the substrate and the reaction mixture chromatographed (collidine–NH_3–water), a metabolite (R_f 0.15) migrating slower than thyroxine (R_f 0.49) was detected by radioautography. Thyroxine was liberated from this compound after treatment with β-glucuronidase. In its chromatographic behavior and the results of enzymatic hydrolysis, this metabolite resembles the thyroxine conjugate found in rat bile by Taurog, *et al.*[2b] (Cpd. U), and Roche, *et al.*[2c] (Cpd. A), and considered by them to be thyroxine glucuronide.

The glucuronide conjugating reaction involving UDPGA and the microsomal system appears to be a general mechanism for the formation of phenolic and alcoholic glucuronides. However, demonstration of the specificity of the enzyme system involved must await purification of the microsomal preparation.

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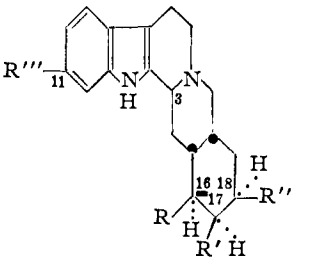
RECEIVED DECEMBER 16, 1954

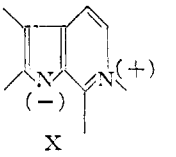
RAUWOLFIA ALKALOIDS. XVIII.[1] ON THE CONSTITUTION OF DESERPIDINE AND RESERPINE

Sir:

In a recent publication[2] we have proposed a structure for deserpidine, a minor alkaloid of many Rauwolfia species, and have pointed out its close chemical and biological similarly to reserpine.[3] We have now been able to convert this alkaloid to α-yohimbine (rauwolscine)[4] by the following series of reactions. Methyl deserpidate tosylate (II) on treatment with sodium iodide or lithium bromide yielded the corresponding 18-halogen compounds III (bromide, m.p. 179–182°, calcd. for $C_{22}H_{27}BrN_2O_3$: C, 59.06; H, 6.08; N, 6.26. Found: C, 58.98; H, 6.31; N, 6.43). These we dehalogenated with zinc in acetic acid to the 18-desoxy compound IV, m.p. 272–275°, (calcd. for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.94; H, 7.49; N, 7.67). Cleavage of the 17-methoxy group with hydrobromic acid and reesterification of the resulting hydroxyamino acid V with diazomethane afforded α-yohimbine (VI), m.p. 240–242° $[\alpha]^{23}D$ −22 ± 2 (ethanol) (calcd. for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.08; H, 6.96; N, 7.77). The infrared spectrum was identical with that of α-yohimbine isolated from *Rauwolfia canescens* leaves.[5]

A further linking of the two alkaloids was accomplished by treatment of the tosylate II with lithium aluminum hydride to form deserpidinol VII, m.p. 232–236° (calcd. for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.78; H, 8.38; N, 8.29). This compound when subjected to ether cleavage gave rauwolscinyl alcohol (VIII),[6] m.p. 229–231° (calcd. for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03. Found: C, 73.55; H, 7.96); infrared spectrum identical with that of a sample of rauwolscinyl alcohol prepared by the reduction of α-yohimbine (rauwolscine).





X

	R	R′	R″	R‴	C-3
I	$COOCH_3$	OCH_3	3,4,5-Trimethoxybenzoyloxy	H	α
II	$COOCH_3$	OCH_3	Tosyloxy	H	α
III	$COOCH_3$	OCH_3	Br or I	H	α
IV	$COOCH_3$	OCH_3	H	H	α
V	COOH	OH	H	H	β
VI	$COOCH_3$	OH	H	H	β
VII	CH_2OH	OCH_3	H	H	α
VIII	CH_2OH	OH	H	H	β
IX	CH_2OH	OCH_3	OH	OCH_3	α
XI	CH_2OH	OCH_3	OH	OCH_3	β

Since α-yohimbine has been shown to have the alloyohimbane structure[7] it would seem logical on the basis of the above interconversion to assign the same stereochemical configuration to the basic ring system of deserpidine. However we have accumulated considerable evidence which shows that resperine and its derivatives, (methyl reserpate, reserpinediol, reserpinol) and with less ease also deserpidine and its derivatives undergo an acid or base catalyzed epimerization at the C_3 center. That this and only this center is involved is shown by the successive lead tetraacetate oxidation of (for example) reserpinediol (IX) to tetradehydroreserpinediol (X) [isolated as the hydrochloride: m.p. 280–282°; calcd. for $C_{22}H_{27}N_2O_4Cl\cdot{}^1/_2H_2O$: C, 61.75; H, 6.34; N, 6.55. Found: C, 62.07; H, 6.63; N, 6.59; ultraviolet maxima at 251–2 mμ (log ε 4.52) and 325 mμ (log ε 4.33)] and reduction with sodium borohydride to 3-iso-reserpinediol (XI), m.p. 220–222° (calcd. for $C_{22}H_{30}N_2O_4\cdot{}^1/_2H_2O$: C, 66.83; H, 7.59. Found: C, 66.35; H, 8.06. Diacetate: m.p. 210–212°, calcd. for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.40; H, 7.41; N, 5.91), which was identical with a sample prepared by the acid or base catalyzed epimerization of reserpinediol. Therefore, it seemed probable that in the conversion of deserpidine to α-yohimbine inversion has taken place. Evidence to show that this was actually so was obtained by treating 3-epi-α-yohimbine[1] under the demethylation condition described above. After reesterification we obtained α-yohimbine, a transformation which has also been accomplished by oxidation and subsequent reduction of ring C[1].

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We therefore propose that deserpidine and reserpine are derivatives of 3-epi-α-yohimbine.

Regarding the stereochemistry of the substituents in ring E of these alkaloids, we feel that the formation of the γ-lactone of reserpic acid[3] and of deserpidic acid together with other evidence which we have obtained from elimination reactions, point to an all *cis* configuration.

Although we do not believe that the relationship between C-15 and C-16 has been sufficiently established in the case of α-yohimbine[4,7] to permit at this time the definite assignment of a complete configuration to deserpidine and reserpine, we do favor the one expressed in formula I.

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RECEIVED JANUARY 21, 1955

RESOLUTION AND SYNTHESIS OF AN OPTICALLY ACTIVE FLUORO COMPLEX

Sir:

The role of fluoride ion in complex formation has been of especial interest in studies on bond type in coördination compounds.[1,2] Magnetic evidence has indicated that fluoride is capable of forming bonds with tervalent cobalt of the extreme ionic type, *viz.*, in $[CoF_6]^{=}$, but is also able to enter into covalent bond formation when present in partially substituted cobalt ammines.[3] Except for the information inferred from the fact that the latter type of complexes are diamagnetic, little is known about the nature of the Co–F bond in these complexes.

We have recently succeeded in resolving the complex, *cis*-$[Co\ en_2F_2]^+$ (I) by use of *l*-dibenzoyltartaric acid (II) and have prepared (I), as well as *cis*-$[Co\ en_2NH_3F]^{+2}$ (III), in active form through reactions of the analogous chloro complexes. This is believed to be the first instance in which a complex containing coördinated fluoride has been resolved.

The resolution consisted in bringing together stoichiometric quantities of *cis*-$[Co\ en_2F_2]I$, Ag_2CO_3 and (II), removing AgI and precipitating the *d*-$[Co\ en_2F_2]^+$ salt of (II) with acetone. Purification of the latter was effected by dissolving it in a small quantity of water and chilling sharply, whereby a crystalline product was obtained having $[\alpha]^{28}D$ +120°. The resolving agent was removed by triturating the diastereomer with acetone containing a little concd. HNO_3, yielding thereby *d*-$[Co\ en_2F_2]NO_3$ with $[\alpha]^{28}D$ +220.

Active (I) was also prepared by the reaction of *l*-$[Co\ en_2Cl_2]Cl$ ($[\alpha]_D$ +610) in 1:1 ethanol–HF, in which an excess of Ag_2CO_3 had been dissolved. For the purified substance, isolated as the nitrate, $[\alpha]^{28}D$ +220. The *dextro* isomer of (III) was prepared in like manner by starting with *d*-$[Co\ en_2NH_3Cl]Cl_2$ ($[\alpha]_D$ +140°). For the bromide of (III), $[\alpha]^{28}D$ +170. The salts of (I) and (III) were isolated in microcrystalline form, that of (I) being red, and that of (III) being salmon in color.

Kinetic studies now in progress on a number of cobalt fluoro complexes indicate that the rates of racemization and aquation are slower than those of the analogous chloro complex. At 35° in 0.1 *N* HNO_3 (I) mutarotates to about one half the original rotation at a moderate rate (half-life, 1 hr.) and then loses its remaining activity over a period of several days. A study of the reactions undergone by the active fluoro complexes with a number of reagents to determine the nature of active products is also being undertaken.

A more detailed account of this work as well as other results will be communicated in the near future.

The authors gratefully acknowledge the support of grants from the National Science Foundation and the Atomic Energy Commission. They wish also to express thanks to Dr. F. P. Dwyer for his helpful suggestions and interest in this work.

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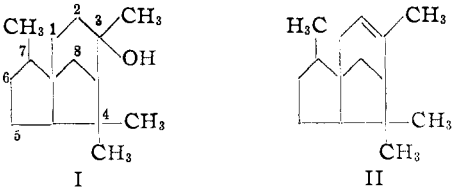
RECEIVED JANUARY 10, 1955

THE TOTAL SYNTHESIS OF CEDROL AND CEDRENE

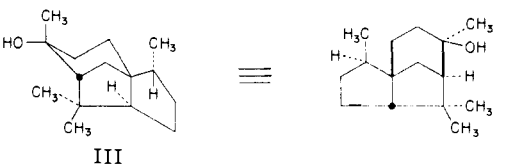
Sir:

We have recently outlined the considerations which led us to propose structure I for the tricyclic sesquiterpene cedrol[1] and II for the related cedrene.



I II

Our communications on the subject did not deal with the stereochemistry of the five asymmetric centers present in I, but various considerations have led us to consider III the most likely representation of the stereochemistry of cedrol.



III

We have now completed an unambiguous, stereospecific total synthesis of cedrol which confirms the stereochemistry illustrated by formula III and incidentally provides unambiguous proof that no rearrangement is involved in the dehydration of cedrol to cedrene:

Diethyl 4,4-dimethyl-5-keto-1,3-cyclopentane dicarboxylate[2] was alkylated with benzyl α-bromopropionate, and the resulting triester was hydrogenolyzed over palladium charcoal to the acid IV, m.p. 113–115°. (Found: C, 58.47; H, 7.43).

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