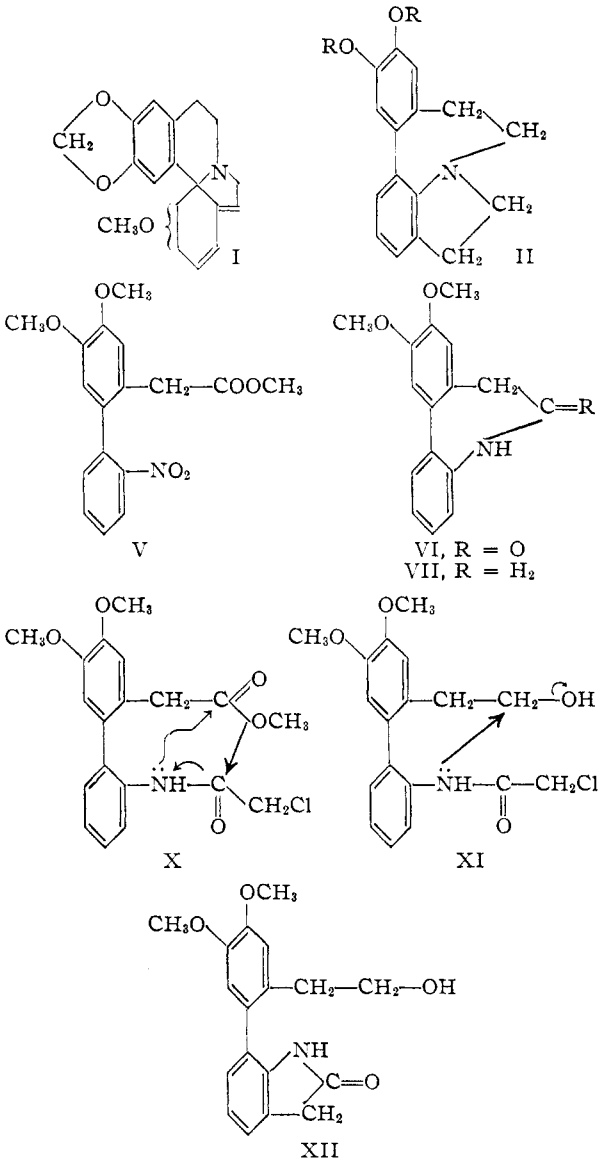
(2) Z. Valenta and K. Wiesner, *Chemistry & Industry*, 402 (1954).

(3) A. J. Manson and K. Wiesner, *ibid.*, 641 (1953).

(4) B. Belleau, THIS JOURNAL, **75**, 5765 (1953).

(5) W. E. Bachman and W. S. Struve in Roger Adams, "Organic Reactions I," John Wiley and Sons, Inc., New York, N. Y., 1942.

FORMULA TABLE I



It was assumed that closure of the five-membered ring is made difficult by the presence of the seven-membered ring, since otherwise the different behavior of the model compound could not be explained. Consequently, the N-chloroacetylaminoester X was prepared by hydrogenating the nitroester V and immediately chloroacetylating the product. However, heating of X with aluminum chloride followed by remethylation with diazomethane gave the lactam VI mentioned above. The mechanism of this reaction is indicated by the arrows in formula X.

In another attempt the aminoester prepared by hydrogenation of V was further reduced to the corresponding aminoalcohol by lithium aluminum hydride; the N-chloroacetyl derivative XI was then prepared from this compound. Heating of XI with aluminum chloride gave as main product the already described chloroacetyl derivative of VII. The mechanism by which the latter compound is formed is indicated by the arrows in formula XI. A trace of a second product was obtained by fractional crystallization. This compound was obtained in so small a quantity that it could not be purified for analysis; but its ultraviolet spectrum shows general similarity to the spectrum of 7-phenyloxindole (see Fig. 2). Very probably it was the desired product XII.

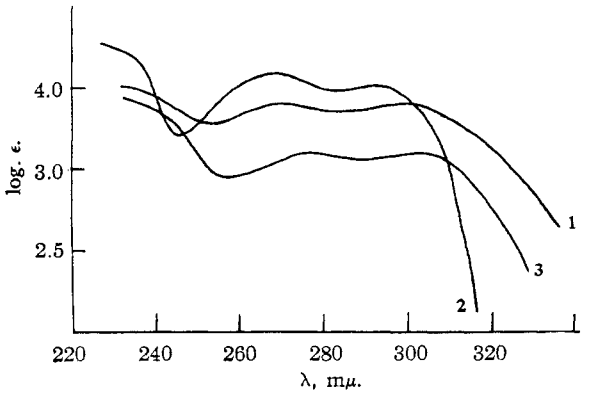


Fig. 1.—Ultraviolet spectra in ethanolic hydrochloric acid: 1, dimethylapoerysopine; 2, compound VII; 3, x-bromodimethylapoerysopine.

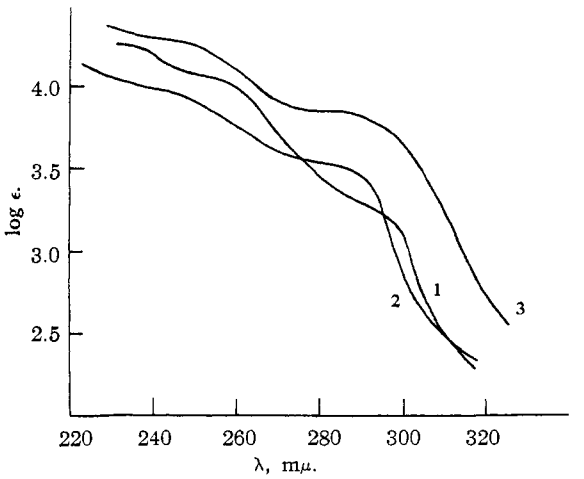


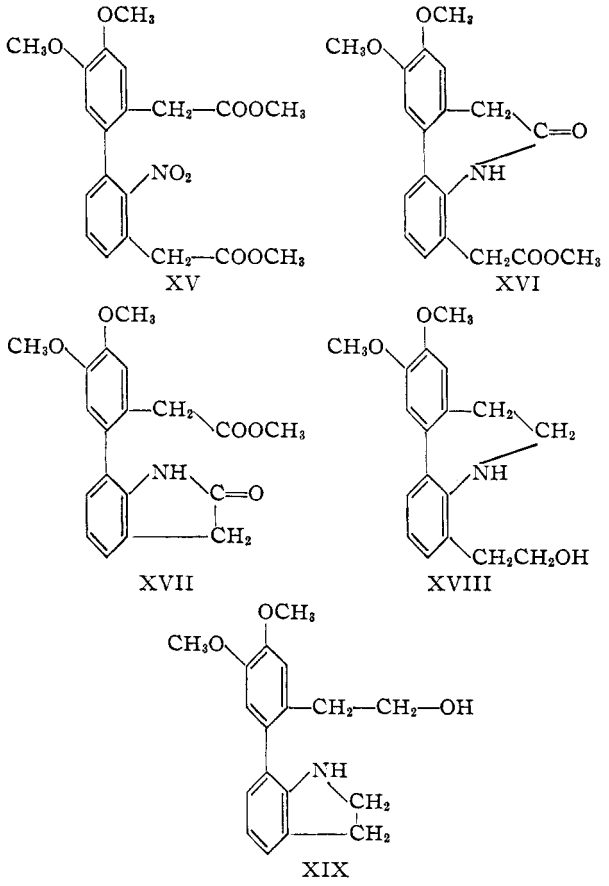
Fig. 2.—Ultraviolet spectra in ethanol: 1, 7-phenyloxindole; 2, compound XII; 3, compound XVII.

At this stage it was decided to synthesize an intermediate of the type XII by an approach which would not require the formation of a carbon–carbon bond in the ultimate cyclization. The Ullmann reaction between 2-nitro-3-bromotoluene[6] and methyl 6-bromoveratrate was performed and the mixture was worked up exactly as in the previous case. This led to the isolation of 2-carboxy-4,5-dimethoxy-2′-nitro-3′-methylbiphenyl (XIII). On oxidation of XIII with permanganate 2,3′-dicarboxy-4,5-dimethoxy-2′-nitrobiphenyl XIV was isolated in 45% yield. The dichloride of XIV was prepared by the action of thionyl chloride and the Arndt–Eistert reaction performed on this compound gave the diester XV. The corresponding amino diester was obtained as an oil by Raney nickel hydrogenation and was not characterized. On sublima-

(6) L. A. Elson, C. S. Gibson and J. D. A. Johnson, *J. Chem. Soc.*, **129**, 2735 (1929).

tion with a cold finger the amino diester yielded a mixture. One of the components was very insoluble in methanol and could be separated in crystalline form. It was the lactam ester XVI since its absorption spectrum is practically identical with that of the previously described lactam VI. The mother liquors after the separation of XVI consisted practically entirely of the oily oxindole XVII. This was characterized by its ultraviolet spectrum which does not leave much doubt as to its identity (see Fig. 2). The infrared spectra of all three oxindoles IX, XII and XVII have an amide carbonyl band at 1690 cm.$^{-1}$.

FORMULA TABLE II



The crude mixture of compounds XVI and XVII was reduced with lithium aluminum hydride to give a mixture of the alcohols XVIII and XIX. This was heated with phosphorus tribromide in benzene on a water-bath, after which the solution was diluted with methanol and added with rapid stirring to a boiling suspension of sodium carbonate in methanol under nitrogen. The reaction product was chromatographed and converted into a picrate. Analysis and mixed melting point showed the identity of this picrate with dimethylapoerysopine picrate. The liberated free base had ultraviolet (see Fig. 1) and infrared spectra identical with those of authentic dimethylapoerysopine.

It is of interest to note that the use of phosphorus pentabromide in the above sequence leads to a compound $C_{18}H_{18}NO_2Br$ which contains bromine. Its ultraviolet (see Fig. 1) and infrared spectra are almost identical with those of dimethylapoerysopine. Treatment of authentic dimethylapoerysopine with phosphorus pentabromide converts it into the same product. It is obviously an x-bromodimethylapoerysopine with a bromine atom substituted in one of the two benzene nuclei.

The work described in the previous section establishes beyond any reasonable doubt the correctness of the structure proposed by Carmack, MacKusick and Prelog[1] for the erythrina alkaloids. We have therefore extended our synthetic studies with a view to developing methods which could ultimately lead to a synthesis of various members of the erythrina class. Model experiments were first performed to study the reaction of quaternary 1-alkyl-dihydroisoquinolinium salts with a large excess of Grignard reagent.

The methobromide XX, vigorously stirred in refluxing ether, was treated with an excess of ethyl and allylmagnesium bromide. The 1,1-dialkyl tetrahydroisoquinolines XXI and XXII were obtained in good yield. Both products showed the typical ultraviolet spectra of 6,7-dimethoxytetrahydroisoquinolines, with a sharp maximum at 283 mμ (log ϵ 3.6). The next step was to repeat the preceding reaction using a compound in which three rings of the erythrina skeleton are already present. Heating of γ-butyrolactone with homoveratrylamine gave a mixture of N-homoveratrylpyrrolidone XXIII and the hydroxyamide XXIV. The compounds were separated easily by chromatography. The infrared spectrum of XXIII showed no band in the hydroxy region and a carbonyl band at 1675 cm.$^{-1}$. Compound XXIV on the other hand showed in the infrared a prominent hydroxyl band and an amide carbonyl at 1660 cm.$^{-1}$. Compound XXIII gave on reflux with phosphorus oxychloride in toluene a base which was converted by hydrobromic acid to the quaternary bromide XXV (X = Br).[7] The ultraviolet spectra of the free base corresponding to the bromide XXV were taken in neutral, acidic and alkaline alcohol and were identical with the spectra reported by us previously[8] for compounds of analogous structure. Treatment of XXV (X = Br) with allylmagnesium bromide under identical conditions as before gave 40% of XXVI. The ultraviolet spectrum of XXVI was again identical with the spectrum of a 6,7-dimethoxytetrahydroisoquinoline. At this stage we were encouraged by preliminary indications[9] that the compounds XXI, XXII and XXVI exhibit an effect on frog muscle similar to that of curare.

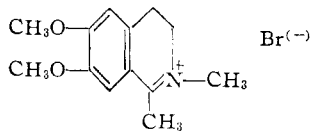
For a final approach to the erythrina alkaloids it is necessary to have a chain on the five-membered ring which will be capable of cyclization with the angular group inserted by the Grignard reaction. This cyclization should at the same time produce functional groups capable of transformation into the functional groups of an actual erythrina alkaloid. In order to obtain such a compound (which however does not necessarily have to be the one ulti-

(7) Compound XXV (X = Cl) has been reported previously by R. Child and F. L. Pyman, *J. Chem. Soc.*, 36 (1931).

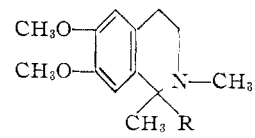
(8) K. Wiesner, F. H. Clarke and S. Kairys, *Can. J. Research*, **B28**, 234 (1950).

(9) For this we are greatly indebted to Professor Althea Warren of the Biology department of this University.

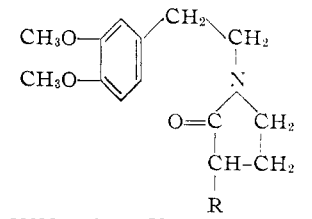
FORMULA TABLE III



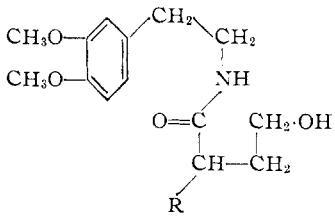
XX



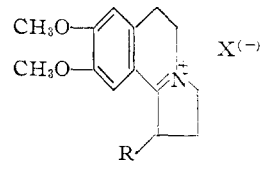
XXI, R = C_2H_5
XXII, R = $-CH_2-CH=CH_2$



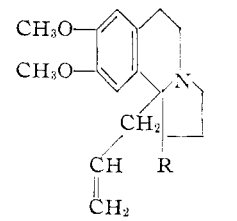
XXIII, R = H
XXVIII, R = $-CH_2-CH=CH_2$



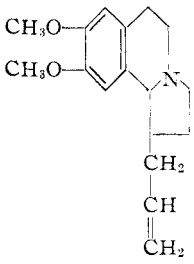
XXIV, R = H
XXVII, R = $-CH_2-CH=CH_2$



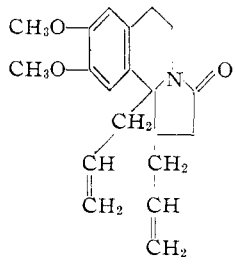
XXV, R = H
XXIX, R = $-CH_2-CH=CH_2$



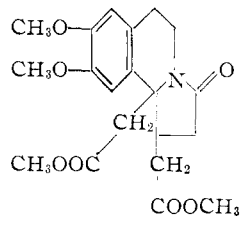
XXVI, R = H
XXX, R = $-CH_2-CH=CH_2$



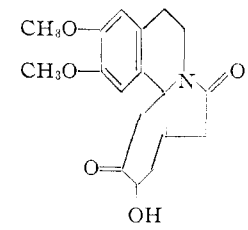
XXXI



XXXII



XXXIII



XXXIV

mately most useful) the above synthesis was repeated using α-allyl γ-butyrolactone. The latter compound was easily prepared by treating the sodio derivative of allyl malonate with 2-chloroethanol, followed by saponification of the product and lactonization of the resulting substituted malonic acid with simultaneous loss of carbon dioxide. Fusion of this substituted butyrolactone with homoveratrylamine gave a good yield of the hydroxyamide XXVII. The infrared spectrum of this compound again showed a strong hydroxy band and an amide carbonyl at 1640 cm.$^{-1}$.

A second oily product was separated by chromatography and although it was not analyzed it obviously was the pyrrolidone XXVIII. Its infrared spectrum had no hydroxy band and showed a carbonyl band at 1680 cm.$^{-1}$. Identity was established by the subsequent cyclization reaction. Cyclization in exactly the same way as before with phosphorus oxychloride converted XXVIII into a crystalline base, which in aqueous solution may be represented by XXIX (X = OH). As the base was unstable and the bromide gummy, the compound was characterized as the picrolonate which crystallized with one molecule of water. The ultraviolet spectra of the free base in neutral, acidic and alkaline alcohol were identical with those of the base XXV.

The hydroxyamide XXVII, subjected to cyclization in the same way as described for XXVIII, produced a chlorine-containing base in good yield. On standing in dry ether in the ice-box overnight this base was converted by intramolecular quaternary salt formation into XXIX (X = Cl). This was confirmed by the identity of its picrolonate and of the ultraviolet spectra with those of the product obtained by the cyclization of XXVIII. It is thus possible to perform the cyclization reaction on the mixture of XXVIII and XXVII which is obtained quantitatively by fusing allylbutyrolactone with homoveratrylamine. The bromide XXIX (X = Br) was further characterized by reduction with sodium borohydride.[10] The reduction product XXXI gave a crystalline picrate.

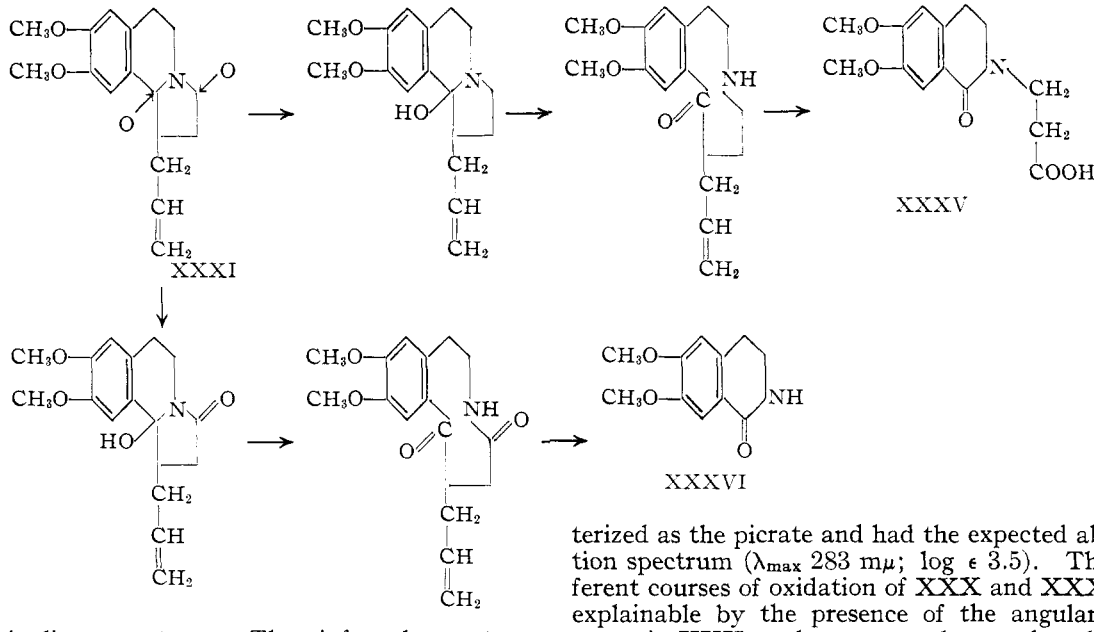
The gummy bromide XXIX was deposited on quartz sand and treated with an excess of allylmagnesium bromide in the same way as in the previous cases. A 65% yield of XXX was obtained. This compound gave a homogeneous picrate. A careful search in the mother liquors for a second isomer proved fruitless. As it may be assumed that the Grignard reagent approaches from the less hindered side we believe that the two allyl groups in XXX are in the *trans* configuration.

Attention was then directed toward oxidation of XXX and XXXI in order to develop the synthesis further and at the same time obtain corroboration of the structures assigned. Oxidation of XXX in acetone with ten moles of potassium permanganate gave a small amount of neutral material and a considerable yield of acidic material which was very soluble in water.

The neutral substance crystallized after chromatography. The structure XXXII was assigned to it on the basis of its analysis, ultraviolet and infrared spectra. The ultraviolet spectrum was identical with the typical 6,7-dimethoxytetrahydro-

(10) B. Witkop and J. B. Patrick, THIS JOURNAL, **75**, 4474 (1953).

FORMULA TABLE IV



isoquinoline spectrum. The infrared spectrum had no band in the OH–NH region and an amide carbonyl at 1684 cm.$^{-1}$.

The acidic material was esterified with diazomethane and the crystalline lactam diester XXXIII isolated by chromatography on neutral alumina. The ultraviolet spectrum of XXXIII is identical with that of XXXII. The infrared shows no band in the OH–NH region, a lactam carbonyl at 1700 cm.$^{-1}$ and an ester carbonyl at 1725 cm.$^{-1}$.

In the preliminary experiments to be reported in a later communication, the cyclization of XXXIII to XXXIV by the method of Sheehan[11] was explored and seems to be promising; however, in the present communication we wish to draw attention to the interesting course of the oxidation of compound XXXI.

XXXI was oxidized in acetone at room temperature with six moles of permanganate. A crystalline acid $C_{14}H_{17}NO_5$ and a small yield of a neutral crystalline substance $C_{11}H_{13}NO_3$ was obtained. The acid may be formulated as XXXV and the neutral substance as XXXVI. The formation of these two products under mild conditions may be rationalized by the formula scheme XXXI–XXXVI which is self-explanatory.

The ultraviolet spectra of XXXV and XXXVI (λ_{max} 230 mμ (log ϵ 4.1); 263 mμ (log ϵ 3.8); 297 mμ (log ϵ 3.7)) are in agreement with this formulation. The infrared spectrum of XXXVI shows a prominent NH peak at 3100 cm.$^{-1}$ and a strong amide carbonyl band at 1660 cm.$^{-1}$. Compound XXXVI has already been described in the literature[12] and the reported melting point (175°) agrees with that found by us.

Esterification of the acid XXXV with diazomethane and reduction with lithium aluminum hydride gave 6,7-dimethoxy-N-hydroxypropyltetrahydroisoquinoline (XXXVII). This was characterized as the picrate and had the expected absorption spectrum (λ_{max} 283 mμ; log ϵ 3.5). The different courses of oxidation of XXX and XXXI are explainable by the presence of the angular allyl group in XXX, and consequently may be adduced as evidence of the correctness of the structures assigned to these compounds.

Acknowledgments.—We wish to thank the National Research Council, Ottawa, for the support of these investigations over the past two years. We also thank Howard Smith Paper Mills Ltd. for a gift of a large amount of vanillin and the Merck Company, Montreal, for the gift of a large amount of solvents. It is a pleasant duty to express our gratitude to Professor F. J. Toole, Dean of the School of Graduate Studies, for his constant support of our work as well as for reading and revising this manuscript. The analyses were performed by Dr. R. Dietrich, Zürich, and Dr. S. M. Nagy, M. I. T. The infrared spectra were taken by Dr. R. L. Bohon, Champaign, Illinois.

Experimental

2-Carboxy-4,5-dimethoxy-2′-nitrobiphenyl (III).—Methyl 6-bromoveratrate (43 g.) and *o*-nitrobromobenzene (86 g.) were subjected to the Ullmann reaction with 129 g. of activated copper powder.[13] The mixture of both substances was heated to 240° under constant stirring with a thermometer and the copper slowly added in the course of 45 minutes. After cooling the mixture was extracted in a Soxhlet apparatus with methanol and the extracted material saponified by refluxing for 5 hours with one liter of 10% sodium carbonate; the acidic material was then separated in the usual way. The yield of acids was 56 g. The acid mixture was recrystallized once from a small volume of methanol using charcoal to remove the brown color. The crystalline mixture was then dissolved in 1,300 ml. of chloroform and shaken with the same volume of phosphate buffer *p*H 7. The chloroform layer was then separated and shaken with two more equal amounts of the same buffer. The identical procedure was then repeated six times using the same three buffer solutions and six equal amounts of pure chloroform. All seven portions of chloroform were then combined. After evaporating the chloroform to dryness, almost pure compound III was obtained. The yield was 19 g. after one recrystallization. The analytical sample melted at 207° after crystallization from methanol. It was dried in high vacuum for analysis.

(11) J. C. Sheehan, R. A. Coderre and P. A. Cruickshank, THIS JOURNAL, **75**, 6231 (1953).

(12) E. Späth and A. Dobrowsky, *Ber.*, **58**, 1274 (1925).

(13) E. C. Kleiderer and R. Adams, THIS JOURNAL, **55**, 4225 (1933).

Anal. Calcd. for $C_{15}H_{13}NO_6$: C, 59.42; H, 4.32; N, 4.62; OCH_3, 20.44. Found: C, 59.43; H, 4.39; N, 4.73; OCH_3, 19.93.

The dicarboxylic acid IV was obtained by strong acidification of the buffer solution. It was recrystallized to a melting point 261° from a mixture of methanol and benzene.

Anal. Calcd. for $C_{18}H_{18}O_8$: C, 59.68; H, 5.01; OCH_3, 34.28. Found: C, 59.75; H, 4.87; N, 0.00; OCH_3, 34.32.

The Nitroester V.—Compound III (36 g.) was dissolved in 2.5 l. of dry benzene and treated with an equal weight of oxalyl chloride. The solution was kept at 30° until the gas evolution ceased. The solvent and oxalyl chloride were then removed *in vacuo* at 30° and several small volumes of dry ether were added and evaporated to dryness. The acid chloride was then dissolved in 2.5 liters of dry ether and added slowly to a stirred solution of diazomethane (prepared from 60 g. of nitrosomethylurea) in ether at 0°. The yellow diazoketone deposited slowly and the mixture was stirred overnight at room temperature. The diazoketone melted, after filtering and washing with ice-cold ether, at 127°. It was suspended in 2 liters of dry methyl alcohol and treated with approximately 5 g. of freshly prepared silver oxide which was gradually added. The mixture was kept at 50–60°. The heating was continued until gas evolution completely ceased. The mixture was then refluxed for 15 minutes, when charcoal was added and the mixture was filtered. The dark-colored residue which remained after evaporating the solvent was sublimed and recrystallized from methanol (yield 29 g.). The product, compound V, formed light yellow crystals, m.p. 51°. It was resublimed for analysis.

Anal. Calcd. for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.13. Found: C, 61.57; H, 5.15.

Lactam VI.—Compound V was hydrogenated in alcohol with freshly prepared Raney nickel; the theoretical amount of hydrogen was consumed in one hour. The resulting aminoester melted at 117° after recrystallization from methanol. It was immediately converted to the lactam VI by heating for 30 minutes under nitrogen to 180°. The lactam was recrystallized from methanol (m.p. 202°) and sublimed for analysis.

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 70.88; H, 5.62; N, 5.20. Found: C, 71.32; H, 5.61; N, 5.41.

Cyclic Amine VII.—Reduction of VI with lithium aluminum hydride was performed in the standard manner using the Soxhlet technique because of the insolubility of the compound in ether. The amine VII, recrystallized from ether–petroleum ether, melted at 147–148°. It was sublimed in high vacuum for analysis.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.48; OCH_3, 24.31. Found: C, 75.36; H, 6.62; N, 5.63; OCH_3, 24.19.

N-Chloroacetyl VII.—To compound VII (500 mg.), dissolved in 50 ml. of dry acetone, 320 mg. of dry pyridine was added. The solution was cooled on ice and 680 mg. of chloroacetyl chloride in acetone was added with stirring. After standing one hour at room temperature the solution was refluxed for 10 minutes, evaporated to a small volume and chloroform added. The chloroform solution was then washed with dilute sulfuric acid, dried and evaporated to dryness. The product was recrystallized from alcohol–ether (m.p. 152°).

Anal. Calcd. for $C_{18}H_{18}NO_3Cl$: C, 65.20; H, 5.50; N, 4.22; Cl, 10.71; OCH_3, 18.69. Found: C, 65.27; H, 5.40; N, 4.24; Cl, 10.60; OCH_3, 18.64.

N-Chloroacetyl-2-aminobiphenyl.—The chloroacetylation of aminobiphenyl was performed in exactly the same manner as in the above experiment, except that dry ether was used as solvent. The product was recrystallized from chloroform–petroleum ether and melted at 97.5–98°.

Anal. Calcd. for $C_{14}H_{12}NOCl$: C, 68.42; H, 4.93; N, 5.70; Cl, 14.43. Found: C, 68.25; H, 4.77; N, 5.84; Cl, 14.55.

7-Phenyloxindole (IX).—Aluminum chloride (4 g.) was added slowly, with stirring and careful exclusion of moisture, to powdered chloroacetylaminobiphenyl (3.5 g.). When addition was complete, the temperature was slowly raised first to 100° and after one hour to 160–170°. The mixture was kept at this temperature until gas evolution ceased. It was then decomposed by addition of ice and dilute hydrochloric acid and extracted exhaustively with chloroform. The crude residue obtained on evaporation of the chloroform extract yielded 651 mg. of a crystalline product on cold-finger sublimation. It was recrystallized from alcohol to a melting point 231° and resublimed for analysis.

Anal. Calcd. for $C_{14}H_{11}ON$: C, 80.35; H, 5.31; N, 6.69. Found: C, 80.42; H, 5.31; N, 6.74.

7-Phenyldihydroindole.—Compound IX was reduced with lithium aluminum hydride in ether using the Soxhlet method and gave a quantitative yield of an oily product which crystallized on sublimation. Recrystallization from petroleum ether gave a product, m.p. 68–70°. It was resublimed for analysis.

Anal. Calcd. for $C_{14}H_{13}N$: C, 86.12; H, 6.71; N, 7.18. Found: C, 86.14; H, 6.68; N, 7.42.

Chloroacetylaminoester (X).—The aminoester obtained by hydrogenation of the nitroester V was chloroacetylated in dry acetone in the presence of pyridine exactly as in the case of compound VII. The product X was recrystallized from methanol to a melting point 119°; it was obtained in a 75% yield.

Anal. Calcd. for $C_{19}H_{20}NO_5Cl$: C, 60.39; H, 5.30; N, 3.71; Cl, 9.40. Found: C, 60.32; H, 5.37; N, 3.91; Cl, 9.25.

Reaction of Compound X with Aluminum Chloride.—Compound X was heated with aluminum chloride under the conditions used for the preparation of 7-phenyloxindole. The reaction mixture was decomposed and extracted in the usual way. The chloroform extract was evaporated to dryness, dissolved in methanol and remethylated with an excess of ethereal diazomethane overnight. The solution was then evaporated to a small volume and clarified with charcoal, when the substance crystallized. It was obtained in a 70% yield and melted at 199° after crystallization from methanol. In admixture with this substance the melting point of compound VI was not depressed. The infrared and ultraviolet spectra of both compounds were identical.

Reduction of V to the Aminoalcohol.—The nitroester V was reduced to the aminoester by hydrogenation as already described. The aminoester was subsequently reduced by lithium aluminum hydride in ether using the Soxhlet method. After recrystallization from ether the aminoalcohol melted at 101–102°. A sample was dried in high vacuum at 70°.

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.35; H, 6.95; N, 5.13. Found: C, 70.50; H, 7.02; N, 5.14.

N-Chloroacetyl Aminoalcohol XI.—The above compound (836 mg.) was chloroacetylated in acetone with 2 g. of pyridine and 2 g. of chloroacetyl chloride. The yield of neutral material obtained by working up as before was 1.062 g. of a yellowish oil. This product was treated with 794 mg. of potassium hydroxide in 198 ml. of methanol and 2 ml. of water for 24 hours at room temperature. After evaporation of the solution *in vacuo* to a small volume, chloroform was added, and the chloroform solution was washed first with water, then successively with dilute sulfuric acid and dilute potassium hydroxide and finally with water until neutral. After evaporating the chloroform, the oily product was crystallized from methanol by addition of a few drops of water. The yield was 550 mg. of a compound which was further recrystallized from ether to a melting point 128–129°. A sample was dried in high vacuum at 70°.

Anal. Calcd. for $C_{18}H_{20}NO_4Cl$: C, 61.75; H, 5.72; N, 4.00; Cl, 10.15. Found: C, 61.75; H, 5.58; N, 4.20; Cl, 10.21.

Reaction of Compound XI with Aluminum Chloride.—Compound XI (2 g.) was heated with 2.5 g. of powdered aluminum chloride in the same way as described previously. The cooled reaction mixture was decomposed with ice and dilute hydrochloric acid; the precipitate was filtered off and washed with hydrochloric acid and water until neutral. It was then methylated in methanol with an excess of ethereal diazomethane overnight and the crude methylated product was purified by a cold finger sublimation in high vacuum. The semi-solid sublimate dissolved in 3 ml. of methanol deposited a few milligrams of crystals which after recrystallization from methanol–ether melted at 144°. The ultraviolet and infrared spectra indicated that this compound was probably the oxindole XII.

From the mother liquors of compound XII, 20 mg. of the N-chloroacetyl derivative of compound VII was obtained.

It was identified by mixed melting point and by infrared and ultraviolet spectra.

2-Carboxy-4,5-dimethoxy-2'-nitro-3'-methyldiphenyl (XIII).—Methyl 6-bromoveratrate (212 g.) and 2-nitro-3-bromotoluene (111 g.) were subjected to the Ullmann reaction with 323 g. of activated copper powder. The reaction conditions, working up to the products and even the separation of compound XIII from the dicarboxylic acid IV were the same as in the Ullmann synthesis described above. However, the yield of XIII was in this case only 12.5 g. of pure product. It was recrystallized from methanol to a melting point of 216° and formed beautiful pale yellow crystals. A sample was dried in high vacuum at 100°.

Anal. Calcd. for $C_{16}H_{15}NO_6$: C, 60.57; H, 4.79; N, 4.42. Found: C, 60.44; H, 4.56; N, 4.62.

2,3'-Dicarboxy-4,5-dimethoxy-2'-nitrobiphenyl (XIV).—The acid XIII (2.7 g.) was dissolved in 200 ml. of water containing 0.5 g. of potassium hydroxide. Solid powdered potassium permanganate (5.4 g.) was added with stirring over a period of 2 hours. The solution was then heated on the water-bath for 18 hours. More permanganate (2.7 g.) was then added in 100 ml. of water and the heating continued for 2 hours when the precipitated manganese dioxide was filtered off and washed with hot water. The combined filtrates were acidified strongly with hydrochloric acid and the precipitate was filtered off and washed with water. The filtrate was extracted continuously with ether. The combined yield of filtered and extracted acidic material was 2.385 g. The starting material was quantitatively separated from the dicarboxylic acid XIV by the abbreviated countercurrent distribution which had already served to separate III from IV. Three portions of phosphate buffer *p*H 7 (350 ml. each) were used and 6 layers of the same volume of chloroform were passed successively through them. Acidification of the buffer gave 1.32 g. of the pure product XIV. Evaporation of the chloroform gave 1 g. of starting material XIII.

The dicarboxylic acid XIV was recrystallized for analysis to a melting point 240° and dried in high vacuum at 80°.

Anal. Calcd. for $C_{16}H_{13}NO_8$: C, 55.33; H, 3.77; N, 4.04. Found: C, 55.14; N, 3.87; N, 4.01.

The Nitrodiester XV.—The acid XIV (1.015 g.) was refluxed gently with 6 ml. of thionyl chloride for 3 hours. The excess reagent was then removed by evaporation at room temperature *in vacuo* and the last traces of it removed by repeated evaporation with dry benzene. The Arndt–Eistert reaction with the crude dichloride was carried out in the way already described above (compound V). The final product, the ester XV, was obtained as a yellow oil by sublimation on a cold finger. The yield was 769 mg. The compound was dissolved in methanol and crystallized after standing for some time in the ice-box. The yield of pure crystalline product, melting at 104°, showed that the original oil was essentially pure. Nevertheless, recrystallized material with the correct melting point was always used for further work.

Anal. Calcd. for $C_{20}H_{21}NO_8$: C, 59.54; H, 5.24; N, 3.47; OCH_3, 30.98. Found: C, 59.54; H, 5.31; N, 3.54; OCH_3, 30.80.

Lactams XVI and XVII.—The nitrodiester XV was hydrogenated in alcohol with Raney nickel, the theoretical volume of hydrogen being consumed in 1 hour. The corresponding aminodiester was obtained in quantitative yield as a colorless oil. It was heated in a nitrogen atmosphere for 30 minutes to 170° and subjected to a cold finger sublimation in high vacuum at 180°.

The white semi-solid sublimate (200 mg.) was suspended in a small volume of methanol. Very insoluble crystalline material settled out immediately and was filtered off after standing in the ice-box. The yield from 260 mg. of aminodiester was 100 mg. It was recrystallized to a melting point of 166° from methanol and sublimed for analysis in high vacuum. According to the ultraviolet spectrum it was the seven-membered lactam XVI.

Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.86; H, 5.57. Found: C, 66.58; H, 5.70.

The first mother liquors of the above compound were evaporated to a very small volume and left in the deep-freeze for several days, when more of the lactam XVI settled out. After this had been separated, the remaining solution was taken to dryness leaving a colorless glass; its ultraviolet and infrared spectra showed it to be probably the oxindole XVII.

Dimethylapoerysopine.—The mixture of compounds XVI and XVII obtained as described above (973 mg.) was reduced with lithium aluminum hydride in ether using the Soxhlet method. The yield was 684 mg. of a strongly fluorescent oil. This was dissolved in 10 ml. of dry benzene and treated with 250 mg. of phosphorus tribromide. The mixture was refluxed for two hours when 200 ml. of methanol was added. The resulting solution was added over a period of 2 hours to a vigorously stirred and boiling suspension of 10 g. of sodium carbonate in 300 ml. of methanol. The reaction was performed under careful exclusion of oxygen by a stream of purified nitrogen. After the addition was completed, the mixture was refluxed for 15 hours after which the methanol was evaporated to a small volume *in vacuo*. Water was then added and the aqueous solution extracted exhaustively with chloroform. After drying, the chloroform was evaporated to dryness and a brown residue of 700 mg. was obtained. As a precaution which probably was unnecessary, this was exposed to ethereal diazomethane in methanol overnight. After evaporating to dryness again, the product was filtered through a column of 20 g. of alumina (Fisher). The first chloroform fraction (70 ml.) contained 492 mg. of a light yellow oil. This product when treated with methanolic picric acid gave 500 mg. of an orange picrate in beautiful long needles. The melting point was 180–186° and after several crystallizations from methanol reached the constant value of 191°. The substance did not depress the melting point of the picrate of authentic dimethylapoerysopine obtained by methylation of apoerysopine with diazomethane.

Anal. Calcd. for $C_{24}H_{22}N_4O_9$: C, 56.47; H, 4.31; N, 10.98. Found: C, 56.49; H, 4.57; N, 10.80.

The free dimethylapoerysopine was liberated from its picrate by filtering a chloroform solution through a column of alumina. After sublimation in high vacuum, it was used to determine ultraviolet and infrared spectra.

X-Bromodimethylapoerysopine.—The procedure followed in the synthesis of dimethylapoerysopine was used on 471 mg. of the mixture of aminoalcohols XVIII and XIX. However, phosphorus pentabromide (1 g. in 10 ml. of benzene) was used instead of phosphorus tribromide. The final yield was 300 mg. of a picrate which crystallized in orange plates and was recrystallized to a melting point of 172°.

Anal. Calcd. for $C_{24}H_{21}N_4O_9Br$: C, 48.90; H, 3.57; N, 9.51; Br, 13.58. Found: C, 49.06; H, 3.82; N, 9.29; Br, 14.02.

Bromination of Authentic Dimethylapoerysopine.—Authentic dimethylapoerysopine (188 mg.) was dissolved in 10 ml. of dry benzene and refluxed for 2 hours with 600 mg. of phosphorus pentabromide. Chloroform was then added and the organic layer was washed well with a sodium carbonate solution and water. On evaporation to dryness, a brown residue (240 mg.) was obtained. This was chromatographed on 10 g. of alumina. The first chloroform fraction (188 mg.) gave a quantitative yield of an orange picrate crystallizing in plates. Recrystallized to a constant melting point (172°), it gave no depression of the melting point of the above compound.

Anal. Calcd. for $C_{24}H_{21}N_4O_9Br$: C, 48.90; H, 3.57; Br, 13.58. Found: C, 49.14; H, 3.70; Br, 13.47.

The free bases of this compound and the synthetic x-bromodimethylapoerysopine were liberated by chromatography on alumina in chloroform and were found to have identical ultraviolet and infrared spectra.

N-Methyl-4,5-dimethoxyphthalimide.—Compound III (5 g.) was hydrogenated in alcohol in the presence of exactly a molar quantity of sodium hydroxide. After the theoretical volume of hydrogen was taken up, the solution was filtered and evaporated to dryness *in vacuo*. The residue was dissolved in 200 ml. of water and 2 g. of sodium hydroxide. A solution of 42.2 g. of potassium permanganate in 1600 ml. of water then was added over a period of 2 hours. The mixture was stirred for 18 hours at room temperature and then for 5 hours at 90°. Sulfur dioxide was then bubbled through the cooled solution until all the manganese dioxide had dissolved. Continuous extraction gave 1.542 g. of a yellowish solid, which was recrystallized once from methanol–ether, and then dissolved in 100 ml. of 5% ammonium hydroxide and treated with a calcium chloride solution. The precipitated calcium oxalate was filtered off and the

solution acidified again and extracted continuously. The yield was 423 mg. of a crystalline solid. This was treated repeatedly with a 30% solution of methylamine, evaporated to dryness after every addition, and finally sublimed on a cold finger. The sublimate (390 mg.) was recrystallized from chloroform–methanol to a constant melting point (262°). It did not give depression of melting point with an authentic specimen of N-methyl-4,5-dimethoxyphthalimide. The ultraviolet spectra of both compounds were identical.

Grignard Reaction of Dihydroisoquinolinium Bromides

1-Ethyl-1,2-dimethyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (XXI).—The reaction was carried out in a three-necked flask equipped with a reflux condenser, dropping funnel, inlet for purified dry nitrogen and a powerful rapid stirrer. The Grignard reagent was prepared in the usual manner from 2.2 g. of magnesium powder and 9.5 g. of ethyl bromide in dry ether. The Grignard reaction was started in 50 ml. of dry ether to which, after all the magnesium had dissolved, 1 liter of the same solvent was added. The powdered methobromide XX (900 mg.) was then added and the mixture stirred and refluxed for 24 hours. The reaction mixture then was poured on crushed ice in a 10% ammonium chloride solution. When decomposition was completed the aqueous layer was made strongly alkaline with ammonia and extracted exhaustively with ether.

The basic material from the ether extract was isolated in the usual way and purified by cold finger sublimation in high vacuum. The yield was 629 mg. of waxy crystals which were recrystallized from petroleum ether to a melting point of 57°.

For analysis the compound was converted into its picrate which was recrystallized from methanol to a melting point of 169°.

Anal. Calcd. for $C_{21}H_{26}N_4O_9$: C, 52.72; H, 5.48; N, 11.71. Found: C, 52.57; H, 5.24; N, 11.46.

1-Allyl-1,2-dimethyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (XXII).—The procedure described above was followed, substituting allylmagnesium bromide for ethyl magnesium bromide. The quantities were as follows: magnesium, 2.05 g.; allyl bromide, 6.3 g.; methobromide XX, 1.12 g. The yield was 624 mg. of a viscous oily base. The picrate melted at 151–152° after crystallization from methanol.

Anal. Calcd. for $C_{22}H_{26}N_4O_9$: C, 53.87; H, 5.34; N, 11.42. Found: C, 54.03; H, 5.36; N, 11.41.

If as sometimes happens the reaction is incomplete the product may be separated from the starting material by a 9-funnel countercurrent distribution between chloroform and phosphate buffer (*p*H 3.3). The starting material, which is the stronger base, remains in the first 3 funnels.

Compound XXVI.—The above procedure was used; quantities: magnesium, 1.29 g.; allyl bromide, 8.05 g.; bromide XXV (X = Br), 0.75 g. (for preparation of this compound *vide infra*). The yield was 0.276 g. of an oily base. The picrate melted at 134–136°.

Anal. Calcd. for $C_{23}H_{26}N_4O_9$: C, 54.97; H, 5.22; N, 11.15. Found: C, 54.78; H, 4.91; N, 11.57.

Compound XXX.—The same procedure was used; quantities: magnesium, 1.29 g.; allyl bromide, 8.05 g.; bromide XXIX (X = Br), 570 mg. (for preparation of bromide XXIX *vide infra*). The bromide XXIX was oily and was therefore dissolved in methanol, soaked up on quartz sand and dried for 24 hours at 80° in high vacuum. The quartz sand was then added to the reaction mixture. The yield was 340 mg. of an oily base, which gave a picrate, m.p. 139–140°.

Anal. Calcd. for $C_{26}H_{30}N_4O_9$: C, 57.56; H, 5.57; N, 10.33. Found: C, 57.68, 57.54; H, 5.55, 5.59; N, 10.05, 10.35.

In large runs it was found advantageous to filter the crude basic product in chloroform solution through a column of alumina before converting it to the picrate. In all the cases described the picrates were decomposed by chromatography on alumina in chloroform for determination of ultraviolet and infrared spectra.

Condensation of Butyrolactone with Homoveratryl Amine.—Homoveratrylamine (12.6 g.) and butyrolactone (6.3 g.) were heated together at 200° for one hour under nitrogen. The mixture was then dissolved in chloroform and washed with dilute hydrochloric acid, sodium carbonate and water. The yield of the crude neutral product was 11.7 g. It was chromatographed on 400 g. of alumina (Fisher). Ether-chloroform (1:1) eluted 4.17 g. of crystalline material which was recrystallized from ether–petroleum ether to a melting point of 57°. The compound was the N-homoveratryl pyrrolidone XXIII.

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.66; N, 5.62. Found: C, 67.19; H, 7.41; N, 5.67.

The hydroxyamide XXIV was then eluted from the column by 10% methanol in chloroform. The yield was 7.04 g. It was recrystallized from ether to a melting point of 68–69°.

Anal. Calcd. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.69; H, 7.80; N, 5.44.

Ring Closure of Compound XXIII with Phosphorus Oxychloride to Compound XXV.—The N-homoveratryl pyrrolidone XXIII (0.870 g.) was dissolved in 8 ml. of absolute toluene and 2.2 ml. of phosphorus oxychloride. Dry purified nitrogen was passed through the solution which was refluxed for 90 minutes. Petroleum ether was then added and the mixture put into the refrigerator for 12 hours; the supernatant liquid was then poured off and the brown crystalline material dissolved in water. The acidic aqueous solution was extracted with ether and the ether discarded. The aqueous layer was then made strongly alkaline with sodium hydroxide and the precipitated basic material extracted with ether. The yield was 0.781 g. of a crystalline base. This was converted into the bromide XXV (X = Br) by dissolving it in methanol and adding an equivalent amount of alcoholic hydrobromic acid. Recrystallization from acetone gave beautiful crystals melting at 201–203°.

Anal. Calcd. for $C_{14}H_{18}NO_2Br$: C, 53.86; H, 5.81; N, 4.49; Br, 25.60. Found: C, 53.49; H, 5.80; N, 4.25; Br, 25.39.

α-Allyl-γ-butyrolactone.—To a solution of 2.38 g. of sodium in absolute ethanol allylmalonic acid diethyl ester (19 g.) was added under constant stirring at 60°. 2-Chloroethanol (12.9 g.) was then added over a period of 30 minutes. The mixture was refluxed for 3 hours, after which time it was filtered to remove the precipitated sodium chloride; a solution of 15 g. of potassium hydroxide in 120 ml. of 80% methanol was then added. The mixture was refluxed for 8 hours, when the alcohol was distilled off *in vacuo* and water was added. The acidic material was isolated in the standard manner. The yield of acid was 11.5 g. The acid was heated to 120° when decarboxylation started. The temperature was then raised to 160° and kept at this point until gas evolution stopped. The product was purified by distillation in a Claisen flask and boiled at 64–69° (1 mm.). The yield of α-allyl-γ-butyrolactone was 80% (calcd. on the malonic acid).

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.52; H, 7.80.

The infrared spectrum showed no hydroxy band and a γ-lactone band at 1775 cm.$^{-1}$.

Condensation of α-Allyl-γ-butyrolactone with Homoveratrylamine.—Homoveratrylamine (68.9 g.) was condensed with 51 g. of allylbutyrolactone in the same manner as described above. The resulting neutral material was a clear oil (107 g.). A small portion (2.05 g.) was separated by chromatography on alumina (Fisher). Ether eluted 0.409 g. of pyrrolidone XXVIII which did not crystallize. The hydroxyamide XXVII was subsequently eluted with 5% methanol in chloroform. It was recrystallized for analysis from ethyl acetate and melted at 77–78°.

Anal. Calcd. for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.47; H, 8.07; N, 4.37.

Ring Closure of Pyrrolidone XXVIII with Phosphorus Oxychloride.—The pyrrolidone XXVIII was cyclized in the same manner as described for the compound XXIII. The resulting base was obtained in a yield of 80%. It was characterized as the picrolonate crystallizing from aqueous methanol with a mole of water and was dried *in vacuo* at room temperature. It melted at 71° with loss of water.

Anal. Calcd. for $C_{27}H_{29}N_5O_7 \cdot H_2O$: C, 58.55; H, 5.66; N, 12.65. Found: C, 58.92; H, 5.58; N, 12.77.

Ring Closure of the Hydroxyamide XXVII.—The hydroxyamide XXVII (990 mg.) was cyclized in the same way as the N-homoveratryl pyrrolidones. To the basic fraction, dissolved in ether, anhydrous sodium sulfate was added and

the ether solution left in the ice-box for 24 hours. A dilute solution of sodium hydroxide then was added until all the sodium sulfate dissolved; the ether layer was separated after thorough shaking and dried again with sodium sulfate. The resulting product was obtained in a yield of 794 mg. and was converted into a picrolonate.

This compound melted at 70° and gave no depression on admixture with the previous product. The free bases liberated from both picrolonates had identical ultraviolet spectra in neutral, alkaline and acidic alcohol.

Reduction of the Compound XXIX (X = Br) with Sodium Borohydride.—The free base of XXIX was converted into the bromide by treatment with an equivalent of hydrobromic acid in methanol and evaporating to dryness. The bromide proved to be gummy. It was (16 g.) dissolved in 200 ml. of methanol and treated with 15 g. of sodium borohydride. The mixture was refluxed for 2 hours. Most of the solvent was removed *in vacuo;* dilute sodium hydroxide was added and the basic product extracted with ether. The yield was 10.3 g. of a light yellow oil. The product was characterized as a picrate. It melted at 158° after crystallization from methanol and was assigned structure XXXI.

Anal. Calcd. for $C_{23}H_{26}N_4O_9$: C, 54.97; H, 5.22; N, 11.15. Found: C, 54.98; H, 5.18; N, 11.01.

Oxidation of Compound XXXI with Potassium Permanganate.—Compound XXXI (1.03 g.) was dissolved in 100 ml. of acetone and a solution of potassium permanganate (2.98 g.) in 200 ml. of acetone was added dropwise with cooling to 0° and stirring. After the addition was complete the solution was stirred overnight at room temperature. The precipitated manganese dioxide was filtered off and the filtrate evaporated to dryness. The residue was dissolved in chloroform and washed with dilute acid and water. The yield was 265 mg. of an amorphous foam (fraction A). The manganese dioxide was suspended in water and chloroform, and cooled with ice, when sulfur dioxide was introduced until a clear solution resulted. The chloroform layer was separated and the aqueous layer repeatedly extracted. The combined chloroform extracts yielded 559 mg. of an amorphous foam (fraction B). The two fractions A and B were combined and separated into acidic and neutral portions in the standard way.

The acidic fraction (546 mg.) crystallized. It was recrystallized from ethyl acetate to a melting point of 174–175°. The structure XXXV was assigned to it.

Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.26; H, 6.45; N, 5.06.

The acid was further characterized by esterification with diazomethane and reduction of the ester with lithium aluminum hydride. The aminoalcohol XXXVII was thus obtained in an 87% yield and characterized as a picrate. It melted at 174–175° after crystallization from methanol.

Anal. Calcd. for $C_{20}H_{24}N_4O_7$: C, 50.00; H, 5.04; N, 11.66. Found: C, 49.86; H, 4.96; N, 11.89.

The neutral material (260 mg.) was purified by chromatography on alumina. The bulk of the product was eluted with 0.5% methanol in chloroform and recrystallized for analysis from ethyl acetate to a melting point of 175°. Structure XXXVI was assigned to it.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.29; H, 6.27; N, 6.87.

Oxidation of Compound XXX with Permanganate.—The compound XXX (1.00 g.) was oxidized and worked up exactly as in the previous experiment. The amount of permanganate used was 5 g. The only difference in the working up was that owing to the great water solubility of the resulting acid all extractions of aqueous layers were performed continuously with ether. The desired dicarboxylic acid was purified conveniently by extracting the acidified aqueous layer with ether in a separatory funnel, discarding the ether extract and extracting the dicarboxylic acid continuously from the aqueous layer. It was obtained as 310 mg. of a foam. The acid was esterified in methanolic solution by ethereal diazomethane and the ester was chromatographed on 14.4 g. of neutral alumina. The purified ester XXXIII was eluted by benzene–ether (1:1) as 130 mg. of a slowly crystallizing oil. It was recrystallized from ether to a melting point of 123°.

Anal. Calcd. for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.57. Found: C, 61.73; H, 6.55; N, 3.86.

The neutral material (251 mg.) was chromatographed on 10 g. of alumina. The lactam XXXII was eluted with ether as 143 mg. of crystalline material. It was recrystallized from ether to a melting point of 109–110°.

Anal. Calcd. for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.22; H, 7.49; N, 3.96.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HARVARD UNIVERSITY]

Schoenocaulon Alkaloids. III. The Bismuth Oxide Oxidation of Veracevine, Cevagenine and Cevine[1a]

BY S. MORRIS KUPCHAN AND DAVID LAVIE[1b]

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Oxidation of cevine with bismuth oxide in acetic acid yields cevinilic acid δ-lactone, $C_{27}H_{41}O_8N$. Similar oxidations of veracevine and cevagenine afford the same product. Veracevine consumes two moles of periodic acid; veracevine triacetate consumes one mole of periodic acid and is stable to chromic acid in acetic acid. These facts are most satisfactorily explained on the basis of the recently-advanced structures I, II and III for veracevine, cevagenine and cevine, respectively.

The view that veracevine and cevine contain the same α-ketol-5-membered hemiketal system and differ only in the configuration of the hydroxyl group of the α-ketol system was entertained in a recent communication.[2] These partial structures were supported by the facts: (1) bismuth oxide oxidation of veracevine, cevagenine and cevine yields the same crystalline hydroxy-δ-lactone, (2) veracevine, like cevine, consumes two moles of periodic acid and (3) veracevine triacetate, like cevine triacetate, is stable to chromic acid in acetic acid, and consumes one mole of periodic acid.

Subsequent rapid developments in several laboratories have led to elaboration of substantially complete formulations for veracevine, cevagenine and cevine (I, II, III).[3] The present paper presents details of our experience with the bismuth oxide oxidation of the schoenocaulon alkamines. The results are interpreted in the light of the above structures.

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(2) Paper II, S. M. Kupchan and D. Lavie, THIS JOURNAL, **76**, 314 (1954).

(3) We thank Professor R. B. Woodward for kindly communicating his deduction of the major aspects of these structures to us prior to publication; *cf.* D. H. R. Barton, O. Jeger, V. Prelog and R. B. Woodward, *Experientia*, **10**, 81 (1954).