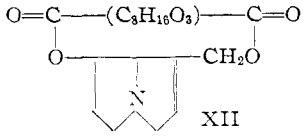
The infrared absorption spectrum of sceleratine shows only one strong band in the 6 $\mu$ region, namely, at 1700 cm.$^{-1}$. From this observation it can be concluded that the acid moiety exists in the alkaloid as part of a cyclic diester XII.[12] Monocrotaline,



XII

which also contains a potential $\gamma$-lactone in the acid moiety has been shown to contain such a diester structure, rather than a monoester-monolactone structure.[13] The orientation of the acid moiety in sceleratine has not, as yet, been determined but can be expected to be similar to the acid moiety orientation of monocrotaline[13] and riddelline.[14]

Sceleranecic acid represents the first C-10 necic acid containing a substituted glutaric acid skeleton. All C-10 necic acids described up to now are substituted adipic acids. The related pyrrolizidine alkaloids from *Crotalaria species* of plants, *viz.*, monocrotaline[13] and dicrotaline,[15] give on hydrolysis substituted glutaric acids with less than ten carbon atoms. The structural relationships of these acids will be discussed in a separate report.[16]

## Experimental

**Infrared Absorption Spectra.**—All spectra were obtained from 5 % solutions in chloroform using a Baird instrument equipped with rock salt optics. The compounds for which spectra are reported in this paper were prepared and purified as described in the earlier papers referred to above.

(12) The two—C(=O)—O— linkages in XII may also be referred to as lactone groupings. However, since these groupings occur in a large ring structure and exhibit infrared absorption in the region characteristic for normal esters, they are referred to as ester linkages in the present discussion.

(13) R. Adams, P. R. Shafer and B. H. Braun, THIS JOURNAL, **74**, 5612 (1952).

(14) R. Adams and B. L. Van Duuren, *ibid.*, **75**, 4638 (1953).

(15) R. Adams and B. L. Van Duuren, *ibid.*, **75**, 2377 (1953).

(16) B. L. Van Duuren, unpublished.

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# The Structure of Pinidine

BY W. H. TALLENT AND E. C. HORNING

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*dl-cis*-2-Methyl-6-propylpiperidine was prepared by synthesis and found to have an infrared absorption spectrum identical with that of dihydropinidine. From the structure of the dihydro derivative, ozonolysis experiments and infrared absorption spectra data, pinidine was assigned the structure (−)-*cis*-2-methyl-6-(2-propenyl)-piperidine.

The isolation of a new alkaloid, pinidine, from *Pinus sabiniana* Dougl. was described recently.[1] It was found to be present in the leaves in moderate quantity (0.28%), and it was accompanied by D-(+)-$\alpha$-pipecoline in lower amount (0.03%). Pinidine was also found to be a constituent of *P. jeffreyi* and *P. torreyana*, and the fact that these pines are unique in the respect that they do not contain $\alpha$- or $\beta$-pinene may indicate a biosynthetic relationship between the formation of the alkaloid and the normal path of synthesis of pinenes. In order to continue the study of this new compound, its structure was investigated. Pinidine was determined to be one of the optically active forms of *cis*-2-methyl-6-(2-propenyl)-piperidine.

Degradative and infrared spectral evidence provided the initial clues to the structure of pinidine. A study of a high-resolution infrared absorption spectrum of pinidine in the 3–4 $\mu$ region indicated that a six-membered ring was present, and the occurrence of a sharp band at 3.31 $\mu$ was taken as evidence for a double bond in either a linear or a six-membered system.[2] Using a procedure related to that of Leonard and Gash,[3] it was established that this double bond was not $\alpha,\beta$ to the nitrogen atom, and ozonolysis experiments, leading to acetaldehyde, indicated that a =CH—$CH_3$ group was present. The amino group was secondary; this conclusion was based on analytical data showing the presence of one active hydrogen atom and the absence of an N-alkyl group, and by the presence of an $N^+$–H band in the infrared spectrum of the methiodide. Nevertheless, it was not possible to obtain acyl derivatives, and this was attributed to steric hindrance. A C-methyl determination showed that two such groups were present.[1]

A vapor-phase, high-temperature (400–500°) catalytic (Pd–C) dehydrogenation reaction led to a new compound which was recognized as a substituted pyridine by its infrared and ultraviolet absorption spectra. This compound was characterized as the chloroplatinate, and it was found to have an empirical formula $C_9H_{13}N$. Since pinidine was known to have the formula $C_9H_{17}N$, it was evident that no substituent groups were lost during the aromatization. A color test showed the presence of at least one $\alpha$-substituent, and oxidation with potassium permanganate gave a pyridinecarboxylic acid. In view of the evidence pointing to 2,6-disubstitution in pinidine, it was considered that this material was probably pyridine-2,6-

(1) W. H. Tallent, V. L. Stromberg and E. C. Horning, THIS JOURNAL, **77**, 6361 (1955). We have been advised that *P. pinceana* Gordon was obtained from northern Mexico rather than from California as reported. We regret the error and wish to thank Dr. N. T. Mirov for calling it to our attention.

(2) Effects in the C–H region due to ring size and unsaturation are discussed in W. H. Tallent and I. J. Siewers, *Anal. Chem.*, **28**, 953 (1956).

(3) N. J. Leonard and V. W. Gash, THIS JOURNAL, **76**, 2781 (1954).

dicarboxylic acid. Unfortunately, pyridinecarboxylic acids are difficult to purify and to identify. In some cases it has been necessary to convert an acid to an ester[4] or to an amide[5] in order to accomplish an identification.

TABLE I

PAPER CHROMATOGRAPHIC DATA FOR PYRIDINEDICARBOXYLIC ACIDS

| Salt[a] | $R_f$ (I)[c] | $R_f$ (II)[c] |
|---|---|---|
| 2,3-Dicarboxylate | 0.69 | 0.69 |
| 2,4-Dicarboxylate | .71 | .75 |
| 2,5-Dicarboxylate | .81 | .74 |
| 2,6-Dicarboxylate | .30 | .66 |
| Unknown[b] | .30 | .66 |

[a] These compounds were in the form of potassium salts. [b] From degradation experiments in the natural series. [c] See Experimental section for solvent systems.

In the present investigation the potassium salt was compared by paper chromatography with the four 2,X-pyridinedicarboxylic acids. $R_f$ values in two solvent systems (butanol–acetic acid–water, 4:1:1, and *sec*-butyl alcohol–formic acid–water, 15:3:2) were in agreement with the 2,6-structure (Table I). Final confirmation of the structure was obtained by preparation of the dimethyl ester, which was found to be identical with authentic dimethyl pyridine-2,6-dicarboxylate.

All of the evidence obtained up to this point indicated that pinidine was one of the stereoisomers of 2-methyl-6-(2-propenyl)-piperidine and that the aromatization product was 2-methyl-6-propylpyridine. The latter indication was confirmed by synthesis. Reaction of the lithium derivative of 2,6-lutidine with ethyl bromide gave synthetic 2-methyl-6-propylpyridine; this material was characterized as the chloroplatinate, and the parent base and its derivative were identical with the alkylated pyridine obtained in the natural series. A different method for synthesizing 2-methyl-6-propylpyridine has been reported[6] with a picrate melting at 134–134.5°. We were unable to obtain this picrate, but in order to confirm the structure of the alkylated pyridine it was prepared by a second method. The lithium derivative of 2,6-lutidine was allowed to react with acetaldehyde, and the resulting alcohol was subjected to catalytic hydrogenolysis conditions. The product was identical with that obtained by direct alkylation.

It was recognized that the conditions of aromatization of pinidine were severe and that a more direct confirmation of its structure was needed. Catalytic reduction of synthetic 2-methyl-6-propylpyridine gave an apparently homogeneous material which was presumed to be *dl-cis*-2-methyl-6-propylpiperidine; the *cis* structure should result from a catalytic hydrogenation procedure.

The infrared absorption spectrum of this material was identical with that of optically active dihydropinidine. The infrared spectra of the *cis* and *trans* forms of 2-methyl-6-propylpiperidine should be similar, but it seems unlikely that they would be identical; unless this unlikely possibility exists, dihydropinidine is (−)-*cis*-2-methyl-6-propylpiperidine.

The optical rotations of dihydropinidine and related compounds (Table II) support the view that the two alkyl groups are *cis*. The low rotation of the dihydro alkaloid may be explained by a cancellation effect resulting from opposite configurations at the two optically active centers. If these had the same configuration, an additive effect, such as that demonstrated in the case of (−)-2,6-dimethylpiperidine, would be expected. This reasoning apparently does not follow for the hydrochloride.

From these results, pinidine may be given the structure (−)-*cis*-2-methyl-6-(2-propenyl)-piperidine. The position assigned to the double bond is in accord with the C–H infrared absorption spectrum and ozonolysis results.

**Acknowledgments.**—We are indebted to Miss C. M. House and Mrs. M. L. Riethof for technical assistance. The instrumental work was carried out by Mrs. I. J. Siewers, Mr. H. F. Byers, Miss F. C. Bateman and Miss C. S. Monaghan. The analytical data were supplied by Dr. W. C. Alford and by the Clark Microanalytical Laboratories.

## Experimental[7]

**Natural Series: Aromatization of Pinidine.**—The catalyst, 20% Pd–C, was prepared by a usual method[8] with the necessary amount of palladium. The dehydrogenation was conducted in a 10 × 2 cm. glass tube packed with a mixture of equal weights of the catalyst and asbestos (B. and A. long fiber, washed and ignited). The inclined tube was heated to an internal temperature of 450–500°, and 6.3 g. of pinidine was introduced dropwise during 1 hour. The product was trapped in a flask submerged in Dry Ice–acetone. After flushing with nitrogen, the product was removed and distilled to give 3.1 g. (51%) of an aromatized product, b.p. 178–179° (764 mm.). The ultraviolet spectrum (ethanol) showed an absorption band with $\lambda_{max}$ 267 mμ and log $\epsilon_{max}$ 3.62 (shoulder at 274 mμ, log $\epsilon$ = 3.50). With 0.05*N* hydrochloric acid in 50% ethanol as the solvent, the spectrum showed one major band; $\lambda_{max}$ 272, log $\epsilon_{max}$ 3.94. The infrared spectrum showed bands at 6.25 and 6.31 μ typical of aromatic systems. A color test (to be reported in another paper) showed the presence of an α-substituent.

A **chloroplatinate** was prepared, m.p. 193–195° dec. after recrystallization from water.

*Anal.* Calcd. for $C_{18}H_{28}N_2 \cdot PtCl_6$: C, 31.77; H, 4.15; N, 4.12; Pt, 28.69. Found: C, 31.79; H, 4.05; N, 4.10; Pt, 28.51.

**Oxidation Experiments.**—The pinidine aromatization product (0.84 g.) in 10 ml. of water was stirred and heated (steam) while 10 g. of solid potassium permanganate was added in small portions over a period of 10 hr. The manganese dioxide was removed by filtration and the filtrate was washed well with chloroform. After treatment with Amberlite Resin IRC-50 ($H^+$), the aqueous solution was evaporated to dryness to yield a crude pyridinedicarboxylate salt.

The same procedure was used for the preparation of authentic specimens of salts of 2,3-, 2,4- and 2,6-pyridinedicarboxylic acids (the corresponding lutidines were oxidized). 2-Methyl-5-ethylpyridine was oxidized to give the 2,5-dicarboxylate.

**Paper Chromatographic Experiments.**—Comparison compounds were placed on Whatman 1 paper, using one drop of solutions containing 10 mg. of salts per ml. of water. The

(4) G. Black, E. Depp and B. B. Corson, *J. Org. Chem.*, **14**, 14 (1949).

(5) H. Rapoport and H. D. Baldridge, THIS JOURNAL, **74**, 5365 (1952).

(6) E. Graef, J. M. Fredericksen and A. Burger, *J. Org. Chem.*, **11**, 257 (1946).

(7) All melting points were taken on a Kofler stage. Optical rotations were determined with a Rudolph photoelectric-matching polarimeter. Ultraviolet spectra were taken with a Cary Recording Spectrophotometer (Model 11). Infrared spectra were obtained with Perkin–Elmer (Model 21) and Beckman IR-3 instruments.

(8) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 385, Method D.

TABLE II

SPECIFIC AND MOLAR ROTATIONS

| Compound bases | $c^a$ | $[\alpha]_{589}$ | $[M]_{589} \times 10^{-2}$ | $[\alpha]_{436}$ | $[M]_{436} \times 10^{-2}$ |
|---|---|---|---|---|---|
| D-(+)-α-Pipecoline | 1.53 | + 5.6 (22°) | + 5.5 | +16.2 (22°) | +16.0 |
| (−)-2,6-Dimethylpiperidine[b] | | −13.8 | −15.6 | | |
| D-(+)-Coniine[c] | | + 8.1 | +10.3 | | |
| (−)-*cis*-2-Methyl-6-propylpiperidine (dihydropinidine) Hydrochlorides | 1.62 | − 1.2 (25°) | − 1.7 | − 2.8 (25°) | − 3.9 |
| D-(+)α-Pipecoline | 1.22 | − 3.9 (23°) | − 5.3 | − 8.5 (23°) | −11.6 |
| D-(+)-Coniine[d] | 1.16 | − 6.9 (24°) | −11.3 | −13.9 [24°) | −22.6 |
| (−)-*cis*-2-Methyl-6-propylpiperidine (dihydropinidine) | 1.07 | +12.7 (25°) | +22.6 | +26.2 (25°) | −46.5 |

[a] In ethanol. [b] A. D. Kuzokov and G. P. Men'shikov, *J. Gen. Chem.* (*U.S.S.R.*), **20,** 1524 (1950); *C.A.* **45,** 2485 (1951). [c] W. Liethe, *Monatsh.*, **50,** 40 (1928). [d] Prepared from a small sample of D-(+)-coniine that was available and recrystallized from ethyl acetate–ethanol, m.p. 215–217°, reported (A. Ladenburg, *Ann.*, **247,** 1 (1888)) 217.5–218.5°.

papers were developed by an ascending procedure in either (I) butanol–acetic acid–water, 4:1:1, or (II) *sec*-butyl alcohol–formic acid–water, 15:3:2. The pyridine acids were detected by spraying with brom cresol green reagent. $R_f$ values are given in Table I. Additional details of this general method for the chromatography of salts of organic acids are described elsewere.[9]

**Dimethyl 2,6-Pyridinedicarboxylate.**—The salt (873 mg.) obtained by oxidation of the pinidine aromatization product was dissolved in hot 10% hydrochloric acid (5 ml.). The free acid crystallized on cooling; the yield was 107 mg. This material was recrystallized from water several times.

A 0.5-ml. quantity of approximately 0.6 *N* diazomethane in ether was swirled while 10 mg. of the pyridinedicarboxylic acid was added. One drop of water was added to initiate the reaction; after cessation of nitrogen evolution, the ether was evaporated and the residue was recrystallized from water to yield a sample of ester melting at 121–124°. The melting point was not depressed on mixture with an authentic sample of dimethyl 2,6-pyridinedicarboxylate, (reported[10] m.p. 124–125°) prepared in the same way from 2,6-pyridinedicarboxylic acid obtained by oxidation of 2,6-lutidine.

**Synthetic Series: 2-Methyl-6-propylpyridine, Method A.**—To a stirred solution of phenyllithium from 13.9 g. of lithium and 157 g. of bromobenzene in 500 ml. of anhydrous ether was added 107 g. of 2,6-lutidine over a 10-minute period. After stirring for 30 minutes at room temperature, 107 g. of ethyl bromide was added dropwise over a 30-minute period at reflux temperature. There was added 50 ml. of methanol and 1 l. of 1 *N* hydrochloric acid; the layers were separated and the organic base was isolated by the usual manipulations. Distillation yielded 26.6 g. (20%) of 2-methyl-6-propylpyridine, b.p. 179–180° (756 mm)., $n^{25}D$ 1.4889.

*Anal.* Calcd. for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.76; H, 9.68; N, 10.23.

The reported picrate could not be obtained. The **chloroplatinate,** m.p. 193–195° dec., was identical with that prepared from the aromatization product of pinidine (mixed m.p. and infrared spectra). The ultraviolet and infrared absorption spectra of the base were identical with those from the pinidine product, except that log $\epsilon_{max}$ at 267 mμ was 3.65 instead of 3.62.

**Method B.**—Acetaldehyde (57.5 g.) was introduced in vapor phase beneath the surface of a stirred ether solution of 2,6-lutidyllithium prepared as described in the previous experiment. The addition required 2 hr.; the reaction mixture was kept at 0–5°. After the addition of methanol and 1 *N* hydrochloric acid, the organic base was isolated in the usual way. Distillation yielded 16.5 g. (10%) of **2-methyl-6-(2-hydroxypropyl)-pyridine,** b.p. 78–80° (1 mm.), $n^{24}D$ 1.5158. The infrared spectrum showed a broad hydroxyl band near 3.0 μ.

*Anal.* Calcd. for $C_9H_{13}ON$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.59; H, 8.56; N, 9.28.

The **phenylurethan** was recrystallized from benzene–hexane, m.p. 95–96°.

*Anal.* Calcd. for $C_{16}H_{18}O_2N_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.11; H, 6.50; N, 10.32.

A hydrogenolysis of 2-methyl-6-(2-hydroxypropyl)-pyridine was carried out with 1.48 g. of the alcohol in 20 ml. of acetic acid containing one drop of 70% perchloric acid, with 0.55 g. of 5% Pd–barium sulfate catalyst[11] at atmospheric pressure and at room temperature. The theoretical amount of hydrogen was absorbed in 26 hr. The organic base was isolated in a usual way to give, after distillation, 0.87 g. (65%) of product which was the same as that obtained by the direct alkylation method. The infrared spectra of the two samples were identical, and the chloroplatinates of both materials also had identical spectra and melting points. A mixed melting point of the chloroplatinates showed no depression.

***dl-cis*-2-Methyl-6-propylpiperidine.**—The hydrogenation of 2-methyl-6-propylpyridine to the corresponding piperidine was carried out with 4.5 g. of the base in 5 ml. of acetic acid with a platinum catalyst from the reduction of 0.5 g. of the oxide. The theoretical amount of hydrogen was absorbed after 50 hr. at atmospheric pressure and room temperature. The product was isolated in a usual way. Distillation at atmospheric pressure gave 0.85 g. (19%) of product, b.p. 176–177° (752 mm.), $n^{25}D$ 1.4453, and left a considerable quantity of dark viscous residue. The infrared spectrum was identical with that of the corresponding material in the natural series. In view of the method of preparation, this compound has been assigned the *cis*-configuration.

*Anal.* Calcd. for $C_9H_{19}N$: C, 76.52; H, 13.56; N, 9.92. Found: C, 76.63; H, 13.43; N, 10.11.

The **hydrochloride** was recrystallized from ethyl acetate–ethanol, m.p. 219–220°. The infrared spectrum was identical with that of optically active dihydropinidine hydrochloride.

*Anal.* Calcd. for $C_9H_{20}NCl$: C, 60.82; H, 11.34; N, 7.88. Found: C, 61.10; H, 11.28; N, 7.49.

**Infrared Absorption Spectra.**—High-resolution spectra in the 3–4 μ range were compared with those for a number of model compounds; these data are in another paper dealing with C–H absorption bands.[2] Reference spectra for the alkaloid and derivatives are available through a previous paper.[1]

BETHESDA 14, MD.

(9) W. H. Tallent, *J. Org. Chem.*, in press.

(10) R. A. Barnes and H. M. Fales, THIS JOURNAL, **75,** 975 (1953).

(11) Ref. 8, 1955, p. 685, Method A.