[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

The Synthesis of 1-Benzazepine Derivatives as Model Compounds Related to Apo-β-Erythroidine[1,2]

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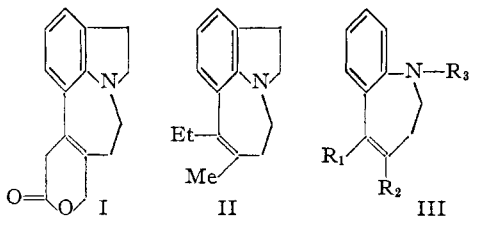
A series of derivatives of 1-benzazepine have been prepared and their use as possible precursors for a synthesis of apo-β-erythroidine and related compounds has been investigated. Although this approach appears to be of limited value for the over-all objective, several compounds of interest resulted from this study. Compound XIX, having essentially the same conjugated system believed to be present in apo-β-erythroidine, was prepared and found to show very similar absorption characteristics in the ultraviolet to that of the natural material.

Although all of the erythrina alkaloids are now believed to be derivatives of the same unusual spiro-amine system,[2,3] there has as yet been no synthetic confirmation for this system nor has there been any direct correlation between the aromatic members of this group and the two remaining alkaloids, α- and β-erythroidine. One of the important steps in the degradation of these alkaloids is the rearrangement occurring in the presence of acid, known as the apo-rearrangement,[4,5] which ruptures the spiro-amine system to give an indoline derivative. In the case of the aromatic members, methylation of the product resulting from this rearrangement gives a compound known as apoerysotrine whose structure has been established recently through independent synthesis by Valenta and Wiesner.[6] Thus far, no comparable synthetic confirmation for the structures assigned to apo-β-erythroidine (I) or any of its derivatives has been made. For this reason the preparation of derivatives of 1-benzazepine of the type shown by III was undertaken in the hope of developing a feasible synthetic route to apo-β-erythroidine (I) or a degradation product such as desoxyapo-β-erythroidinol (II), as well as to provide interesting model compounds for physiological testing.



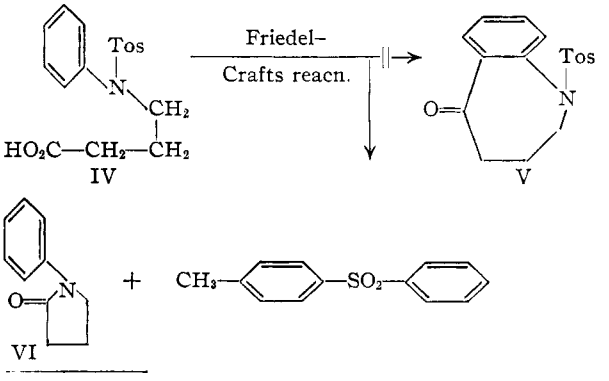
I II III

Our initial efforts were directed toward preparing 2,3,4,5-tetrahydro-5-keto-1-benzazepine (V). It was hoped that the procedure used by Johnson, Woroch and Buell[7] for the preparation of 1,2,3,4-tetrahydro-4-ketoquinoline likewise would be applicable here to its homolog. However, when N-tosyl-γ-anilinobutyric acid (IV) was subjected to the usual conditions for cyclization in the Friedel–Crafts reaction, the product isolated was N-phenyl-α-pyrrolidone (VI). Use of the corresponding acid chloride in benzene with aluminum chloride as catalyst yielded *p*-tolylphenylsulfone in addition to N-phenyl-α-pyrrolidone. The formation of *p*-tolylphenylsulfone must result from the union of an expelled tosyl group with a molecule of solvent. Unfortunately under the conditions used in acid-catalyzed cyclizations, ring closure to nitrogen appears favored over that to the aromatic ring.

The preparation of the desired 2,3,4,5-tetrahydro-5-keto-1-benzazepine eventually was solved using methyl anthranilate as starting material. This on alkylation with methyl γ-bromobutyrate followed by methylation with methyl iodide gave the corresponding diester VII. A Dieckmann cyclization of VII using potassium *t*-butoxide as catalyst led, after hydrolysis, to the expected 1-benzazepine derivative VIII in good yield.

It should be noted that attempts to introduce the carbomethoxypropyl group by means of the Späth procedure[8] were quite unsuccessful. Treatment of either anthranilic acid or methyl anthranilate with γ-butyrolactone at elevated temperatures resulted in elimination of the carboxy or carbomethoxy group and gave either N-phenyl-α-pyrrolidone (III) or aniline as the final product.

To make certain that the structure assigned to VIII was correct, the carbonyl group was removed by the Wolff–Kishner procedure and the picrate of the resulting base was shown by comparison to be identical with the picrate of an authentic sample of N-methyl-2,3,4,5-tetrahydro-1-benzazepine (IX). For the preparation of the authentic



(1) This investigation was supported by a research grant from the United Cerebral Palsy Associations, Inc.

(2) Paper XII in this series; for the preceding communication see J. C. Godfrey, D. S. Tarbell and V. Boekelheide, THIS JOURNAL, **77**, 3342 (1955).

(3) V. Boekelheide and V. Prelog, "Progress in Organic Chemistry," Vol. III, Edited by J. W. Cook, Academic Press, Inc., New York, N. Y., 1955.

(4) G. L. Sauvage and V. Boekelheide, THIS JOURNAL, **72**, 2062 (1950).

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

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

(7) W. S. Johnson, E. L. Woroch and B. G. Buell, THIS JOURNAL, **71**, 1901 (1949).

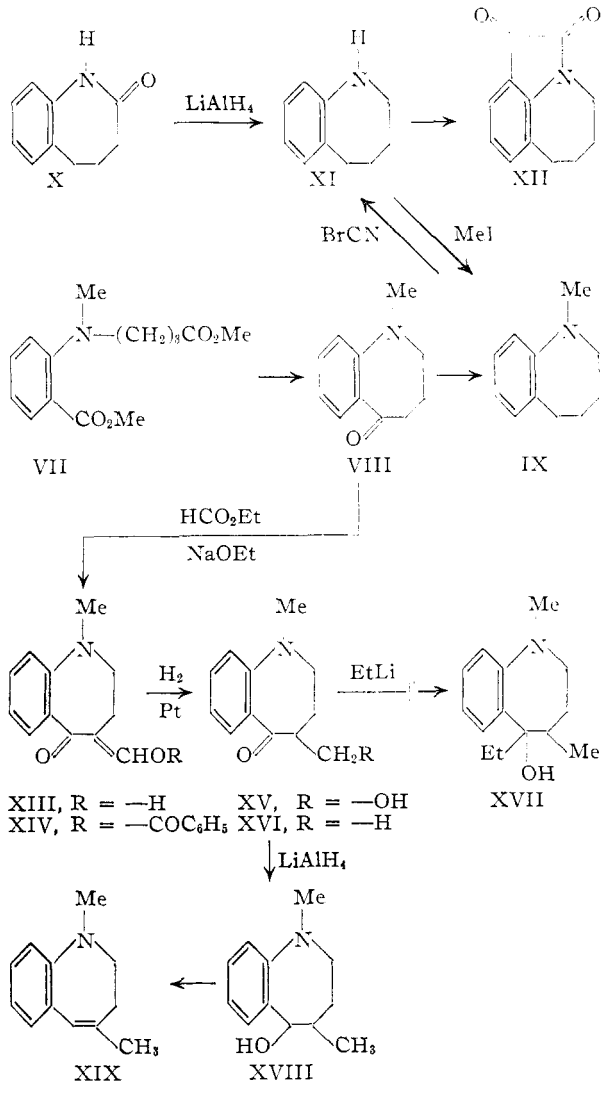
(8) E. Späth and J. Lintner, *Ber.*, **69**, 2727 (1936).

sample of IX, homodihydrocarbostyril (X) was reduced with lithium aluminum hydride to give XI and this on methylation yielded IX.

To achieve the eventual goal of this study it was necessary that a method be available for converting properly substituted 1-benzazepine derivatives to tricyclic molecules of the type represented by desoxyapo-β-erythroidinol (II). For this reason the conversion of IX to a tricyclic molecule was next investigated. As has been reported by von Braun,[9] treatment of IX with cyanogen bromide followed by hydrolysis was found to be effective in removing the methyl group and regenerating homotetrahydroquinoline (XI). Although attempts to convert XI to an indole derivative by the Hinsburg[10] or Stollé[11] procedures were unsuccessful, the conversion of XI to the corresponding isatin derivative XII occurred in fair yield. This was accomplished by treating XI with chloral hydrate and hydroxylamine hydrochloride to produce the N-nitrosoacetyl derivative which, in the presence of sulfuric acid, yielded XII. Presumably the isatin grouping should undergo total reduction to the corresponding indoline; however, this was not investigated. Instead, our attention was then directed toward obtaining a properly substituted 1-benzazepine derivative from VIII.

Although compound VIII showed absorption in the infrared at 5.97 μ, indicative of a carbonyl group in conjugation with an aromatic ring,[12] and was reduced in low yield by the Wolff–Kishner procedure to IX, it did not form either a semicarbazone or a 2,4-dinitrophenylhydrazone derivative under the usual conditions for preparing these derivatives. Presumably this lack of reactivity is largely due to interaction between the carbonyl and amine groups and this is borne out by the fact that whereas VIII is a very feeble base, being almost neutral, its reduction product IX is a normal aromatic amine. When attempts were made to introduce a substituent at the 4-position by treating VIII with methyl iodide and sodamide, a complex mixture resulted and it appeared that enolization was the chief reaction occurring in the presence of strong base. An alternate approach involving more mild conditions was therefore sought and it was found that VIII underwent a smooth reaction with ethyl formate to give the corresponding hydroxymethylene derivative XIII. This product showed the tautomeric and enolic properties to be expected for a β-keto aldehyde.

Catalytic hydrogenation of XIII, either over platinum oxide or Raney nickel catalyst, led to the simple dihydro derivative XV in which both oxygens were retained. To effect hydrogenolysis, the hydroxymethylene derivative was converted to the corresponding benzoate XIV and this on reduction over platinum oxide gave XVI in good yield. The remaining step to obtain a benzazepine having the proper substituents in the heterocyclic ring was the introduction of an ethyl group at the 5-position. Despite repeated efforts to accomplish



the addition of ethyllithium to XVI, this reaction failed completely. Examination of molecular models indicates that there is considerable steric hindrance to the approach of any reagent to the carbonyl group in XVI and this probably accounts for the fact that the only apparent reaction with ethyllithium was enolization.

Treatment of XVI with lithium aluminum hydride readily converted it to the corresponding carbinol XVIII and this underwent dehydration to give XIX with extreme ease. Since compound XIX presumably has the same conjugated system as that present in apo-β-erythroidine, it was of interest to compare the properties of the two compounds. Both are weak bases having remarkably similar ultraviolet absorption spectra. Thus, the absorption maxima for apo-β-erythroidine occur at 230 (log ε 4.42), 272 (log ε 3.64) and 330 mμ (log ε 3.46) with its minima at 262 (log ε 3.61) and 298 mμ (log ε 3.13); whereas compound XIX has its maxima at 235 (log ε 4.40), 274 (log ε 3.70) and 330 mμ (log ε 3.48) with its minima at 264 (log ε 3.52) and 295 mμ (log ε 3.20). The close correspondence of these two spectra strongly suggests that the two compounds are similarly constituted and thus

(9) J. von Braun and J. Seeman, *Ber.*, **55**, 3818 (1922).
(10) O. Hinsburg, *ibid.*, **21**, 110 (1888).
(11) R. Stollé, *J. prakt. Chem.*, **128**, 1 (1930).
(12) V. Boekelheide and J. C. Godfrey, THIS JOURNAL, **75**, 3679 (1953).

supports the presently accepted structure for apo-β-erythroidine.

Experimental[13]

N-Tosyl-γ-anilinobutyric Acid (IV).—N-Phenyl-α-pyrrolidone (VI) was prepared by heating a mixture of 10 g. of γ-butyrolactone and 10 g. of aniline in a sealed tube at 200° for 12 hours. After the reaction mixture was distilled, the distillate was taken up in ether and washed with dilute acid. Concentration of the ether solution gave 10.2 g. (58%) of crystals. This was obtained, after crystallization from hexane, as white crystals, m.p. 70–71.5° (lit.[14] m.p. 68–69°). A suspension of 10.2 g. of the N-phenyl-α-pyrrolidone so obtained in a solution of 15 g. of barium hydroxide in 400 ml. of water was boiled under reflux for 12 hours. When the mixture had cooled, it was decanted and the residue was washed with water. A stream of carbon dioxide then was passed into a mixture of the decantates and washings until barium carbonate was no longer precipitated. The solution was filtered and the precipitate was washed with water. Treatment of the combined washings and filtrate with an excess of 10% aqueous solution of silver nitrate caused the precipitation of the silver salts of γ-anilinobutyric acid.[15] This precipitate was collected, washed successively with water, ethanol and ether, and then dried. A suspension of the resulting dry powder in 200 ml. of ether was treated with hydrogen sulfide gas until silver sulfide was no longer precipitated. To the ethereal solution remaining after removal of the silver sulfide there was added 50 ml. of pyridine and the solution was concentrated to remove almost all of the ether. There were then added 150 ml. of benzene and 20 g. of *p*-toluenesulfonyl chloride and the mixture was boiled under reflux for 12 hours. When the solution had cooled, the precipitate of pyridine hydrochloride was separated and the remainder of the pyridine was removed by washing the solution with aqueous acid. Concentration of the benzene solution followed by cooling caused the deposition of 10.0 g. (47.5%) of N-tosyl-γ-anilinobutyric acid as white prisms, m.p. 159–161°. Extraction of the mother liquors from the crystallization with alkali followed by acidification gave an additional 2.7 g. of identical material. A sample prepared for analysis by recrystallization from benzene melted at 163.5–164.5°.

Anal. Calcd. for $C_{17}H_{19}NO_4S$: C, 61.25; H, 5.75. Found: C, 61.16; H, 5.79.

Attempted Cyclization of N-Tosyl-γ-anilinobutyric Acid (IV).—A. With Aluminum Chloride.—To a solution of 1.5 g. of N-tosyl-γ-anilinobutyric acid (IV) in 15 ml. of dry, thiophene-free benzene there was added 1.1 g. of phosphorus pentachloride. After the solution had been heated to effect solution of the phosphorus pentachloride and evolution of hydrogen chloride, the reaction mixture was subjected to slow distillation with concurrent addition of benzene so that the phosphorus oxychloride would be removed completely. Concentration of the benzene solution then left a crystalline solid which was taken up once again in 25 ml. of benzene and added dropwise with stirring to a solution of 2.0 g. of aluminum chloride in 40 ml. of benzene maintained between 0 and 10°. When the addition was complete, the solution was held for 17 hours at room temperature with stirring. The reaction mixture then was decomposed by the addition of 50 ml. of ether and 100 ml. of 6 *N* hydrochloric acid and the organic layer was removed. After successive washings with dilute acid, sodium bicarbonate and water, the ether solution was concentrated to yield an oily residue which slowly crystallized. The greasy crystals were collected on a filter and washed with ether. The resulting solid, after recrystallization from methanol, gave 750 mg. (72%) of white plates, m.p. 124.5–125.5°, which from their composition and properties (lit.[16] m.p. 125.5°) must be *p*-tolyl phenyl sulfone.

Anal. Calcd. for $C_{13}H_{12}O_2S$: C, 67.23; H, 5.21. Found: C, 67.13; H, 5.18.

Concentration of the ethereal washings of *p*-tolyl phenyl sulfone gave an oil which, after distillation, crystallized to give 0.52 g. (71%) of white prisms, m.p. 70–71°. A mixture of this product and a sample of the N-phenyl-α-pyrrolidone previously described showed no depression of melting point.

B. With Polyphosphoric Acid.—A solution of 700 mg. of N-tosyl-γ-anilinobutyric acid (IV) in 7.5 g. of polyphosphoric acid was heated at 100° for 2.5 hours. The mixture then was poured into 40 ml. of water and extracted with ether. The ethereal solution after being washed with aqueous sodium bicarbonate was concentrated to give 320 mg. (94%) of white prisms, m.p. 70–71°. These were shown to be identical with N-phenyl-α-pyrrolidone by the method of mixed melting points.

Condensations of Anthranilic Acid and Methyl Anthranilate with γ-Butyrolactone.—A mixture of 9.0 g. of anthranilic acid and 6.0 g. of γ-butyrolactone was heated in a sealed tube at 275° for 18 hours. It then was treated with ether, the ether-insoluble material (1.5 g.) separated and after concentration of the solution, the residue was distilled. After the forerun, consisting of 2.1 g. of γ-butyrolactone, there was collected a yellow oil, b.p. 50–60° at 2 mm. This, on treatment with hexane, gave 6.0 g. of white prisms, m.p. 70–71°. The identity of these crystals with N-phenyl-α-pyrrolidone was shown by a mixed melting point determination with an authentic sample.

Similarly, a mixture of 15.0 g. of methyl anthranilate and 9.0 g. of γ-butyrolactone gave, after heating in a sealed tube at 240° for 12 hours, 6.1 g. (60%) of aniline and 2.5 g. of an ether-insoluble substance identical with that obtained in the case of anthranilic acid. The ether-insoluble substance was characterized to the following extent. Although sparingly soluble in such solvents as acetone, benzene or hexane, it could be recrystallized from methanol to yield silky, yellow needles, m.p. 296–297°. The substance was unaffected by cold acid or alkali, but on treatment with warm sodium hydroxide it dissolved to give a colorless solution. Acidification of this alkaline solution reprecipitated the original compound as yellow needles, m.p. 293–295°.

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.76, 74.73; H, 4.26, 4.41; N, 9.60, 9.63.

Methyl N-(γ-Carbomethoxypropyl)-anthranilate.—A mixture of 100 g. of methyl anthranilate and 50 g. of methyl γ-bromobutyrate was heated at 100° for 14 hours. To the resulting crystalline mass there was added 300 ml. of water and then solid sodium bicarbonate to the mixture until effervescence had ceased. The oily organic layer was extracted with ether, dried and concentrated. Distillation of the residual oil gave three fractions. The first fraction consisted of 4.7 g. of methyl γ-bromobutyrate, b.p. 66–69° at 15 mm.; the second fraction amounted to 62.0 g. of methyl anthranilate, b.p. 125–135° at 15 mm.; and the final fraction consisted of 42.0 g. (66%, based on unrecovered methyl anthranilate) of a colorless oil, b.p. 185–187° at 2 mm., $n^{28}D$ 1.5468.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.83; H, 6.43; N, 5.96.

Methyl N-Methyl-N-(γ-carbomethoxypropyl)-anthranilate (VII).—The following procedure for the methylation of methyl N-(γ-carbomethoxypropyl)-anthranilate was found to be the most satisfactory of those that were tried. A mixture containing 48.0 g. of methyl N-(γ-carbomethoxypropyl)-anthranilate and 70.0 g. of methyl iodide was divided into four portions and heated in separate sealed tubes at 85° for 4 hours. The contents were then poured into a mixture of 50 ml. of ether and 100 ml. of water and solid sodium bicarbonate was added until the solution was slightly alkaline. The organic layer was removed by extraction with ether, dried, and the ethereal solution was concentrated. Distillation of the residue gave 32.3 g. (64%) of a colorless oil, b.p. 146–147° at 1.0 mm., $n^{25}D$ 1.5284.

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.35; H, 7.23; N, 5.38.

1-Methyl-2,3,4,5-tetrahydro-5-keto-1-benzazepine (VIII).—To a suspension of 1.2 g. of potassium chips in 100 ml. of dry toluene maintained under a nitrogen atmosphere there was added dropwise with stirring 9.0 g. of *t*-butyl alcohol. The mixture was heated under reflux with stirring until all of the potassium had dissolved and then the excess of *t*-butyl alcohol was removed by azeotropic distillation.

(13) Analyses by Miss A. Smith and the Micro-Tech Laboratories. All melting points are corrected.

(14) R. Anschütz and C. Beavis, *Ann.*, **295**, 29 (1897).

(15) E. Späth and J. Lintner, *Ber.*, **69**, 2727 (1936).

(16) C. A. Buehler and J. E. Masters, *J. Org. Chem.*, **4**, 262 (1939).

To the vigorously stirred and boiling solution 3.50 g. of methyl N-methyl-N-(γ-carbomethoxypropyl)-anthranilate (VII) was added dropwise over a period of 4 hours. After the reaction mixture had been heated under reflux for an additional 22 hours, it was cooled and extracted 5 times with 15-ml. portions of 6 *N* hydrochloric acid. The acid extracts were combined with an additional 20 ml. of concentrated hydrochloric acid and the entire solution was boiled under reflux in a nitrogen atmosphere for 45 minutes. After the cold solution had been made strongly alkaline with aqueous sodium hydroxide, it was extracted with chloroform. The chloroform extract after drying and concentration was distilled using a short-path still to give 1.22 g. (52%) of a yellow oil, b.p. (pot temperature) 150–170° at 2 mm. Samples of the ketone obtained in this manner decomposed on standing. However, when a 10.6-g. sample of this product was subjected to careful fractionation using a spinning band column, it gave 8.0 g. of a light yellow oil (b.p. 112° at 0.07 mm., $n^{29}D$ 1.5992) which remained unchanged when kept for several months at 5°. The oil was insufficiently basic to form a stable picrate or picrolonate derivative.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.93; H, 7.65; N, 8.39.

1-Methyl-2,3,4,5-tetrahydro-1-benzazepine (IX). A. From 1-Methyl-2,3,4,5-tetrahydro-5-keto-1-benzazepine.—A mixture consisting of 500 mg. of 1-methyl-2,3,4,5-tetrahydro-5-keto-1-benzazepine, 4 ml. of hydrazine hydrate and 1.0 g. of potassium hydroxide in 20 ml. of triethylene glycol was heated at 180° for 1.5 hours to remove any water formed and then the temperature was raised to 200° for an additional 3 hours. After the solution had cooled, it was poured into water and extracted 3 times with 50-ml. portions of chloroform. The combined chloroform extracts were dried and concentrated. Distillation of the residue gave 196 mg. of a colorless oil, b.p. (bath temperature) 110–115° at 15 mm.

Anal. Calcd. for $C_{11}H_{15}N$: N, 8.69. Found: N, 8.68.

The picrate of 1-methyl-2,3,4,5-tetrahydro-1-benzazepine was prepared in ethanol and obtained, after recrystallization from the same solvent, as yellow needles, m.p. 140–140.5° (lit.[9] m.p. 139°). A mixed melting point determination of this material with an authentic sample of the picrate of 1-methyl-2,3,4,5-tetrahydro-1-benzazepine, as prepared below, showed no depression of melting point.

B. From Homodihydrocarbostyril (X).—A solution of 2.0 g. of homodihydrocarbostyril[17] in 100 ml. of ether was added dropwise with stirring to a suspension of lithium aluminum hydride in 70 ml. of ether and the resulting mixture was boiled under reflux for 12 hours. The reaction mixture then was decomposed by addition of 10 ml. of water followed by 100 ml. of 10% aqueous sodium hydroxide solution. The ethereal layer was separated, dried and concentrated. Distillation of the residue gave 1.73 g. (95%) of a colorless oil, b.p. (bath temperature) 130–135° at 15 mm. The formation of the corresponding picrate, m.p. 179–181°, and hydrochloride, m.p. 187–188°, showed the product to be 2,3,4,5-tetrahydro-1-benzazepine (for 2,3,4,5-tetrahydro-1-benzazepine, von Braun[18] gives a picrate, m.p. 179–181°, and a hydrochloride, m.p. 188°).

When the above oil was heated with methyl iodide, it was possible to isolate a tertiary base which readily formed a picrate. This, after recrystallization from ethanol, melted at 140–141° as previously described for the picrate of N-methyl-2,3,4,5-tetrahydro-1-benzazepine.[9]

Conversion of 1-Methyl-2,3,4,5-tetrahydro-1-benzazepine (IX) to 2,3,4,5-Tetrahydro-1-benzazepine (XI).—A mixture of 1.0 g. of 1-methyl-2,3,4,5-tetrahydro-1-benzazepine (IX) and 1.2 g. of cyanogen bromide was warmed gently until methyl bromide ceased to be evolved (30 min.). The solution then was poured into ether and filtered to remove a minute quantity of quaternary salts. After the ether solution had been washed with acid to remove any of the starting base, it was dried and concentrated. Distillation of the residue gave 700 mg. of 1-cyano-2,3,4,5-tetrahydro-1-benzazepine as a colorless oil, b.p. 180–200° at 12 mm. A solution containing 540 mg. of this oil in 24 ml. of concentrated hydrochloric acid was boiled under reflux for 3 hours. When the solution was made alkaline and extracted with ether, concentration of the ether extracts followed by distillation gave 410 mg. of 2,3,4,5-tetrahydro-1-benzazepine (XI), identified as its picrate, m.p. 179–181°.[18]

1-Trichloroacetyl-2,3,4,5-tetrahydro-1-benzazepine.—To a solution of 2.0 g. of 2,3,4,5-tetrahydro-1-benzazepine (XI) in 200 ml. of ether there was added slowly with cooling a solution of 1.26 g. of trichloroacetyl chloride in 20 ml. of ether. A vigorous reaction occurred followed by the separation of 2,3,4,5-tetrahydro-1-benzazepine hydrochloride. This was removed by filtration and the ether solution was concentrated to give a solid residue. Recrystallization of this solid from aqueous ethanol gave 1.65 g. (83%) of white crystals, m.p. 114–115°. Attempts to convert this material to the corresponding oxindole derivative by Friedel-Crafts type cyclization were unsuccessful.

Anal. Calcd. for $C_{12}H_{12}NOCl_3$: C, 49.24; H, 4.13. Found: C, 49.32; H, 4.28.

1,7-Butanoisatin (XII).—To a mixture prepared by adding a solution of 5.6 g. of chloral hydrate in 50 ml. of water to a solution of 8.5 g. of hydroxylamine hydrochloride in 100 ml. of water there was added 4.7 g. of 2,3,4,5-tetrahydro-1-benzazepine. An addition of 3.5 ml. of concentrated hydrochloric acid was made to ensure a homogeneous solution. After the addition of 75 g. of solid sodium sulfate, the mixture was raised slowly to boiling over a period of 40 minutes. It was boiled under reflux for 5 minutes and then allowed to cool over a period of two hours. The dark oil which separated slowly crystallized to give 4.8 g. (68%) of a tan solid (1-isonitrosoacetyl-2,3,4,5-tetrahydro-1-benzazepine). This product could not be recrystallized readily and was used directly without further purification following the procedure of Sandmeyer[19] for preparing isatin derivatives. To 20 g. of concentrated sulfuric acid maintained at 55° a 4.5-g. sample of the 1-isonitroso derivative was added slowly with stirring over a period of 20 minutes and then the resulting solution was heated an additional 20 minutes at 72°. When the solution was poured onto crushed ice, a reddish-brown precipitate separated which was collected and dried. Recrystallization of this solid from *n*-hexane gave 1.8 g. (30%) of orange crystals, m.p. 155.0–155.5°. These crystals dissolved in aqueous sodium hydroxide solution but were regenerated on addition of acid, as would be expected for an isatin derivative. Also, the crystals gave an intense blue indophenine reaction characteristic of isatin derivatives. The ultraviolet absorption spectrum of these crystals showed maxima at 249 (log ε 4.43), 310 (log ε 3.62) and 440 mμ (log ε 2.86), which by comparison with N-methylisatin (maxima at 245 (log ε 4.35) 299 (log ε 3.37) and 420 mμ (log ε 2.70)[20]) likewise substantiates the isatin structure.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.48; H, 5.63; N, 7.06.

1-Methyl-4-formyl-5-keto-2,3,4,5-tetrahydro-1-benzazepine (XIII).—To a suspension of 7.5 g. of dry, methanol-free sodium methoxide in 50 ml. of benzene there was added a solution of 25 g. of freshly distilled ethyl formate in 25 ml. of dry benzene. A solution of 20 g. of 1-methyl-2,3,4,5-tetrahydro-5-keto-1-benzazepine (VIII) in 200 ml. of benzene then was added dropwise with stirring to the resulting mixture maintained at ice-bath temperatures. When the mixture was allowed to warm, an exothermic reaction occurred and the solution turned orange. After the mixture had been allowed to stand at room temperature for 1 hour, it was boiled under reflux for 10 minutes and then decomposed by the addition of 100 ml. of water. The benzene layer was separated, washed with aqueous sodium carbonate solution and the combined alkaline extracts were acidified to *p*H 6 with hydrochloric acid. The yellow oil which separated was extracted with ether and dried. Concentration of the ethereal solution gave a yellow solid which, after recrystallization from *n*-hexane, gave 15.5 g. (72%) of yellow plates, m.p. 57–57.5°. This material was amphoteric and gave a strong ferric chloride test for an enol. Concentration of the benzene extract led to the recovery of 1.5 g. of VIII.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.13; H, 6.48; N, 7.13.

1-Methyl-4-hydroxymethyl-5-keto-2,3,4,5-tetrahydro-1-benzazepine (XV).—A solution of 300 mg. of 1-methyl-4-

(17) L. H. Briggs and G. C. De Ath, *J. Chem. Soc.*, 456 (1937).

(18) J. von Braun and B. Bartsch, *Ber.*, **45**, 3378 (1912).

(19) T. Sandmeyer, *Helv. Chim. Acta*, **2**, 234 (1919).

(20) R. G. Ault, E. L. Hirst and R. A. Morton, *J. Chem. Soc.*, 1653 (1935).

formyl-5-keto-2,3,4,5-tetrahydro-1-benzazepine (XIII) in 150 ml. of ethanol was subjected to hydrogenation over Raney nickel catalyst at room temperature and atmospheric pressure. Approximately one mole of hydrogen was absorbed in 2 hours. After removal of the catalyst and solvent, the residue was taken up in ether and washed with aqueous sodium hydroxide. The ether solution, after drying and concentration, gave a yellow oil in excellent yield that was purified by distillation using a short-path still. This product gave no color with ferric chloride solution. When this experiment was repeated substituting Adams catalyst for the Raney nickel catalyst, the results were essentially identical.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.51; H, 7.58; N, 6.85.

1-Methyl-4-benzoyloxymethylene-5-keto-2,3,4,5-tetrahydro-1-benzazepine (XIV).—To a solution of 300 mg. of XIII in 1.5 ml. of pyridine there was added a solution of 400 mg. of benzoic anhydride in 10 ml. of ether and the resulting mixture was allowed to stand at room temperature for 20 hours. After the ether had been removed *in vacuo*, the residue was poured into water from which there separated an oil that slowly solidified. Recrystallization of this solid from methanol gave 400 mg. (89%) of yellow plates, m.p. 108–109°. These crystals gave no color with ferric chloride solution.

Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.12, H, 5.49; N, 4.52.

1,4-Dimethyl-5-keto-2,3,4,5-tetrahydro-1-benzazepine (XVI).—A solution of 230 mg. of 1-methyl-4-benzoyloxymethylene-5-keto-2,3,4,5-tetrahydro-1-benzazepine (XIV) in 20 ml. of ethanol was subjected to hydrogenation over platinum oxide catalyst (100 mg.) at room temperature and atmospheric pressure. When two moles of hydrogen had been absorbed (40 min.), the hydrogenation was stopped and the catalyst and solvent were removed. The residue was taken up in ether and washed 3 times with 25-ml. portions of a saturated sodium bicarbonate solution. Acidification of the alkaline solution gave 82 mg. (89%) of benzoic acid, m.p. 121°. When the ether solution was concentrated and the residue distilled, there was obtained 135 mg. (95%) of a pale yellow oil, b.p. 90–110° at 0.5 mm.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.21; H, 8.18; N, 7.05.

1,4-Dimethyl-5-hydroxy-2,3,4,5-tetrahydro-1-benzazepine (XVIII).—A suspension containing 410 mg. of 1,4-dimethyl-5-keto-2,3,4,5-tetrahydro-1-benzazepine (XVI) and 100 mg. of solid lithium aluminum hydride in 100 ml. of ether was stirred at room temperature for 4 hours. The excess of lithium aluminum hydride was destroyed by addition of ethyl acetate followed by water. After separation from the precipitated hydroxides, the ethereal solution was dried and concentrated. Distillation of the residue gave 310 mg. (76%) of a pale yellow oil, b.p. (bath temperature) 90–120° at 0.3 mm. The infrared absorption spectrum of this oil showed a strong peak in the hydroxyl region (3.0 μ), as is in accord with structure XVIII.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H. 8.96; N, 7.32. Found: C, 75.69; H, 9.20; N, 7.28.

When a sample of the above oil was treated with ethanolic picric acid, there was obtained yellow needles, m.p. 154–155° after recrystallization from absolute ethanol. The composition of this picrate, as well as a mixed melting point determination with an authentic sample, demonstrated that it was the picrate of compound XIX. Evidently the dehydration of XVIII occurs with such ease that picric acid is sufficiently acidic to accomplish this conversion.

Anal. Calcd. for $C_{18}H_{18}N_4O_7$: C, 53.78; H, 4.51. Found: C, 54.22; H, 4.89.

1,4-Dimethyl-2,3-dihydro-1-benzazepine (XIX).—A solution of 240 mg. of 1,4-dimethyl-5-hydroxy-2,3,4,5-tetrahydro-1-benzazepine (XVIII) in 15 ml. of 6 *N* hydrochloric acid was boiled gently under reflux for 15 min. The solution was then made basic by addition of aqueous ammonium hydroxide and extracted with ether. Concentration of the ether extract followed by distillation of the residue gave 210 mg. (97%) of a pale yellow oil, b.p. 115–117° at 0.3 mm. The infrared spectrum of this oil showed no absorption in the hydroxyl region but did reveal absorption at 6.13 μ, supposedly due to the trisubstituted double bond in XIX.

Anal. Calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 82.85; H, 8.99; N, 8.10.

The picrate of XIX formed readily in ethanol and was obtained, after recrystallization from this solvent, as yellow needles, m.p. 155–156°.

Anal. Calcd. for $C_{18}H_{18}N_4O_7$: C, 53.78; H, 4.51. Found: C, 53.89; H, 4.69.

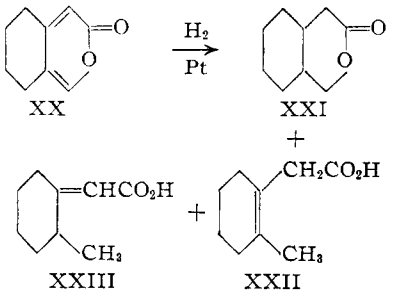
The methiodide of XIX was prepared in ethanol and obtained after recrystallization from benzene as pale yellow crystals, m.p. 159–161°. The crystals appeared to decompose to some extent on recrystallization and a sample of high purity could not readily be obtained.

Anal. Calcd. for $C_{13}H_{18}NI$: C, 49.42; H, 5.77. Found: C, 48.18; H, 5.80.

Attempted Reaction of Ethyllithium with 1,4-Dimethyl-5-keto-2,3,4,5-tetrahydro-1-benzazepine (XVI).—To a solution prepared by adding 1.2 g. of ethyl bromide to 150 mg. of lithium chips in 40 ml. of dry ether and maintained under an atmosphere of nitrogen there was added a solution of 690 mg. of 1,4-dimethyl-5-keto-2,3,4,5-tetrahydro-1-benzazepine (XVI) in 50 ml. of ether. The reaction mixture was boiled under reflux for 6 hours and then decomposed by addition of water. After the ether solution was separated and concentrated, the residue was distilled to give 550 mg. (80% recovery) of an oil whose ultraviolet and infrared absorption spectra were identical with that of XVI. Although a number of similar attempts to accomplish the desired reaction were made under varying conditions, in each case the starting material was recovered. A similar result also occurred when methyllithium was substituted for ethyllithium in the above experiment.

Hydrogenation of 4,5-Butano-α-pyrone (XX).—Plattner, Treadwell and Scholtz[21] have reported the conversion of 2-benzoyloxymethylenecyclohexanone to 4,5-butano-α-pyrone. If compound XIV could be carried through a similar transformation and then reduced in the proper manner, it would give the lactone ring system of apo-β-erythroidine (I). For this reason model studies were made with 4,5-butano-α-pyrone to determine whether such a hydrogenation would be successful. When a solution of 578 mg. of 4,5-butano-α-pyrone[21] (XX) in 100 ml. of ethanol was subjected to hydrogenation at room temperature and atmospheric pressure over 100 mg. of prereduced platinum oxide, a rapid uptake of hydrogen occurred until two moles had been absorbed. After removal of the catalyst and solvent, the residue was taken up in ether and extracted with an aqueous 5% solution of sodium carbonate. Concentration of the ether solution followed by distillation of the residue gave 365 mg. (63%) of a colorless oil, b.p. 70–75° at 1 mm. The infrared spectrum of this oil showed absorption at 5.81 μ, corresponding to the carbonyl group of a δ-lactone, and no other absorption indicating unsaturation. Therefore this product has been assigned structure XXI.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.01; H, 9.14.



When the sodium carbonate extract from the above experiment was acidified, an oil separated which was extracted with chloroform. Concentration of the chloroform extract followed by distillation of the residue gave 200 mg. of a colorless oil, b.p. 75–80° at 1 mm. The infrared spectrum of this oil has no absorption in the region where a terminal methylene group should absorb, although a small peak was present at 12.53 μ, suggesting the presence of a

(21) Pl. A. Plattner, P. Treadwell and C. Scholtz, *Helv. Chim. Acta*, **28**, 771 (1945).

trisubstituted double bond. It would seem probable that this acidic fraction is a mixture of compounds XXII and XXIII.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.57; H, 9.36.

ROCHESTER, NEW YORK

[CONTRIBUTION FROM RIKER LABORATORIES, INC.]

Alkaloids of *Rauwolfia canescens* Linn. II.[1] The Isolation and Structure of Canescine

BY M. W. KLOHS, F. KELLER, R. E. WILLIAMS AND G. W. KUSSEROW

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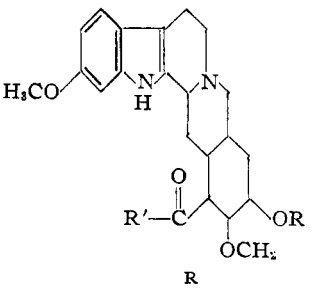
Canescine ($C_{32}H_{38}O_8N_2$), a new alkaloid possessing hypotensive and sedative activity, has been isolated from *Rauwolfia canescens* Linn. On basic hydrolysis canescine yielded canescic acid and one mole each of 3,4,5-trimethoxybenzoic acid and methanol. Selenium dehydrogenation of methyl canescate afforded yobyrine. On the basis of chemical and spectral data, a tentative structural formula for canescine is proposed.

An extension of our search for alkaloids possessing hypotensive activity has resulted in the isolation of a new alkaloid, **canescine**, from *Rauwolfia canescens* Linn. Previous reports on the alkaloids present in this species have dealt with the isolation of rauwolscine,[2] reserpine,[1] yohimbine and serpentine.[3]

Pharmacological studies[4] with canescine have shown it to possess the same order of sedative activity as reserpine, and hypotensive activity comparable to reserpine and rescinnamine. The latter two alkaloids, to which a large measure of the hypotensive and sedative activity of *Rauwolfia serpentina* Benth has been ascribed, have been shown to possess the structures



	R	R′
I, Reserpine[5]	3,4,5-$(OCH_3)_3C_6H_2CO$–	OCH_3
II, Rescinnamine[6]	3,4,5-$(OCH_3)_3$-$C_6H_5CH{=}CHCO$–	OCH_3
III, Reserpic acid[5]	H	OH

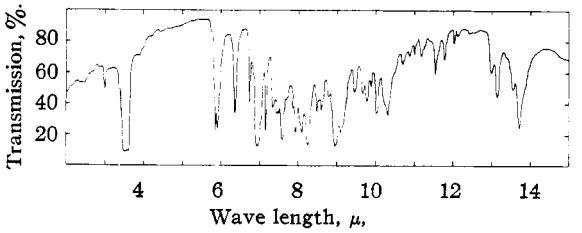


Fig. 1.—Infrared spectrum of canescine (Nujol).

Canescine was isolated by chromatographic separation of the crude reserpine fraction obtained from the roots of *Rauwolfia canescens*, and could be crystallized from methanol in several interconvertible crystalline modifications. A 24-plate countercurrent distribution of this material between 5% acetic acid and methylchloroform gave a single peak which corresponded well with the theoretical curve for a single substance.

The analyses of canescine and three of its salts were in agreement with the empirical formula $C_{32}H_{38}O_8N_2$, showed the presence of five methoxyl groups, and the absence of a C-methyl group. The infrared spectrum of canescine (Fig. 1) was quite similar to the spectra of reserpine and rescinnamine, exhibiting the characteristic free >NH band at 2.95 μ, the double ester carbonyl bands at 5.81, 5.88 μ and aromatic absorption at 6.30, 6.70 μ. An important difference was noted, however, in the absence of a band at 6.2 μ, previously shown to be due to polarization of an indole nucleus by a methoxyl group in the 6-position.[7] This difference suggested that, unlike reserpine and rescinnamine, which differ only in their acid conjugates, canescine must differ in its alkamine moiety. The significance of this, from the point of view of a structure–activity relationship, was of particular interest. In view of these preliminary data, the most expeditious approach to the structural elucidation of canescine appeared to be an examination of its hydrolysis products.

On subjecting canescine to basic hydrolysis with dilute methanolic sodium hydroxide, two acidic fragments were isolated, one as a free acid which was identified readily as 3,4,5-trimethoxybenzoic acid, and the other as the nitrate salt of an amino acid which proved to be a new compound, canescic acid nitrate ($C_{21}H_{26}O_4N_2 \cdot HNO_3$). On treating a methanolic solution of this salt with ammonium hydroxide the free acid, canescic acid, was obtained which had an infrared spectrum typical of a zwitterionic amino acid. On treatment with diazomethane, canescic acid yielded methyl canescate (isolated as its nitrate salt), which was identical with the compound obtained on methanolysis of canescine. The ultraviolet spectrum of methyl canescate nitrate compared very well with that exhibited by an α,β-disubstituted indole chromophore such as is found in yohimbine; thus the

(1) For the first paper of this series see M. W. Klohs, M. D. Draper, F. Keller and F. J. Petracek, THIS JOURNAL, **76**, 1381 (1954).

(2) A. Mookerjee, *J. Indian Chem. Soc.*, **18**, 33 (1941).

(3) A. Popelak, H. Spingler and F. Kaiser, *Naturwissenschaften*, **41**, 479 (1954).

(4) This work was carried out in the Biological Sciences Section of this Laboratory, and the results will be published elsewhere by Dr. G. E. Cronheim.

(5) *Cf.* L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Muller, E. Schlittler, R. Schwyzer and A. F. St. Andre, *Helv. Chim. Acta*, **37**, 59 (1954), and references cited therein.

(6) M. W. Klohs, M. D. Draper and F. Keller, THIS JOURNAL, **76**, 2843 (1954).

(7) N. Neuss, H. E. Boaz and J. W. Forbes, *ibid.*, **76**, 2463 (1954).