was triturated with 80 ml. of ether followed by the addition of *ca.* 300 ml. of petroleum ether (60–90°) and the yellow product collected. The filter cake was washed with additional petroleum ether and sucked dry; wt. 3.0 g. (80% yield), m.p. 115–120° dec. The same procedure was employed to prepare IXh, m.p. 119–125°.

(**IXc**).—To a solution of 1.7 g. of *p*-nitrobenzaldehyde (0.011 mole) in 40 ml. of absolute ethanol was added 2.0 g. of IIa (0.01 mole). The addition of 5 drops of concentrated hydrochloric acid provided a homogeneous mixture from which a brown solid was deposited on cooling. The product was collected and sucked dry (wt. 1.4 g.), and oxidized to a tetrazolium betaine.

3,5-Diaryl-1-(5′-tetrazolyl)(1H)tetrazolium Betaines (X).—The oxidative ring closure of the benzaltetrazenes (IX) was accomplished in all cases with concentrated nitric acid. The yields reported in Table II are based on the corresponding 1-(5′-tetrazolyl)-3-aryltetrazene (II), rather than IX, since the degree of purity of the benzal derivatives was uncertain. The preparation of Xe is presented as a typical example.

Crude 1-(5′-tetrazolyl)-3-(*p*-chlorophenyl)-4-(*p*-chlorobenzal)-tetrazene (IXe) (3.0 g.), obtained from 2.0 g. of 1-(5′-tetrazolyl)-3-(*p*-chlorophenyl)tetrazene (IIb) (0.008 mole) was added portionwise to 30 ml. of cold concentrated nitric acid. The solid dissolved readily with a slight evolution of gas with the temperature rising to 20°. The yellow solution was poured onto ice, the off-white colored solid collected, washed with water and sucked dry; wt. 2.8 g. (93% yield), m.p. 304–307° dec. An analytical sample was obtained by recrystallization from glacial acetic acid, m.p. 306–307° dec. (*cf.* Table I for analysis). It was convenient to recrystallize Xa, c, f, j and k from ethanol. On the other hand Xd, e, g and h are best recrystallized from glacial acetic acid.

Acid Degradation of 3,5-Diphenyl-1-(5′-tetrazolyl)(1H)-tetrazolium Betaine (Xa).—A suspension of 4.0 g. of Xa (0.014 mole) was suspended in 130 ml. of concentrated hydrochloric acid and the mixture refluxed for 48 hours. During this period the solid slowly disappeared and a yellow oil was deposited at the bottom of the flask. In addition a small amount of solid crystallized in the condenser. To the cooled reaction mixture was added 20 ml. of water and the yellow oil, which solidified, was collected; wt. 1.8 g., m.p. 91–98°. This material was combined with the solid which was deposited in the condenser and the solid crystallized from ethanol in the form of white needles, wt. 2.55 g., m.p. 101–102°.

Anal. Calcd. for $C_{13}H_{10}N_4$: C, 70.27; H, 4.50; N, 25.22. Found: C, 70.21; H, 4.51; N, 24.90.

This product proved to be 2,5-diphenyltetrazole (XII), m.p. (lit.[22] 101–101.5°).

The acid filtrate was evaporated to dryness on a steam-bath in a stream of air and the residue heated to boiling with 40 ml. of water. The insoluble material, 0.6 g., m.p. 296–300°, was identified as starting material. The aqueous filtrate was treated with Norit, filtered and the filtrate concentrated to *ca.* 5 ml. A white solid was deposited on cooling, wt. 0.5 g., m.p. 253–255°. A second crop of the same solid was obtained on further concentration of the mother liquor, wt. 0.1 g., m.p. 249–253°. This material failed to depress the melting point of an authentic sample of 5-hydroxytetrazole (XI).

The conversion of Xa to 2,5-diphenyltetrazole and 5-hydroxytetrazole was 98 and 60%, respectively.

(22) O. Dimroth and S. Merzbacher, *Ber.*, **40**, 2402 (1907).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Aromatic Cyclodehydration. XXXVI.[1,2] The Synthesis of (±)-Cryptopleurine

BY C. K. BRADSHER AND H. BERGER

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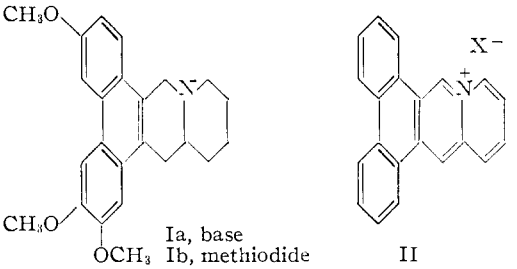
The correctness of the structural formula proposed by Fridrichsons and Mathieson for (±)-cryptopleurine methiodide has been demonstrated by synthesis. The first steps involved preparation of 2,3,6-trimethoxy-9-phenanthroic acid (VI) *via* the Pschorr synthesis. The carboxyl group of acid VI was converted in three steps to the bromomethyl group and the resulting compound IX used as the halide component in an acridizinium ion synthesis. The crude X thus obtained was reduced to yield (±)-cryptopleurine (Ia).

The alkaloid cryptopleurine, isolated[3] from the bark of an Australian laurel *Cryptocarya pleurosperma* (White and Francis), is a vesicant[3,4] which has been reported to stimulate the growth of nerve tissue[5] and to be highly toxic to animals.[3] To date there are no reports to indicate that the alkaloid has been synthesized, or degraded to compounds of known structure. In arriving at the unusual formula (Ia) shown, Fridrichsons and Mathieson[6] had available chemical evidence concerning the composition[7] and the presence of three methoxyl groups,[3,7] as well as spectral evidence for the presence of a phenanthrene or triphenylene nucleus,[7] but relied almost completely upon their own X-ray crystallographic studies on what is now[8] known to be the methiodide (Ib) of (±)-cryptopleurine.



Ia, base
Ib, methiodide
II

Since cryptopleurine (Ia) is closely related in structure to the dibenzo[h,j]acridizinium ion (II) which has been prepared earlier[9] by the aromatic cyclodehydration method, it seemed probable that the alkaloid could be synthesized. The 2,3,6-trimethoxy-9-phenanthroic acid needed was pre-

(1) For the preceding communication of this series see THIS JOURNAL, **79**, 6033 (1957).

(2) This work was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health, Public Health Service. This paper was presented at the 132nd National Meeting of the American Chemical Society in New York, N. Y., September 10, 1957. A preliminary report appeared as a Communication to the Editor, THIS JOURNAL, **79**, 3287 (1957).

(3) I. S. de la Lande, *Australian J. Exp. Biol. Med. Sci.*, **26**, 181 (1948).

(4) L. J. Webb, *Australian J. Sci.*, **11**, 26 (1948).

(5) H. Hofmann, *Australian J. Exp. Biol. Med. Sci.*, **30**, 541 (1952).

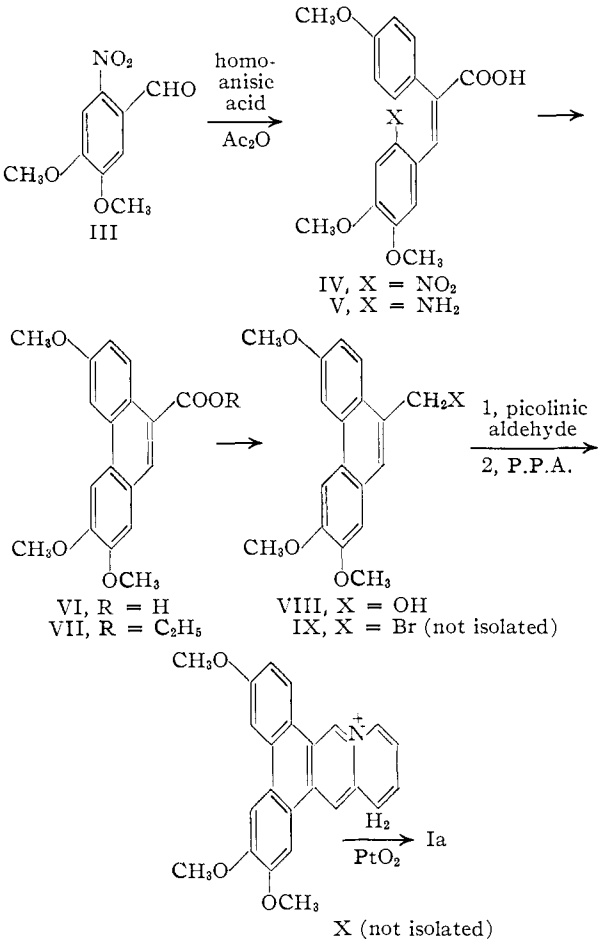
(6) J. Fridrichsons and A. Mathieson, *Acta Cryst.*, **8**, 761 (1955); *cf. Nature*, **173**, 732 (1954).

(7) E. Gellert and N. V. Riggs, *Australian J. Chem.*, **7**, 113 (1954).

(8) E. Gellert, *ibid.*, **9**, 489 (1956).

(9) C. K. Bradsher and L. E. Beavers, THIS JOURNAL, **78**, 2459 (1956).

pared by the Pschorr synthesis.[10] The condensation of 6-nitroveratraldehyde[11] (III) with homoanisic acid afforded the expected product (IV, 50% yield) which was reduced by the action of ferrous sulfate to the amine (V, 80% yield). A number of conditions were tried for the cyclization of the amine V, but best results were obtained (54% yield) when the diazonium salt was formed in acetone solution and allowed to decompose slowly in the presence of copper.



While the methyl ester of the phenanthroic acid (VI) proved too insoluble for satisfactory reduction with lithium aluminum hydride, the ethyl ester afforded a 98% yield of the expected carbinol VIII. The crude bromide IX, obtained by the action of hydrogen bromide, was used directly in the quaternization experiments with picolinic aldehyde. The great insolubility of the bromide made it impossible to form the quaternary salt satisfactorily either in the direct manner[12] or in the presence of a small quantity of methanol,[1] but quaternization was rapid at 80° in the presence of a small quantity of dimethylformamide.

It had been anticipated that ether cleavage during the cyclization step might be difficult to avoid, for it had been shown[1] that 8-methoxyacridizinium bromide underwent ether cleavage after only three minutes in boiling 48% hydrobromic acid.[13] Cyclization in polyphosphoric acid at 80° afforded a substance having the properties expected for the dibenzoacridizinium derivative X. The substance proved very insoluble and could not be obtained in a state of analytical purity.

Reduction of the salt X proved very difficult until it had been purified by passing it through an anion exchange column loaded with chloride ion. The reduction product, purified by chromatography on alumina, melted at 199–200°[14] as compared with 197–198° reported[7,8,15] for (±)-cryptopleurine. The ultraviolet absorption spectrum of the synthetic base is very similar to that reported[7] for (−)-cryptopleurine and tne infrared absorption spectrum is identical in almost every detail with that reported by Gellert[7,16] for the active base.

The methiodide of our synthetic base when first prepared melted at 214–215° as compared with 270–272° reported by Gellert and Riggs[7] for (±)-cryptopleurine methiodide. When a solution of our low-melting methiodide was seeded with a single crystal of (±)-cryptopleurine methiodide[17] (reported[7] m.p. 270–272°) all of our methiodide was converted to the higher melting form (m.p. 272–274°[14]). The infrared spectrum for our higher melting methiodide was identical with that for (±)-cryptopleurine methiodide.

It is interesting to note that the low-melting form of the methiodide (m.p. 214–215°) gives a slightly different infrared spectrum from that of the higher melting form (272–274°). The fact that the lower melting point corresponds roughly to that of (−)-cryptopleurine methiodide (215–217°) suggests that the lower melting form may be a racemic mixture while the higher melting form is a racemic compound.[18]

Experimental[19]

6-Nitro-3,4,4′-trimethoxy-α-phenylcinnamic Acid (IV).—A solution of 25 g. of dry potassium homoanisate[20] and 31 g. of 6-nitroveratraldehyde[11] (III) in 90 ml. of freshly distilled acetic anhydride was stirred and heated for eight hours at 105–115°, care being taken to exclude moisture. The excess anhydride was hydrolyzed by the addition of 200 ml. of hot water, care being taken to keep the temperature below 105°. The mixture was cooled in ice while stirring was continued for two hours. The resulting crystalline material was col-

(10) For an excellent review on this subject see P. H. Leake, *Chem. Revs.*, **56**, 27 (1956).

(11) J. T. Cassaday and M. T. Bogert, THIS JOURNAL, **61**, 2462 (1939).

(12) C. K. Bradsher and L. E. Beavers, *ibid.*, **77**, 4812 (1955).

(13) Although by use of a hydrochloric acid cyclizing medium it has been possible to prepare acridizinium salts having alkoxyl groups (ref. 1), it should be noted that in all of the cases reported cyclization occurred *ortho* or *para* to an alkoxyl group.

(14) This melting point was determined on the Kofler block and is corrected.

(15) Dr. Gellert has kindly compared our preparation with (±)-cryptopleurine and reports that there is no significant melting point depression when the samples are mixed.

(16) The slight difference in infrared spectra can be attributed to the fact that both the synthetic base and optically active base were examined in the solid phase, by the potassium bromide plate and the Nujol-mull methods, respectively.

(17) We are indebted to Dr. Gellert for this sample as well as for several useful suggestions.

(18) We are indebted to Dr. Robert E. Lutz for this suggestion.

(19) Except as noted all melting points were determined on the Fisher–Johns block and are uncorrected. Infrared absorption spectra were determined by the potassium bromide plate method using the Perkin–Elmer model 21 infrared spectrophotometer. Except as mentioned, all analyses were by Micro-Tech Laboratories, Skokie, Ill.

(20) The homoanisic acid (m.p. 83–85°) required was prepared in 59% yield by the general method of E. Schwenk and E. Bloch (THIS JOURNAL, **64**, 3050 (1942)).

lected and washed with ethanol. The product was recrystallized from ethanol (Norite) discarding some very slightly soluble impurity; yield 21 g. of small yellow diamond-shaped crystals, m.p. 183–184° with preliminary melting and resolidification at 90–120°. By working up the mother liquor of the reaction mixture, an additional 1 g. can be obtained making a total of 22 g. (50%). The analytical sample melted at 185–186°.

Anal. Calcd. for $C_{18}H_{17}NO_7 \cdot H_2O$: C, 57.29; H, 5.08; N, 3.71. Found: C, 57.11; H, 4.77; N, 3.90.

6-Amino-3,4,4′-trimethoxy-α-phenylcinnamic Acid (V).—A solution containing 10 g. of the nitro acid IV in dilute ammonium hydroxide was added in the course of three or four minutes to a boiling solution containing 60 g. of ferrous sulfate and 14 ml. of concentrated ammonium hydroxide solution in 175 ml. of water. During the course of the next 1.25 hours a total of 132 ml. of concentrated ammonium hydroxide was added slowly to the boiling mixture. It was found advantageous to add octyl alcohol to prevent foaming. After the mixture had been cooled to 40°, it was filtered and the residue thrice extracted with hot dilute ammonium hydroxide solution. The combined ammoniacal solutions were acidified with acetic acid. The crude amino acid was purified, first by reprecipitation from ammonium hydroxide, and then by recrystallization from alcohol as yellow needles, m.p. 203°, yield 7.5 g. (80%). The analytical sample melted at 206–207°.

Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.54; H, 5.51; N, 4.67.

2,3,6-Trimethoxy-9-phenanthroic Acid (VI).—Five grams of the amino acid V was suspended in 200 ml. of pure acetone, and 25 ml. of 20% sulfuric acid was added. On stirring for 15 minutes a white suspension of the sulfate was formed. This suspension was cooled to 3–5° and 2.6 g. of isoamyl nitrite was added. At the end of a half or three-quarters hours at the same temperature, 3 g. of Gattermann copper powder was added to the clear red solution, and the mixture stirred at the same temperature for several hours longer, and finally overnight at 30–35°. The acetone solution was filtered to remove inorganic material and poured into 1.5 l. of water. The light orange precipitate was collected, dried, and recrystallized from ethanol, m.p. 217–218°, yield 2.6 g. (54%). The analytical sample was obtained as small pale yellow elongated rectangular plates, m.p. 222°.

Anal. Calcd. for $C_{18}H_{16}O_5 \cdot H_2O$: C, 65.44; H, 5.49. Found: C, 65.54; H, 5.36.

The ethyl ester VII was formed by refluxing 5 g. of acid in 150 ml. of absolute ethanol containing 4 ml. of sulfuric acid. Worked up in the usual way the ester formed small colorless irregular crystal aggregates from ethanol, m.p. 135–138°; yield 4.8 g. (89%). The analytical sample melted at 136.5–137°.

Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.45; H, 5.83.

2,3,6-Trimethoxy-9-phenanthrylcarbinol (VIII).—To a suspension of 1.5 g. of lithium aluminum hydride in a mixture containing 140 ml. of dry ether and 20 ml. of dry benzene, a solution of 4.5 g. of the ethyl ester VII, in a mixture of 40 ml. of benzene and 120 ml. of ether, was added at such a rate as to cause gentle refluxing (formation of a precipitate). The mixture was refluxed an additional hour, after which alcohol was added (to destroy excess hydride), and finally 150 ml. of 6 *M* sulfuric acid was added. The resulting precipitate was collected, washed with dilute ammonium hydroxide, and then taken up in chloroform. The solution was washed with water and concentrated. Crystallization of the product from benzene afforded 3.9 g. (98%) of very small, colorless needles, m.p. 184–187°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.56; H, 6.17.

2′,3′,6′-Trimethoxyphenanthro[9′,10′,2.3]quinolizidine ((±)-Cryptopleurine, Ia).—A slow stream of hydrogen bromide gas was passed through a solution containing 500 mg. of the carbinol VIII in 15 ml. of chloroform for 0.5 hour. The temperature was controlled by cooling the flask in cold water, 10 ml. of benzene was added and the benzene solution was decanted from the small amount of water formed in the reaction. Evaporation of the benzene left a residue which was redissolved in benzene and the solution reevaporated to yield a white solid. The solid which is presumably 2,3,6-trimethoxy-9-bromomethylphenanthrene (IX) was not purified further, but mixed with 0.7 g. of picolinic aldehyde and 0.25 g. of dimethylformamide and the mixture heated at 80° for one hour under a nitrogen atmosphere. The solid which formed was triturated with chloroform and washed with chloroform and ether. The crude salt (about 0.65 g.) thus obtained was dissolved in 15 ml. of polyphosphoric acid and the mixture heated at 80° for five hours under a nitrogen atmosphere. At the end of this period, the mixture was poured into 150 ml. of cold water with the formation of a precipitate. After the mixture had stood for three hours, the precipitate was collected and dissolved in a mixture of 50 ml. of methanol and 15 ml. of 48% hydrobromic acid. After the mixture had stood in the refrigerator for one night the product separated either as a solid or as an oil. The solid was simply collected but, in case the oil formed, the mother liquor was decanted and the oil treated with methanol, which caused it to solidify. From the mother liquor an additional crop could be obtained by addition of ethyl acetate. The total yield of crude yellow powder, presumably the acridizinium derivative (X), was 0.37–0.48 g. No satisfactory method was found for the purification of this product.

In order to carry out the reduction, 250 mg. of the crude product (X) was dissolved in methanol containing a few drops of hydrochloric acid, and the solution percolated through a small column filled with an anion exchange resin (Amberlite IRA 410) loaded with chloride ion.[21] To the solution, 50 mg. of platinum oxide catalyst was added and hydrogenation at atmospheric pressure was carried out until the solution became colorless. Water and a slight excess of sodium carbonate were added to the filtered solution and the base extracted with chloroform. The chloroform solution was dried by filtration through anhydrous sodium sulfate and the solvent evaporated *in vacuo*. The residue was dissolved in benzene and the solution evaporated. The mixture of yellow and white solids obtained was dissolved in benzene and the solution purified by chromatography on alumina. The desired product shows a purple fluorescence under ultraviolet light, and separation of this band using benzene as the eluting solvent, yielded, on evaporation of the solution, 70 mg. of colorless needles, m.p.[14] 199–200° (lit.[7] 197–198°). No improvement in melting point was effected by recrystallization of the sample from benzene–petroleum ether.

The ultraviolet absorption spectrum was determined in 95% ethanol using the Warren Spectracord spectrophotometer; λ_{max} (log ϵ) 258 (4.76), 284 (4.51) and 358 mμ (2.75).

Anal. Calcd. for $C_{24}H_{23}NO_3$: C, 76.36; H, 7.21; N, 3.71. Found[22]: C, 75.85, 76.23; H, 7.17, 7.26; N, 4.00.

The methiodide Ib was obtained by adding methyl iodide to a solution of the base in chloroform. The product, crystallized from ethanol, melted at 215°.[23] A saturated solution of the methiodide in methanol, when seeded with a crystal of authentic (±)-cryptopleurine methiodide, afforded colorless needles, m.p. 272–274°[14] (lit.[7] 270–272°). The methiodide did not depress the melting point of an authentic specimen of (±)-cryptopleurine methiodide and the infrared absorption spectra of the two specimens were identical.

Anal. Calcd. for $C_{25}H_{30}NO_3I$: C, 57.80; H, 5.82; N, 2.70. Found[22]: C, 57.73; H, 6.01; N, 3.00.

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(21) When this ion-exchange step was omitted, reduction was extremely slow and never complete. It may very well be that the benefit derived from this operation is due to the removal of a small quantity of phosphate ion rather than to the replacement of bromide ion by chloride.

(22) Analysis by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(23) Gellert and Riggs (ref. 7) reported that the base obtained by treating (±)-cryptopleurine methiodide at 250° with potassium hydroxide in glycol afforded a base which yielded a methiodide, m.p. 215–217°. Since Gellert (ref. 8) has shown the base in question to be (±)-cryptopleurine, it seems probable that they too have encountered the low melting dimorph of the methiodide.