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 $[CoF_6]^{\equiv}$, 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.

DEPARTMENT OF CHEMISTRY
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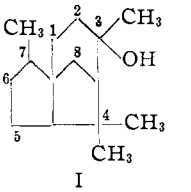
RECEIVED JANUARY 10, 1955

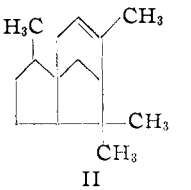
THE TOTAL SYNTHESIS OF CEDROL AND CEDRENE

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).

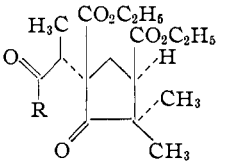
(1) W. C. Fernelius, *Record Chem. Progress (Kresge-Hooker Sci. Lib.)*, **2**, 17 (1950).

(2) H. Taube, *Chem. Rev.*, **50**, 69 (1952).

(3) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1945, pp. 116–117.

(1) G. Stork and R. Breslow, THIS JOURNAL, **75**, 3291 (1953).

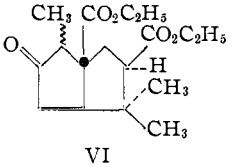
(2) *Cf.* C. S. Gibson, K. V. Hariharan and J. L. Simonsen, *J. Chem. Soc.*, 3009 (1927).



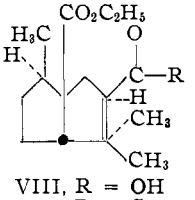
IV, R = OH
V, R = CH_3

The dry sodium salt of IV was transformed by oxalyl chloride into the corresponding acid chloride which reacted readily with diazomethane to give a crystalline diazoketone. The diazoketone was converted into the chloromethyl ketone, m.p. 72–73° (Found: C, 56.41; H, 7.08), which was readily reduced to the crystalline methyl ketone (V) (Found: C, 62.34; H, 7.92. Semicarbazone, m.p. 191–193°; Found: C, 56.41; H, 7.91).

Short treatment with potassium *t*-butoxide changed the diketone (V) into the bicyclic aldol which was readily dehydrated by heating with *p*-toluene sulfonic acid in benzene. The cyclopentenone so obtained (VI) is a mixture of C_7 epimers, one of which had m.p. 65–67°. (Found: C, 66.21; H, 7.87). Epimerism at C_7 at this stage of the synthesis is irrelevant, and the 65° isomer was reduced with lithium and liquid ammonia, or



VI



VIII, R = OH
IX, R = CH_3

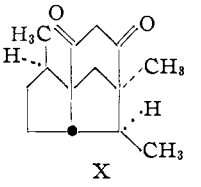
with palladium on charcoal, to the *cis* bicyclic ketone (VII) m.p. 33.5–35.0°; dinitrophenylhydrazone, m.p. 160–161° (Found: C, 56.26; H, 6.04). The stereochemistry at C_7 in this ketone corresponds to that of the more stable epimer since base hydrolysis, followed by reesterification gave back unchanged VII. Transformation of VII into the thioketal, m.p. 75–76° (Found: C, 59.23; H, 7.77) and Raney nickel desulfurization of the latter gave *dl*-diethyl norcedrenedicarboxylate, hydrolyzed to *dl*-norcedrenedicarboxylic acid VIII, m.p. 221–223°. (Found: C, 65.02; H, 8.36). The infrared spectrum of the anhydride of VIII was indistinguishable from that of *l*-norcedrenedicarboxylic anhydride obtained by the degradation of natural cedrene.[3]

Resolution of the *dl*-acid was readily effected by means of the quinine salt, m.p. 209–210°; $(\alpha)^{27}D$ −122° (*c* 1.00 in chloroform). (Found C: 70.13; H, 8.18), which was decomposed to produce *l*-norcedrenedicarboxylic acid, m.p. 212–213°, undepressed on mixture with the natural isomer; the rotation, $(\alpha)^{27}D$ −38.9° ± (*c* 1.08 in acetone), was identical with that of the acid from natural sources.

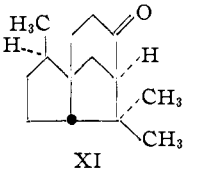
Conversion of the *l*-acid by established paths[4] into the methyl ketone (VIII), followed by treatment of the ester with potassium *t*-butoxide led to the cyclohexane dione (X), m.p. 202–204°. (Found: C, 76.66; H, 9.07). Reduction of X

(3) We thank Dr. T. F. Gallagher for carrying out this comparison.

(4) G. Stork and R. Breslow, THIS JOURNAL, **75**, 3292 (1953).



X



XI

with lithium aluminum hydride gave a mixture of saturated and unsaturated alcohols which, on oxidation with chromic acid, followed by catalytic hydrogenation, gave rise to the saturated ketone (XI); 2,4-dinitrophenylhydrazone, m.p. 146–147°. Reaction of the ketone (XI) with methyl lithium gave *l*-cedrol (III), identical in all respects with the natural product (m.p. and mixed m.p. 86.5–87.5°, identical infrared absorption curves).

The stereochemically simpler cedrene is obtainable by dehydration of cedrol with formic acid, and the synthesis of cedrol is also a synthesis of cedrene.

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RECEIVED JANUARY 28, 1955

ENZYMATIC RACEMIZATION OF β-HYDROXYBUTYRYL-S-CoA AND THE STEREOSPECIFICITY OF ENZYMES OF THE FATTY ACID CYCLE[1]

Sir:

Some evidence has been presented that the enzymes crotonase[2,3] and β-hydroxybutyryl-S-CoA dehydrogenase (β-keto reductase)[4,5,6] which catalyze reactions (1) and (2) are specific for *d*-BOH-S-CoA.[5,6]

$$\text{Crotonyl-S-CoA} + H_2O \rightleftharpoons d\text{-BOH-S-CoA} \quad (1)$$

$$d\text{-BOH-S-CoA} + DPN^+ \rightleftharpoons \text{acetoacetyl-S-CoA} + DPNH + H^+ \quad (2)$$

However, an "activating" enzyme of liver forms both the *d*- and *l*-isomers of BOH-S-CoA from the corresponding free acids,[5] probably according to reaction (3).

$$BOH + \text{CoA-SH} + ATP \rightleftharpoons \text{BOH-S-CoA} + AMP + PP \quad (3)$$

By use of synthetically prepared *l*-BOH-S-CoA and *d*-BOH-S-CoA[7] we have been able to establish directly the stereospecificity of enzymes catalyzing reactions (1) and (2), and have found that liver and other organs contain an enzyme or enzyme system

(1) Supported by grants from the U. S. Public Health Service, the American Cancer Society (recommended by the Committee on Growth National Research Council), the Nutrition Foundation, Inc., and by a contract (N6onr279, T.O. 6) between the Office of Naval Research and New York University, College of Medicine. Abbreviations: Coenzyme A (reduced), CoA-SH; acylcoenzyme A derivatives, acyl-S-CoA; β-hydroxybutyric acid, BOH; β-hydroxybutyryl-S-CoA, BOH-S-CoA; *d* and *l* refer to direction of rotation; DPN^+ and DPNH, oxidized and reduced diphosphopyridine nucleotide; 2-amino-2-methyl-1,3-propanediol, Diol.

(2) J. R. Stern and A. del Campillo, THIS JOURNAL, **75**, 2277 (1953).

(3) S. J. Wakil and H. R. Mahler, *J. Biol. Chem.*, **207**, 125 (1954).

(4) F. Lynen, L. Wessely, O. Wieland and L. Rueff, *Angew. Chem.*, **64**, 687 (1952).

(5) A. L. Lehninger and G. D. Greville, *Biochim. Biophys. Acta*, **12**, 188 (1953).

(6) S. J. Wakil, D. E. Green, S. Mii and H. R. Mahler, *J. Biol. Chem.*, **207**, 631 (1954).

(7) Prepared from *l*-BOH and *d*-BOH (donated by Dr. G. D. Greville) by the general method of T. Wieland and L. Rueff, *Angew. Chem.*, **65**, 186 (1952).