Anal. Calcd. for $C_{19}H_{26}N_2O \cdot CHCl_3$: C, 57.5; H, 6.5; N, 6.7; O, 3.8; Cl, 25.5. Found: C, 57.7; H, 6.6; N, 6.6; O, 4.1; Cl, 25.6.

The free base was obtained by sublimation of the chloroformate at 140° (10 μ) and melted at 84–87°, $[\alpha]^{25}D$ +32° (c 1.0, ethanol); ultraviolet spectrum in ethanol, λ_{max} 247 mμ (ϵ 8500), 301 (3900).

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.5; H, 8.8; N, 9.4; O, 5.4. Found: C, 76.6; H, 8.7; N, 9.3; O, 5.8.

Geissoschizoline picrolonate was prepared in absolute ethanol and was recrystallized from absolute ethanol, m.p. 209–211°.

Anal. Calcd. for $C_{19}H_{26}N_2O \cdot C_{10}H_8N_4O_5$: C, 61.9; H, 6.1. Found: C, 62.0; H, 6.0.

Diacetylgeissoschizoline was prepared by heating a solution of 500 mg. of geissoschizoline and 5 ml. of acetic anhydride in 25 ml. of pyridine on the steam-bath for three hours. This solution was poured onto 100 ml. of ice and extracted with three 150-ml. portions of chloroform after being made alkaline with concd. potassium hydroxide. Evaporation of the chloroform and crystallization of the residue from 25 ml. of acetone gave 340 mg. of diacetylgeissoschizoline, m.p. 196–197°; ultraviolet spectrum in ethanol: λ_{max} 253 mμ (ϵ 13,500), 283 (3,800), 291 (3,300).

Anal. Calcd. for $C_{23}H_{30}N_2O_3$: C, 72.2; H, 7.9; N, 7.3; O, 12.6; acetyl, 22.5. Found: C, 72.4; H, 7.8; N, 7.4; O, 12.7; acetyl, 22.4.

Acid Cleavage of Geissospermine.—Addition of 1 g. of geissospermine to 5 ml. of concd. hydrochloric acid at room temperature led to a homogeneous solution after three minutes. After five more minutes, the solution was poured into 200 ml. of cold, 1 *N* aqueous ammonia, and the mixture was extracted with three 200-ml. portions of chloroform. Drying and evaporating the chloroform left a residue which was chromatographed on alumina (Merck, 35 g.). Elution with benzene removed 200 mg. of apogeissoschizine as the first fraction, then 15% chloroform in benzene removed 450 mg. of geissoschizoline, and finally 10% methanol in chloroform removed 250 mg. of geissoschizine.

Geissoschizoline was crystallized from chloroform–hexane, m.p. 105–108°, and was found to be identical with alkaloid F_3 in every property described above. Mixtures of F_3 and geissoschizoline, and of the diacetyl derivatives, showed no melting point depression, and the infrared spectra were identical.

Geissoschizine was obtained from the 10% methanol–chloroform eluted fraction by digesting the residue with 30 ml. of methanol and filtering after thorough cooling. The crystalline material was recrystallized three times from ethanol (long reflux necessary for complete solution), m.p. 180–182°; ultraviolet spectrum in ethanol, λ_{max} 268 mμ (ϵ 14,600), 290 (7,800).

Anal. Calcd. for $C_{21}H_{24}N_2O_3$: C, 71.6; H, 6.8; N, 8.0; O, 13.6; equiv. wt., 352. Found: C, 71.9; H, 6.8; N, 8.0; O, 13.3; equiv. wt., 351.

Apogeissoschizine was found in the benzene-eluted fraction and was best characterized as the hydrochloride. This was prepared by evaporating the benzene, dissolving the residue in hexane, and passing in dry hydrogen chloride until there was no further precipitation. Apogeissoschizine hydrochloride was recrystallized by dissolving it in several ml. of methanol, adding 50 ml. of ethyl acetate, and then adding hexane until the solution became cloudy, m.p. 139–142°; ultraviolet spectrum in ethanol, λ_{max} 273 mμ (ϵ 19,300), 324 (19,000).

Anal. Calcd. for $C_{21}H_{22}N_2O_2 \cdot HCl$: C, 68.0; H, 6.3; N, 7.6; Cl, 9.6. Found: C, 67.7; H, 6.1; N, 7.7; Cl, 9.5.

BERKELEY, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Flavopereirine, an Alkaloid from *Geissospermum vellosii*

BY NEIL A. HUGHES AND HENRY RAPOPORT

RECEIVED OCTOBER 18, 1957

Flavopereirine, an alkaloid isolated from *Geissospermum vellosii*, has the four-ring indolo[2,3-a]quinolizine (I) chromophore in common with sempervirine, the difference between the two alkaloids arising in the substitution of ring D. Catalytic hydrogenation, which is quite sensitive to acid and alkali, has yielded (1) an octahydro derivative with rings A and D reduced, (2) an octahydro derivative with rings C and D reduced, (3) a tetrahydro derivative with ring D reduced, and (4) a hexahydro derivative in which ring D has undergone hydrogenation and hydrogenolysis. C-Methyl determinations on these hydrogenation products identified the ring D substituent as an ethyl group and located it at positions 1, 2 or 3. Dehydrogenation of the octahydro compound (C and D rings reduced) gave 3-ethyl-2-(5′-ethyl-2′-pyridyl)-indole (desethylalstyrine), thus establishing flavopereirine as 3-ethylindolo[2,3-a]quinolizine. The use of tetrahydroquinoline as solvent and hydrogen donor allowed the dehydrogenation reaction to be applied directly to flavopereirine with excellent results. Critical to the use of this modification was the observation that desethylalstyrine, a base of pK_a' approximately 4.5, was not removed from ether by dilute phosphoric acid.

The bark of *Geissospermum vellosii*, the tree familiarly know as pao pereira in Brazil, is quite rich in alkaloids, and a number in addition to geissospermine have been isolated crystalline.[1] The structure and chemistry of one of these new alkaloids, flavopereirine, is the subject of the present report.[2]

Fractionation of the total crude alkaloids as a function of their basicities and partition coefficients between ether and water led to a strongly basic fraction, termed F, isolated from the aqueous solution by extraction at pH 10. The separation of this fraction into two crystalline alkaloids, F_1 and F_3, has been described in detail.[1] Alkaloid F_1, flavopereirine, was then subjected to a detailed examination.[3]

The empirical formula of flavopereirine, which crystallized as well defined orange rhombs, m.p. 233–235°, was established clearly by analysis of the free base[1] and of a number of salts as $C_{17}H_{14}N_2$. That this (246) rather than any higher multiple was also the molecular formula was definitely indicated by the fact that flavopereirine could be sublimed at 200° and 0.1 mm. pressure. It was optically inactive, had no N-methyl or N-ethyl groups, and showed no C-methyl groups in Kuhn–Roth oxidation.

(1) H. Rapoport, T. P. Onak, N. A. Hughes and M. G. Reinecke, THIS JOURNAL, **80**, 1601 (1958).

(2) Supported in part by a generous grant from Smith, Kline and French Laboratories, Philadelphia, Pa.

(3) After our work had been completed, a short note appeared by O. Bejar, R. Goutarel, M. M. Janot and A. Le Hir, *Compt. rend.*, **244**, 2066 (1957), on the constitution of this alkaloid which they named flavopereirine. Since their material is identical with our F_1, we have adopted their nomenclature. Our conclusion as to the structure of flavopereirine is in agreement with theirs.

Extremely revealing structural information was provided early in the work by flavopereirine's ultraviolet absorption spectra. Comparison with those of sempervirine[4] disclosed a striking similarity both in neutral and alkaline solution as shown in Table I. Similar spectral characteristics have also been established for flavocoryline[5] and flavocorynanthyrine,[6] two degradation products obtained from corynantheine.

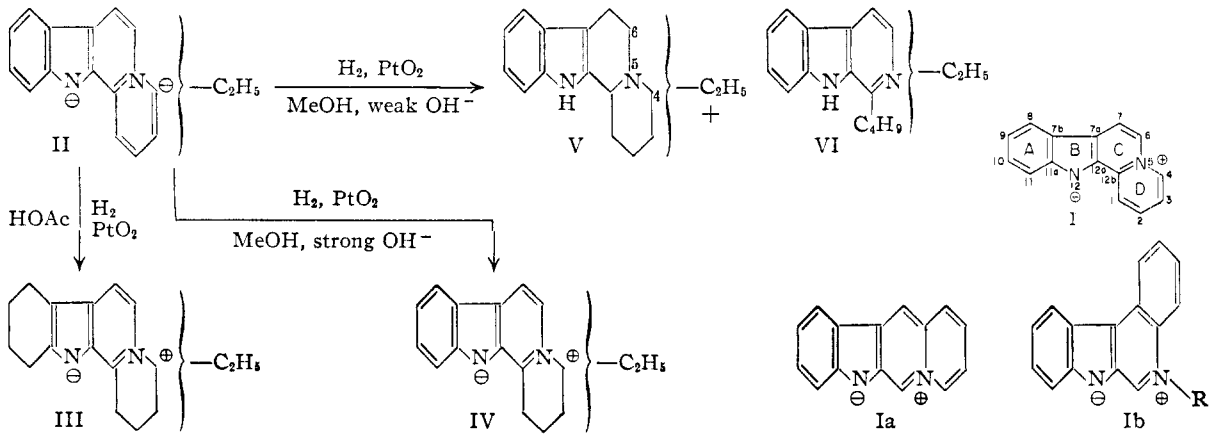
Since these three known compounds all have the indolo[2,3-a]quinolizine (I) chromophore, it was reasonable to assume its presence in flavopereirine also. Two similar chromophoric ring systems, Ia and Ib, also were considered. However, Ib was rejected since flavopereirine has no N-methyl or -ethyl group, and the linear ring system of Ia, was believed less likely since greater spectral differences between it and I might be expected.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA

Flavopereirine				Sempervirine			
In ethanol[a]		In 0.1 *N* ethanolic KOH		In ethanol[a]		In 0.1 *N* ethanolic KOH	
λ, mμ	ε	λ, mμ	ε	λ, mμ	ε	λ, mμ	ε
230	25,300	231	27,600	..	....	..	....
238	27,200	241	26,000	243	38,200	244	31,800
248	24,800	255	17,000	249	36,800	256	23,000
294	13,800	288	29,800	297	16,000	288	32,900
351	17,700	316	14,900	345	18,400	321	16,700
390	13,800	360	21,800	387	17,500	359	23,000

[a] Unchanged in 0.1 *N* ethanolic HCl.



Assuming the indolo[2,3-a]quinolizine (I) ring system for flavopereirine accounts for fifteen of the seventeen carbon atoms in the molecule. The remaining two carbons must be present as an ethyl group or two methyls. In order to locate the position of these side-chains as to rings A, C and D, recourse was made to catalytic hydrogenation. Sempervirine has been found to yield different hydrogenation products, depending on the acidity or alkalinity of the solution,[7-9] and parallel behavior was anticipated for flavopereirine.

When flavopereirine (II) was hydrogenated in glacial acetic acid with a platinum oxide catalyst, hydrogen absorption proceeded slowly and finally halted after a six-day period. The product was an octahydroflavopereirine, and it was assigned the pyrrolopyridine structure III on the basis of its ultraviolet spectra which were practically identical with those of an octahydrosempervirine prepared similarly and shown to have this chromophore.

Reduction of flavopereirine in strongly alkaline methanol solution led to a tetrahydroflavopereirine (IV) and here again a structural assignment could be made with confidence on the basis of the practically identical ultraviolet absorption of IV and alstonine and serpentine,[7,10] two compounds known to contain this chromophore. Both tetrahydroflavopereirine (IV) and octahydroglavopereirine (II) proved to be unstable toward air oxidation as the free bases and consequently they were characterized as their perchlorates.

In order to obtain the octahydroflavopereirine (V) containing the intact indole nucleus, hydrogenation was conducted in methanol to which a trace of potassium hydroxide had been added. These conditions had been shown to effect reduction of similar unsaturated systems to indoles[8,9] and again in this case were successful. A crystalline octahydroflavopereirine (V) was isolated as the main product, and here also comparison of its spectrum with that of β-yohimbine[10] together with the hydrogenation analogy allowed structure V to be assigned with confidence.[11] An accompanying product, in much lower yield, also was obtained crystalline from this hydrogenation. Analysis established its empirical formula as $C_{17}H_{20}N_2$, and hence it had been formed from flavopereirine by addition of six hydrogens. Its ultraviolet spectrum was clearly that of a pyrid[3,4-b]indole (*cf.* harman[10]), indicating hydrogenolysis of the C_4–N_5 bond had occurred and requiring the assignment of structure VI.

With the four hydrogenation products, III, IV, V and VI at hand, C-methyl determinations were used to locate the side-chains, basing our conclu-

(4) We are indebted to Dr. Leo Marion, National Research Council, Ottawa, Canada, for an authentic sample of sempervirine.

(5) R. Goutarel, M. M. Janot and C. Perezamador y Barron, *Bull. soc. chim. France*, 863 (1954).

(6) R. Schwyzer, *Helv. Chim. Acta*, **35**, 867 (1952).

(7) H. Schwartz and E. Schlittler, *ibid.*, **34**, 629 (1951).

(8) A. Le Hir, R. Goutarel and M. M. Janot, *Compt. rend.*, **235**, 63 (1952).

(9) N. J. Leonard and R. C. Elderfield, *J. Org. Chem.*, **7**, 556 (1942).

(10) N. Neuss, "Physical Data of Indole and Dihydroindole Alkaloids," 2nd Ed., Eli Lilly and Co., Indianapolis, Ind., 1956.

(11) The same structure has been assigned to a non-crystalline octahydroflavopereirine in the report by Bejar, *et al.*, ref. 3.

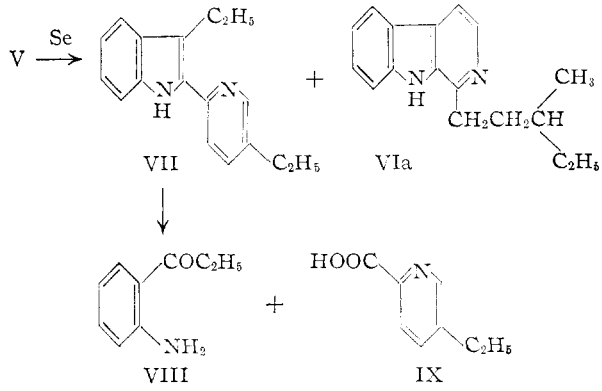
sions on the fact that methyl or ethyl groups on aromatic rings will not be detected as C-methyls by this procedure.[11a] On analysis, compounds III, IV and V all showed the presence of one C-methyl group. Since ring D is the only one that is hydroaromatic in all three, this result placed the side-chain in ring D. Moreover, since in each case only one C-methyl group was found, the side-chain had to be ethyl. Its presence in ring D was confirmed by the finding of two C-methyl groups in VI. The latter result also established the branched nature of the 1-alkyl group in the pyrid-[3,4-b]indole VI and meant that the ethyl group could be only at positions 1, 2 or 3 in the indolo-[2,3-a]quinolizine, flavopereirine (II).

To locate the position of the ethyl group among these three possibilities, dehydrogenation experiments with selenium were employed. Direct selenium dehydrogenation of flavopereirine led to a very low yield of a product, which from its ultraviolet spectrum appeared to be an alstyrine [a 2-(2′-pyridyl)-indole].[12] This low yield is not surprising in view of the fact that the conversion of flavopereirine to an alstyrine requires the addition rather than the removal of hydrogen.

Use of a partially hydrogenated flavopereirine obviously was indicated, and for this purpose the indolic octahydroflavopereirine (V) seemed admirably suited. Aromatization of compound V could proceed either by cleavage of the N_5–C_6 bond with dehydrogenation of ring D to give an alstyrine, or by breaking the N_5–C_4 bond with dehydrogenation of ring C, giving a harman-type product. Usually one or the other of these types of compounds predominates on dehydrogenation of various indole alkaloids, depending on the mode of substitution of ring D.[13–17]

When selenium dehydrogenation was applied to 1,2,3,4,6,7,12,12b-octahydroflavopereirine, two products were isolated. One of these was assigned structure VII, 3-ethyl-2-(5′-ethyl-2′-pyridyl)-indole (desethylalstyrine)[3] on the basis of the agreement in its ultraviolet absorption and in the properties of its picrate, styphnate and hydrochloride with those reported for a synthetic sample of VII.[18]

The other product was of the harman type and was identical with the β-carboline VI, which had been obtained on hydrogenating flavopereirine in weakly alkaline solution. With the alstyrine assigned structure VII, the harman now may be assigned structure VIa, 1-(3′-methylpentyl)-9H-pyrid[3,4-b]indole.



An observation made during these dehydrogenation experiments seems worthy of emphasis. On partitioning the reaction mixture between ether and dilute phosphoric acid, the 1-(3′-methylpentyl)-9H-pyrid[3,4-b]indole (VIa) was found in the aqueous acid phase while the desethylalstyrine (VII) went into the ether. This very clear-cut separation was quite unexpected and an explanation was sought for this abnormal behavior of the desethylalstyrine. The preferred configuration of the molecule, as indicated by models, seemed to be as shown in formula VII with the nitrogens on opposite sides of the bond joining the two ring systems in order to avoid interference between the 3-hydrogen of the pyridine and the 3-ethyl of the indole. If this were the case, one might expect the basic pyridine nitrogen to be quite thoroughly shielded by the 3-ethyl group, leading to a decreased basicity. This hypothesis was disproved, however, when its pK_a' was found to be 4.0 in 50% aqueous ethanol, which may be extrapolated to approximately 4.5 in water. Such a value is reasonable for a pyridine substituted as in VII and should have led to extensive salt formation in the dilute phosphoric acid solution (pH 1.4) used in the extraction.

Only an extremely large true partition coefficient, P (ether/water) for the desethylalstyrine could explain its appearance in the ether phase. From the apparent partition coefficient, P', as determined experimentally at two different pH's, the pK_a', and the equation[19]

$$\frac{P}{P'} = 1 + \frac{(H^+)}{K_a}$$

P was found to be approximately 2×10^5. This unexpectedly high value does account for the fact that, even though sufficiently basic, desethylalstyrine is not extracted from ether by dilute phosphoric acid. Why desethylalstyrine should possess such a large partition coefficient is puzzling. Possibly this might be due to strong intramolecular

(11a) These determinations were made using the procedure of V. H. Tashinian, M. J. Baker and C. W. Koch [*Anal. Chem.*, **28**, 1304 (1956)] in which samples are oxidized for various periods of time. In this way, volatile acids other than acetic acid (*e.g.*, benzoic acid) may be detected and eliminated through further oxidative destruction, the rate of which is extremely slow for acetic acid. With toluene, ethylbenzene and 5-ethyl-2-methylpyridine, this procedure gives less than 10% of one C-alkyl group, whereas with *n*-propylbenzene and 2-isobutylpyridine 90% or more of one C-alkyl group is found.

(12) For the synthesis of a number of alstyrines and references to the obtention of alstyrines by selenium dehydrogenations of various indole alkaloids see T. B. Lee and G. A. Swan, *J. Chem. Soc.*, 771 (1956).

(13) (a) P. Karrer, R. Schwyzer and A. Flam, *Helv. Chim. Acta*, **35**, 851 (1952); (b) P. Karrer, R. Schwyzer, A. Flam and R. Saemann, *ibid.*, **35**, 865 (1952).

(14) M. M. Janot and R. Goutarel, *Bull. soc. chim. France*, 509 (1949).

(15) J. Le Men, *Compt. rend.*, **234**, 1559 (1952).

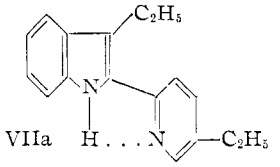
(16) E. Schlittler and H. Schwarz, *Helv. Chim. Acta*, **33**, 1463 (1950).

(17) L. Marion, "The Indole Alkaloids" in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. II, Academic Press, Inc., New York, N. Y., 1952.

(18) R. M. Anderson, G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 2962 (1954).

(19) J. Cymerman-Craig and A. A. Diamantis, *ibid.*, 1619 (1953).

hydrogen bonding if the more stable configuration of the molecule were as in VIIa.

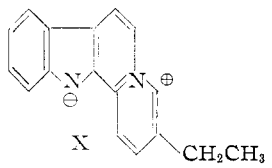


VIIa

However, its infrared spectrum exhibited bands attributable both to free N–H and hydrogen bonded N–H groups, so this cannot be the explanation. In any case desethylalstyrine, and presumably other alstyrines, may be separated from other basic substances by distribution between ether and dilute phosphoric acid.

In order to confirm the structural assignments VII and VIa made above, it was desirable to degrade the desethylalstyrine (VII) to the corresponding *o*-aminopropiophenone (VIII) and 5-ethylpicolinic acid (IX). The preparation of sufficient desethylalstyrine for this purpose by dehydrogenation of octahydroflavopereirine (V) was not very attractive since the over-all yield from flavopereirine was quite poor, and other possible routes were sought. Flavopereirine itself would be the ideal starting material, but a source of hydrogen must be present. Tetrahydroquinoline was chosen as the hydrogen donor since it should easily give up its hydrogen, it was high boiling, and both it and its dehydrogenation products were bases which could be separated readily from any alstyrine produced in view of the previous observation of desethylalstyrine's behavior on partition.

When the reaction was carried out in the presence of tetrahydroquinoline, a much improved yield (50%) of desethylalstyrine was obtained directly from flavopereirine with only a trace of harman-like products being formed. Oxidation with hydrogen peroxide[13a] gave *o*-(5-ethylpicolinoylamino)-propiophenone, and this in turn was hydrolyzed to *o*-aminopropiophenone (VIII) and 5-ethylpicolinic acid (IX). Thus the structure VII was confirmed and flavopereirine was established as 3-ethylindolo-[2,3-a]quinolizine (X).



X

Experimental[20]

Flavopereirine.—Crystallization from acetone or aqueous ethanol gave flavopereirine of m.p. 233–235°, as described previously.[1]

The tetraphenylboronate was prepared by adding a hot solution of 70 mg. of sodium tetraphenylboronate in 2 ml. of 50% aqueous ethanol to a hot solution of 50 mg. of flavopereirine in 2 ml. of ethanol and 2 ml. of 0.1 *N* hydrochloric acid. Precipitation occurred very rapidly and, after five minutes of further heating, the mixture was filtered. Crystallization from methanol gave material melting at 222–224°.

Anal. Calcd. for $C_{17}H_{14}N_2 \cdot HB(C_6H_5)_4$: N, 4.7. Found: N, 5.0.

To prepare the **perchlorate**, flavopereirine (100 mg.) was dissolved in glacial acetic acid (5 ml.) and to this hot solution was added a hot solution of perchloric acid (0.1 ml. of 60%) in glacial acetic acid (5 ml.). Cooling gave yellow crystals which were recrystallized from ethanol, m.p. 316–317° dec. (reported[3] m.p. 308°).

Anal. Calcd. for $C_{17}H_{14}N_2 \cdot HClO_4$: C, 58.9; H, 4.3; N, 8.1; Cl, 10.3. Found: C, 58.7; H, 4.5; N, 7.9; Cl, 10.1.

The methiodide was prepared in ethanol and was crystallized from methanol, m.p. 321–323° dec.

Anal. Calcd. for $C_{17}H_{14}N_2 \cdot CH_3I$: C, 55.7; H, 4.4; N, 7.2; I, 32.8. Found: C, 55.7; H, 4.6; N, 7.0; I, 32.6.

Hydrogenation of Flavopereirine. A. 1,2,3,4,8,9,10,11-Octahydroflavopereirine (III).—Flavopereirine (100 mg.) was dissolved in glacial acetic acid (10 ml.), platinum oxide (15 mg.) was added, and the mixture was hydrogenated at 40 p.s.i. and room temperature for six days. Filtration followed by evaporation under reduced pressure left a sirup which was distributed between chloroform (20 ml.) and 1 *N* potassium hydroxide solution (20 ml.). The aqueous layer was further extracted with two 20-ml. portions of chloroform, the combined chloroform extract was washed with water and then was evaporated under reduced pressure, and the residue was dissolved in ethanol (5 ml.) to which a slight excess of 0.1 *N* ethanolic perchloric acid was added. This solution was concentrated to a sirup, 10 ml. of ethyl acetate was added and the concentration was repeated, and the residue then was crystallized from ethyl acetate (5 ml.). Pale yellow needle-like crystals of the **perchlorate** (83 mg.), m.p. 125–136°, were obtained. Further recrystallization from ethyl acetate did not decrease the melting range nor increase the melting point. For analysis, material was dried at 60° (1 mm.) for 12 hr.; ultraviolet spectra: in ethanol, λ_{max} 248 mμ (ε 21,400), 278 (8000), 332 (8500); in 0.01 *N* potassium hydroxide in ethanol, λ_{max} 246 mμ (ε 20,800), 262 (22,600), 287 (7000), 362 (4900).

Anal. Calcd. for $C_{17}H_{22}N_2 \cdot HClO_4$: C, 57.6; H, 6.5; N, 7.9; Cl, 10.0; 1 C–CH_3, 4.2. Found: C, 57.5; H, 6.3; N, 7.6; Cl, 9.4; C–CH_3, 4.1.

B. 1,2,3,4-Tetrahydroflavopereirine (IV).—A solution of 200 mg. of flavopereirine in 10 ml. of methanol to which 12 mg. of platinum oxide and 50 mg. of potassium hydroxide in 2.5 ml. of methanol were added was hydrogenated at room temperature and atmospheric pressure. Hydrogenation ceased after eight hours and the absorption of 230 mole % of hydrogen, after which the solution was filtered and evaporated to a sirup. This was distributed between water (20 ml.) and chloroform (20 ml.), and two further 20-ml. portions of chloroform were used to complete the extraction. The residue left on evaporation of the combined chloroform extracts was dissolved in ethanol (5 ml.), and excess 0.1 *N* ethanolic perchloric acid was added. Cooling gave the yellow, crystalline **perchlorate** (166 mg.), m.p. 220–222°. Further crystallization from ethanol gave material of m.p. 224–225° which was dried at 87° (1 mm.) for 12 hr. for analysis; ultraviolet spectra: in ethanol, λ_{max} 253 mμ (ε 32,600), 307 (21,500), 367 (4300); in 0.01 *N* potassium hydroxide in ethanol, λ_{max} 284 (ε 51,500), 329 (11,000).

Anal. Calcd. for $C_{17}H_{18}N_2 \cdot HClO_4$: C, 58.2; H, 5.4; N, 8.0; 1 C–CH_3, 4.3. Found: C, 58.5; H, 5.5; N, 8.1; C–CH_3, 3.8.

C. 1,2,3,4,6,7,12,12b-Octahydroflavopereirine (V) and 1-(3′-Methylpentyl)-9H-pyrid[3,4-b]indole (VIa).—Platinum oxide (180 mg.) was added to a solution of flavopereirine (3.0 g.) in 75 ml. of methanol containing 10 mg. of potassium hydroxide, and the mixture was shaken at 40 p.s.i. pressure and room temperature for 18 hr. Filtration and evaporation of the solution was followed by distribution of the residue between water (50 ml.) and chloroform (3 × 50 ml.). The residue obtained on evaporation of the combined chloroform extracts was crystallized from aqueous ethanol using decolorizing carbon to give 1.41 g. of the **octahydroflavopereirine (V)**, m.p. 163–164°, after drying at 87° (1 mm.) for 12 hr.; ultraviolet spectrum in ethanol: λ_{max} 225 mμ (ε 37,800), 284 (7570), 290 (6260).

Anal. Calcd. for $C_{17}H_{22}N_2$: C, 80.3; H, 8.7; N, 11.0; 1 C–CH_3, 5.9. Found: C, 80.4; H, 8.7; N, 11.2; C–CH_3, 5.0.

The mother liquors were evaporated until free of ethanol and then were extracted with chloroform (3 × 20 ml.). The gum left on removal of the chloroform was dissolved in

(20) All melting points are corrected and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley.

15 ml. of benzene–chloroform (1:1) and this solution was introduced on to a column (16 cm. × 4 cm.) of 80 g. of alumina (Merck). Using benzene–chloroform (1:1) as the eluting solvent, six 50-ml. fractions were collected, followed by a seventh fraction of 300 ml. of benzene–chloroform (1:3). Fractions 5, 6 and 7 yielded additional (210 mg.) octahydroflavopereirine (V). Fractions 3 and 4 were combined (330 mg.) and were crystallized from hexane to give material of m.p. 122–135°. This was further purified by sublimation (125° (0.05 mm.)) and crystallization from cyclohexane, affording the pure **1-(3'-methylpentyl)-9H-pyrid[3,4-b]indole (VIa)**, m.p. 140–141°; ultraviolet spectrum in ethanol: λ_{max} 235 mμ (ε 38,600), 241 (37,600), 251 (24,800), 283 (10,500), 289 (18,800), 337 (5300), 351 (5500).

Anal. Calcd. for $C_{17}H_{20}N_2$: C, 81.0; H, 7.9; N, 11.1; 2 C-CH_3, 11.9. Found: C, 81.0; H, 8.1; N, 11.1; C-CH_3, 9.9.

Dehydrogenation Experiments. A. Dehydrogenation of Flavopereirine (II).—Flavopereirine (50 mg.) was mixed intimately with selenium (80 mg.) and the mixture was heated in a stream of nitrogen in an apparatus containing a cold finger condenser, the effluent gases being passed into a solution of lead acetate. The temperature of the heating bath was raised from 220 to 300° over 25 minutes and held at 300° for a further five minutes. At no time did the lead acetate solution darken. After being cooled, the reaction mixture was well ground with alumina and the mixture was extracted with ether in a Soxhlet apparatus for six hours. On evaporation of the ether, a residual brown oil was obtained. Its ultraviolet spectrum (λ_{max}^{EtOH} 328, λ_{min} 273 mμ) was similar to that of alstyrine (λ_{max}^{EtOH} 320, λ_{min} 270 mμ). However, the yield of alstyrine-like material was in the order of 2–3 mg. only.

B. Dehydrogenation of 1,2,3,4,6,7,12,12b-Octahydroflavopereirine (V).—The dehydrogenation of 352 mg. of octahydroflavopereirine (V) using 900 mg. of selenium was carried out as described above. In this case, hydrogen selenide evolution took place at 240°. The ethereal extract, after being concentrated to 20 ml., was washed with 20-ml. portions of 0.2 *M* phosphoric acid and water, dried over sodium sulfate and filtered through a short column of alumina. Evaporation of the ether left a gum which was digested with 20 ml. of hexane, and the hexane digest then was decanted and evaporated to a residue. This residue, on solution in 1 ml. of hot ethanol and addition of 1 ml. of saturated ethanolic picric acid, deposited yellow needle-like crystals on cooling, 47 mg., m.p. 165–166°. Recrystallization from methanol gave 20 mg. of pure **desethylalstyrine (VII) picrate**, m.p. 177–179° (reported m.p. 177° dec.,[18] m.p. 178°[3]).

Anal. Calcd. for $C_{17}H_{18}N_2 \cdot C_6H_3N_3O_7$: C, 57.6; H, 4.4. Found: C, 57.8; H, 4.5.

Liberation of the base from the picrate resulted in an oil which could not be crystallized.

The styphnate was obtained as yellow needles from methanol, m.p. 189–191° (reported[18] m.p. 190–191°).

The hydrochloride was obtained as pale green crystals from ethyl acetate, m.p. 160–188° (reported[18] m.p. 149–183°); ultraviolet absorption of hydrochloride: in ethanol or in 0.01 *N* KOH in ethanol, λ_{max} 234 mμ (ε 18,800), 327 (22,400) [reported, 238 (13,800),[21] 325 (14,800),[21] 325 (23,000)[12]]; in 0.1 *N* HCl in ethanol, λ_{max} 218 mμ (ε 30,000), 250 (17,600), 374 (15,000).

The phosphoric acid extract above was made alkaline with potassium hydroxide and extracted with chloroform (20 ml.). After being washed and dried, the chloroform solution was reduced to one-third its volume and was passed through a small column of alumina to remove colored material. The eluate was evaporated, and the residual gum crystallized from hexane to give a solid (44 mg.), m.p. 140–142°. This solid was further purified by sublimation (135° (0.05 mm.)) and recrystallization from cyclohexane, giving **1-(3'-methylpentyl)-9H-pyrid[3,4-b]indole (VIa)** (29 mg.) as short prisms, m.p. 140–141°, undepressed on admixture with the previous material prepared by hydrogenation of flavopereirine (above).

C. Dehydrogenation of Flavopereirine in the Presence of 1,2,3,4-Tetrahydroquinoline.—The same procedure as that used in the previous dehydrogenations (above) was applied to a mixture of 2.5 g. of flavopereirine, 5.5 g. of selenium and 3 ml. of 1,2,3,4-tetrahydroquinoline. The ether extract (100 ml.) was washed with two 50-ml. portions of 0.2 *M* phosphoric acid and then washed with water and dried. Only traces of harman-like products could be detected in the liberated bases from the phosphoric acid wash after quinolines were removed by trituration with hexane, in which harmans are almost insoluble. The ethereal solution was evaporated to a sirup which was partially decolorized by passage of its solution in chloroform through a small column of alumina. The gum obtained on evaporation of the chloroform was digested with hexane (100 ml.) for 10 minutes and the solution was decanted from the insoluble residue. Removal of the hexane and solution of the residual gum in hot ethanol (40 ml.) to which was added slowly a hot solution of ethanol picric acid resulted, on cooling, in the precipitation of 2.3 g. of **desethylalstyrine (VII) picrate**, m.p. 163–165°. Recrystallization from methanol gave 1.9 g. of the pure picrate, m.p. 177–179°.

Oxidation of Desethylalstyrine (VII).—A suspension of 1.06 g. of desethylalstyrine picrate in 20 ml. of methanol to which potassium hydroxide (200 mg.) was added was boiled for 5 minutes and then filtered. The filtrate was evaporated, the residue was distributed between 50 ml. of ether and 50 ml. of water, and the aqueous phase was extracted with a second portion of ether. After being washed with water (30 ml.) and dried over magnesium sulfate, the ether was evaporated to a gum which was dissolved in 7 ml. of glacial acetic acid. Hydrogen peroxide (4 ml., 30%) was added and the solution was set aside at 20° for 24 hr. It was then diluted with 40 ml. of water, made alkaline with potassium hydroxide, and extracted with ether (2 × 50 ml.). The extract was washed with water (30 ml.), dried, and evaporated to a sirup which, dissolved in 5 ml. of chloroform, was passed through a small column of alumina to remove some colored impurities. Evaporation of the chloroform and sublimation of the residue at 100° (0.05 mm.) gave ***o*-(5-ethylpicolinoylamino)-propiophenone** which was crystallized from aqueous methanol; 307 mg., m.p. 77–78° (reported[22] m.p. 80°); ultraviolet spectrum in ethanol: λ_{max} 242 mμ (ε 23,200), 274–281 (12,100), 329 (9100).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.4; H, 6.4. Found: C, 72.4; H, 6.5.

In some experiments in which the oxidation was allowed to proceed for longer periods, an additional product was obtained, m.p. 140–141° from aqueous methanol. This is probably the N_{py}-oxide of *o*-(5-ethylpicolinoylamino)-propiophenone; ultraviolet spectrum in ethanol: λ_{max} 237 mμ (ε 35,400), 255–270 (15,800), 323 (8200).

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.5; H, 6.1. Found: C, 68.8; H, 5.9.

Hydrolysis of *o*-(5-Ethylpicolinoylamino)-propiophenone.—The above amide (182 mg.) was heated under reflux with sulfuric acid (7 ml., 10 *N*) for 4.5 hours. After cooling, excess sodium carbonate was added plus sufficient water to keep the salts in solution. The solution was extracted with ether (3 × 20 ml.), and the extract was washed, dried, and evaporated to a pale yellow sirup which was crystallized from pentane to give 56 mg. of ***o*-aminopropiophenone (VIII)** as pale yellow plates, m.p. 46–47.5° (reported[23] m.p. 47°). **The N-benzoyl derivative**, prepared with benzoyl chloride in pyridine and crystallized from ethanol, melted at 132–133° (reported[23] m.p. 130°).

The aqueous solution, after being adjusted to *p*H 4.0 with sulfuric acid, was extracted continuously with ether for 18 hours. The extract was evaporated, and the residue was dried in a desiccator and recrystallized from hexane to give 64 mg. of **5-ethylpicolinic acid (IX)** as colorless needles, m.p. 107–109° (reported[18] m.p. 101°), undepressed on admixture with an authentic sample. The infrared spectra were also identical.

The authentic sample was prepared by the method of Anderson, Clemo and Swan[18] up to and including the oxidation of 2-styryl-5-ethylpyridine with potassium permanganate in acetone. At the conclusion of the reaction the mixture was filtered through filter-aid and the insoluble material

(21) Apparently these low values for the extinction coefficients reported in ref. 18 are due to a mechanical error of some sort.

(22) M. M. Janot and R. Goutarel, *Bull. soc. chim. France*, 588 (1951).

(23) E. Wohnlich, *Arch. Pharm.*, **251**, 531 (1913).

washed with hot water. The combined washing and filtrate were acidified (pH ~0) with hydrochloric acid and extracted with ether to remove the benzoic acid. Then the solution was adjusted to pH 4 and was continuously extracted with ether for 12 hours. Evaporation of the ether, sublimation (70° (0.05 mm.)) of the residue and crystallization of the sublimate from hexane gave 5-ethylpicolinic acid, m.p. 107–109°.

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[CONTRIBUTION FROM FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Stereochemistry of the Hemlock Alkaloids. I. Conhydrine

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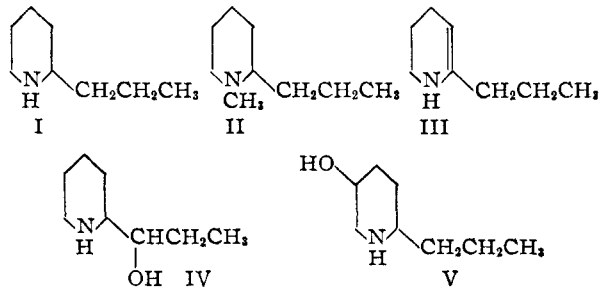
The stereochemistry of the hydroxylated hemlock alkaloid, conhydrine, has been determined. *d,l*-Conhydrine was degraded by Hofmann elimination to 5,6-epoxyoctene-1, which was hydrolyzed and hydrogenated to an octane-3,4-diol. This product was identified by synthesis as the *erythro* isomer, establishing the *erythro* configuration for the alkaloid.

Introduction

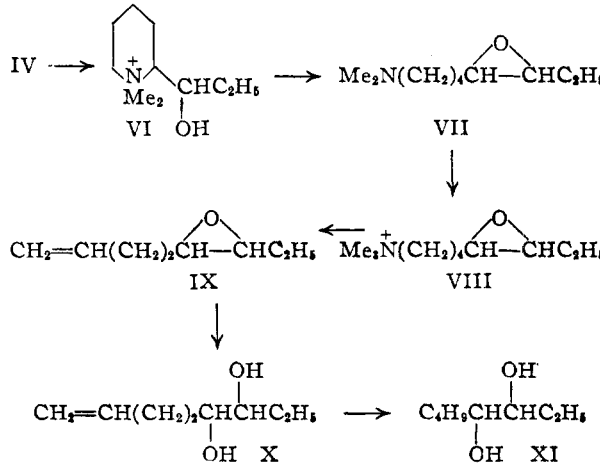
The poisonous properties of the common hemlock, *Coniium maculatum*, have been recognized since antiquity, and the extracts were used in ancient Greece for the execution of criminals. This historic stimulus led to an early investigation of the toxic principle. Coniine, the major alkaloid, was soon shown[1] to be 2-*n*-propylpiperidine (I); it was the first alkaloid ever synthesized.[2] It is accompanied by four congeners of the same skeleton: N-methylconiine (II), γ-coniceine (III), and two hydroxy derivatives, conhydrine (IV) and pseudo-



conhydrine (V). The structure proof of this group of alkaloids was completed in 1933 by Späth's work on the Hofmann degradation of these latter two bases,[3] and was followed, some years later, by their synthesis.[4] Despite the extensive research, both degradative and synthetic, on the structure and reactions of the conhydrines, the question of their stereochemistry remains unanswered. This and the following communication describe the elucidation of the configurations of conhydrine and pseudoconhydrine.

Discussion

In 1933, Späth and Adler[3a] confirmed the position of the hydroxyl group in conhydrine by an elegant application of the Hofmann elimination. The Hofmann reaction on N-methylconhydrine methiodide (VI), taking the course typical of β-hydroxyamines,[5] produced the epoxy-amine VII. A second Hofmann converted this to a mixture of the unsaturated epoxide IX and its hydrolysis product X. The glycol was reduced to an octane-3,4-diol XI; all of these compounds retained optical activity.



It can be seen that, with our present understanding of the stereochemical course of the reactions used by Späth, the configuration of conhydrine could be deduced from the knowledge of the configuration of the glycol XI. Accordingly, the synthesis of both isomeric glycols and a repetition of the Hofmann degradation were undertaken. Because of the unavailability of the alkaloid, and to avoid the necessity for optical resolutions, all reactions were carried out with racemic compounds.

Formation of ethyl-(2-piperidyl)-carbinol by reduction of ethyl-(2-pyridyl) ketone, either catalytically[4a,6] or chemically,[7] or of ethyl-(2-pyridyl)-carbinol,[8] yields an almost equimolar mixture of both possible diastereomers, so that it is impossible to assign the configuration to either. Galinovsky and Mulley,[4a] however, have shown that the higher-melting isomer (m.p. 100°) represents racemic con-

(1) A. Ladenburg, *Ber.*, **18**, 1587 (1885).
(2) A. Ladenburg, *ibid.*, **19**, 439 (1886).
(3) (a) E. Späth and E. Adler, *Monatsh.*, **63**, 127 (1933); (b) E. Späth, F. Kuffner and L. Ensfellner, *Ber.*, **66**, 591 (1933).
(4) (a) F. Galinovsky and H. Mulley, *Monatsh.*, **79**, 426 (1948); (b) F. Sorm and J. Sicher, *Coll. Czech. Chem. Comm.*, **14**, 331 (1949); (c) L. Marion and W. F. Cockburn, THIS JOURNAL, **71**, 3402 (1949); (d) W. Gruber and K. Schlogl, *Monatsh.*, **80**, 499 (1949).
(5) (a) S. Winstein and R. B. Henderson, Chapter 1 in "Heterocyclic Compounds," Vol. 1, edited by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 13–14. (b) Some examples from the field of natural products are listed by B. Witkop and C. M. Foltz, THIS JOURNAL, **79**, 197 (1957).
(6) K. Hess, *Ber.*, **53**, 129 (1920).
(7) C. Engler and F. W. Bauer, *ibid.*, **24**, 2530 (1891).
(8) L. Lautenschlager and A. G. T. Onsager, *ibid.*, **51**, 602 (1918).