from 2,4-bis-(dichloromethyl)-6-hydroxy-*s*-triazine dichloroacetamidine salt (VI) in 63% yield and from 6-hydroxy-2,4-bis-(trichloromethyl)-*s*-triazine trichloroacetamidine salt (II) in 60% yield.

2,4-Dimethyl-6-hydroxy-*s*-triazine Hydrochloride Monohydrate (XX).—Hydrogen chloride was bubbled into a cold solution of 2.5 g. of 2,4-dimethyl-6-hydroxy-*s*-triazine acetamidine salt (XVII) in 15 ml. of 96% ethanol for about 15 minutes. The crystalline reaction product was filtered off and washed with 10 ml. of cold 96% ethanol to remove traces of acetamidine hydrochloride. The yield was 1.7 g. (70%) of product, m.p. 177–179°.

Anal. Calcd. for $C_5H_7N_3O\cdot HCl\cdot H_2O$ (179.6): C, 33.43; H, 5.61; N, 23.40; Cl, 19.74. Found: C, 34.21; H, 5.41; N, 23.79; Cl, 19.71.

2,4-Dimethyl-6-hydroxy-*s*-triazine (XXI).—A solution of 1.17 g. of 2,4-dimethyl-6-hydroxy-*s*-triazine hydrochloride monohydrate (XX) in 15 ml. of methanol was treated with 2.6 ml. of a 10% solution of NaOH in methanol. The methanol was then evaporated *in vacuo* and the residue was sublimed at 150° and 0.05 mm. Recrystallization of the sublimate from acetone gave 0.49 g. of product, m.p. 230–231°.

Anal. Calcd. for $C_5H_7N_3O$ (125.1): C, 47.99; H, 5.64; N, 33.57. Found: C, 47.95; H, 5.73; N, 33.52.

2,4-Dimethyl-*s*-triazine (XXII).—A mixture of 300 mg. of 6-chloro-2,4-dimethyl-*s*-triazine (XVIII), 211 mg. of triethylamine, 1 g. of 10% palladium-on-charcoal catalyst and 20 ml. of anhydrous ether was shaken at 20° with hydrogen. The absorption of the theoretical amount of hydrogen was completed in 5 minutes. The catalyst and the formed triethylamine hydrochloride were filtered off, and the filtrate was evaporated under mild vacuum; yield 120 mg. (52%) of product, m.p. 46°.

Anal. Calcd. for $C_5H_7N_3$ (109.1): C, 55.03; H, 6.47; N, 38.51. Found: C, 54.99; H, 6.50; N, 38.37.

XXII was characterized as the dihydrochloride salt by passing HCl into its ethereal solution. The precipitate is extremely hygroscopic and immediately forms a monohydrate, m.p. 148–150°. *Anal.* Calcd. for $C_5H_7N_3\cdot 2HCl\cdot H_2O$: Cl, 35.62. Found: Cl, 36.12.

COLUMBUS, OHIO

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

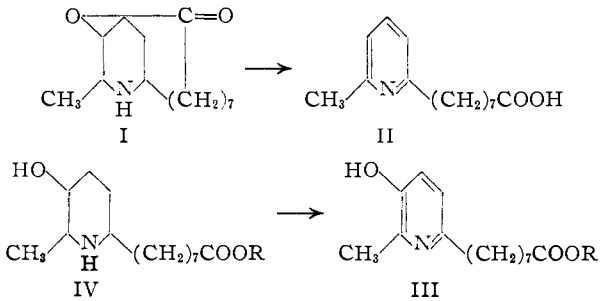
The Synthesis of Desoxycarpyrinic and Carpyrinic Acids

BY HENRY RAPOPORT AND EMIL J. VOLCHECK, JR.[1]

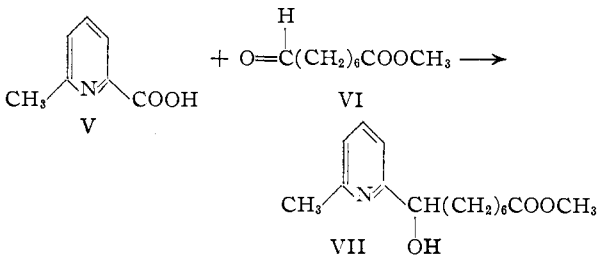
RECEIVED DECEMBER 19, 1955

Desoxycarpyrinic acid and carpyrinic acid, degradation products of carpaine, have been synthesized by application of the Hammick reaction (decarboxylation of a picolinic acid in the presence of a carbonyl compound) to the half-ester aldehyde of suberic acid. The intermediate carbinol group in the one case was converted to the chloride and thence reduced to methylene, while in the other case it was oxidized to the ketone and then converted to methylene. The 5-hydroxy-6-methylpicolinic acid needed for the synthesis of carpyrinic acid was prepared by carboxylation of 3-hydroxy-2-methylpyridine.

As a result of a recent reinvestigation, the structure of carpaine, the chief papaya alkaloid, has been established[2] by degradative methods as I, containing the rather unique thirteen-membered lactone ring fused 2,5- to the piperidine nucleus. In considering synthetic approaches to this and related structures, two compounds seemed most attractive as the objectives of initial synthetic efforts. These compounds are desoxycarpyrinic acid (II) and carpyrinic acid (III), the products of catalytic dehydrogenation, under relatively mild conditions, of carpaine[3] and methyl or ethyl[4] carpamate (IV), respectively. The present report is a description of the synthesis of these two acids.



The synthesis of desoxycarpyrinic acid was investigated first, and the various methods for preparing 2,6-disubstituted pyridines commencing from the readily available 2,6-lutidine were examined. Particularly attractive from the standpoint of economy of steps was the Hammick reaction in which a pyridylcarbinol is formed by decarboxylation of a picolinic acid in the presence of a carbonyl compound.[5] The application of this reaction to the synthesis of desoxycarpyrinic acid (II) would involve the use of 6-methylpicolinic acid (V), easily prepared by oxidation of 2,6-lutidine,[6] and the half-ester aldehyde of suberic acid (methyl 7-formylheptanoate) (VI).



(1) Shell Fellow in Chemistry, 1954–1955.

(2) H. Rapoport, H. D. Baldridge, Jr., and E. J. Volcheck, Jr., THIS JOURNAL, **75**, 5290 (1953).

(3) H. Rapoport and H. D. Baldridge, Jr., *ibid.*, **74**, 5365 (1952).

(4) T. R. Govindachari and N. S. Narasimhan, *J. Chem. Soc.*, 2635 (1953).

(5) (a) D. L.Hammick and B. R. Brown, *ibid.*, **173**, 659 (1949); (b) B. R. Brown, *Quart. Revs.*, **5**, 131 (1951); (c) N. H. Cantwell and E. V. Brown, THIS JOURNAL, **74**, 5967 (1952); **75**, 1489, 4466 (1953); (d) N. S. Sperber, D. Papa, E. Schwenk and M. Sherlock, *ibid.*, **71**, 887 (1949); (e) M. R. Buchdahl and T. O. Soine, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 225 (1952); (f) L. Dorfman, A. Furlenmeier, C. F. Huebner, R. Lucas, H. B. MacPhillamy, J. M. Mueller, E. Schlittler, R. Schwyzer and A. F. St. Andre, *Helv. Chim. Acta*, **37**, 59 (1954).

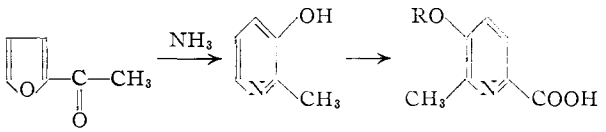
(6) G. Block, E. Depp and B. B. Corson, *J. Org. Chem.*, **14**, 14 (1949).

Before proceeding with this reaction, a number of questions had to be answered. Since previous work with the Hammick reaction had always involved aromatic aldehydes, would the reaction take place as readily with an aliphatic aldehyde? Was the 300 to 600 mole % of aldehyde compared to picolinic acid necessary? This was of special interest in the present case since the aldehyde II is more valuable than the 6-methylpicolinic acid. The Hammick reaction has also been reported with esters,[5a] and since the anticipated application involved an aldehydo ester, would there be sufficient difference in rate to make this process feasible?

These questions were answered in the following way. Using *n*-heptaldehyde and 6-methylpicolinic acid in a one-to-one molar ratio in *p*-cymene as solvent, a 24% yield of the pyridylcarbinol was obtained. This carbinol was then converted to the chloride and reduced with zinc and acetic acid[7] to 2-*n*-heptyl-6-methylpyridine. When 6-methylpicolinic acid was decarboxylated in the same fashion in the presence of ethyl heptanoate, no evidence of condensation was found.

Therefore, the reaction between 6-methylpicolinic acid and the half aldehyde ester of suberic acid (prepared by Rosenmund reduction of the ester-acid chloride) was tried. By taking suitable precaution in the isolation procedure, necessitated by the presence of the easily hydrolyzed ester group, the pyridylcarbinol ester VII was obtained. Replacement of the hydroxyl group by chloride and hydrogenolysis of the chloro compound proceeded as with the model compound. The ester was then hydrolyzed and 6-methyl-2-pyridineoctanoic acid hydrochloride was isolated, identical with desoxycarpyrinic acid hydrochloride (II) from carpaine in melting point behavior (dimorphic), mixed melting point and infrared spectrum.

Application of this synthetic procedure to the synthesis of carpyrinic acid was contemplated in an exactly parallel fashion, except for the substitution of 5-hydroxy- or 5-methoxy-6-methylpicolinic acid. To prepare this picolinic acid, 2-methyl-3-hydroxypyridine (IX) was an attractive starting point, and the latter compound was conveniently prepared in 56% yield by the recently developed method of heating 2-acetylfuran (VIII) with ammonia.[8] The carboxyl group was then introduced by a Kolbe–Schmidt type carboxylation of 3-hydroxy-2-methylpyridine.

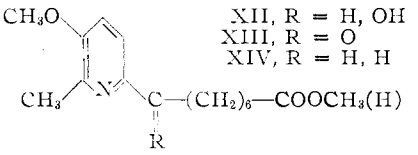


VIII IX X, R = H
XI, R = CH_3

This type of carboxylation appears first to have been applied to the pyridine series by Urbanski[9] who, with 3-hydroxypyridine, obtained either 3-hydroxypicolinic acid or 5-hydroxypicolinic acid under specific conditions. By using the potassium salt of 3-hydroxy-2-methylpyridine intimately mixed with potassium carbonate and heating at 250° and a carbon dioxide pressure of 500 p.s.i., an excellent yield of the picolinic acid X resulted. This was etherified with dimethyl sulfate, and the 5-methoxy-6-methylpicolinic acid (XI) was separated from unmethylated material by fractional sublimation.

Proof was necessary that the carboxyl group was in the α- and not the γ-position in both the hydroxy and methoxy acids, and it was supplied by the following evidence. The pK of picolinic acid has been reported[10] as 5.32. For 5-hydroxy-6-methylpicolinic acid, we have found a pK_1 of 5.13 and a pK_2 of 9.49[11] for the carboxyl and phenol groups, respectively. From the analogy with salicylic acid (pK_1 2.98, pK_2 too weak to measure in water[12]) and *p*-hydroxybenzoic acid (pK_1 4.54, pK_2 9.39),[12] the carboxyl group would be expected to be much stronger and the phenol group much weaker if an *ortho* relationship existed in the picolinic acid. The fact that the pK of the carboxyl is very similar to that of picolinic acid and the phenol is of the expected strength is strong support for the *para* relationship. Confirmation that the carboxyl group is in the α-position was provided by the formation of colored complexes with ferrous and cupric ions. It has been established that such complexes are formed only by α-pyridinecarboxylic acids.[13] 6-Methylpicolinic acid and 5-methoxy-6-methylpicolinic acid gave strong positive tests, whereas isonicotinic acid and 2-methoxybenzoic acid did not form colored complexes.

The Hammick reaction was then applied to 5-methoxy-6-methylpicolinic acid and the aldehydo ester from suberic acid in the same manner as previously except that a shorter heating period was needed for complete carbon dioxide evolution.[14] The product was methyl η-hydroxy-5-methoxy-6-methyl-2-pyridineoctanoate (XII) and it was obtained in 25% yield.



XII, R = H, OH
XIII, R = O
XIV, R = H, H

Replacement of the hydroxyl in XII by chloride was attempted under a variety of conditions, using thionyl chloride, but invariably the sole isolable product was recovered carbinol. When the reaction conditions were made more vigorous, corre-

(7) N. J. Leonard and B. L. Ryder, *J. Org. Chem.*, **18**, 598 (1953).

(8) A. P. Dunlop and S. Swadesh, U. S. Patent 2,636,882 (1953).

(9) H. Bojarska-Dahlig and T. Urbanski, *Prace. Placowek Nauk-Badawez*, **1**, 1 (1952); see also O. Baine, G. F. Adamson, J. W. Barton, J. L. Fitch, D. R. Swayampati and H. Jeskey, *J. Org. Chem.*, **19**, 510 (1954).

(10) R. F. Evans, E. F. G. Herington and W. Kynaston, *Trans. Faraday Soc.*, **49**, 1284 (1953).

(11) These values were determined by potentiometric titration of a 0.01 *M* aqueous solution of the compound with 0.1 *N* sodium hydroxide. The equations given by J. E. Ricci, "Hydrogen Ion Concentration," Princeton University Press, Princeton, N. J., 1952, pp. 67–72, were used to make the calculations.

(12) J. F. J. Dippy, *Chem. Revs.*, **25**, 151 (1939); B. Jones and J. C. Speakman, *J. Chem. Soc.*, 19 (1944).

(13) T. Urbanski, *ibid.*, 1104 (1946); 132 (1947); H. Ley, C. Schwarte and O. Münnich, *Ber.*, **57**, 349 (1924).

(14) The first-order rate constant was 3.3×10^{-3} min.$^{-1}$ for the 5-methoxy acid as compared to 1.2×10^{-3} min.$^{-1}$ for 6-methylpicolinic acid.

spondingly increasing quantities of polymeric material were formed. The carbinol could be acetylated, but both the carbinol and its acetyl derivative were resistant to the usual hydrogenolysis procedures for benzylic alcohols.

Conversion of the carbinol XII to the methylene compound XIV was then investigated *via* oxidation to the ketone XIII followed by Wolff–Kishner reduction, and this route proved successful. Using manganese dioxide in chloroform and observing the shift in the ultraviolet maximum from 282 mμ (ε 5,670) to 288 mμ (ε 13,570) as well as the appearance of a new peak at 270 mμ (ε 11,620), the oxidation was found to reach completion in 23 hours and a 71% yield of crystalline ketone was isolated.

To avoid potential difficulties which the presence of ethylene glycol might cause in the isolation of an amphoteric product, reduction of the ketone XIII was conducted by the sealed tube procedure. Ketone, hydrazine, sodium ethoxide and ethanol were heated at 175° and, after a subsequent saponification, the product was obtained as 5-methoxy-6-methyl-2-pyridineoctanoic acid (XIV) hydrochloride.

All that remained before a comparison could be made with degradation products from carpaine was cleavage of the 5-methoxyl group and this was easily accomplished with pyridine hydrochloride.[15] The cleaved material, 5-hydroxy-6-methyl-2-pyridineoctanoic acid (III), was then characterized as the hydrochloride and the methyl ester. Both derivatives of carpyrinic acid were also prepared and were shown to be identical with the corresponding synthetic compounds[16] through identity of melting points (no depression on mixing) and infrared and ultraviolet spectra.

Experimental[17]

6-Methylpicolinic acid (V) was prepared by the oxidation of 2,6-lutidine[6] and was crystallized from benzene, m.p. 126–128° (reported[6] 126–127°).

1-(6′-Methyl-2′-pyridyl)-1-heptanol.—A solution of 10 g. (0.073 mole) of 6-methylpicolinic acid and 10 g. (0.087 mole) of *n*-heptaldehyde (b.p. 68–69° (40 mm.)) in 60 ml. of *p*-cymene was heated under reflux for 25 hr. after which carbon dioxide evolution ceased (90% of theoretical). The cooled solution was extracted with two 50-ml. portions of 2 *N* hydrochloric acid, the combined acid extracts were alkalinized and extracted with ether and the ether extract was dried and distilled. A 24% yield of 1-(6′-methyl-2′-pyridyl)-1-heptanol was obtained on fractionation, b.p. 122–124° (2 mm.), $n^{25}D$ 1.4987.

Anal. Calcd. for $C_{13}H_{21}ON$: C, 75.3; H, 10.2; N, 6.8. Found: C, 75.1; H, 10.6; N, 6.6.

The picrate was prepared with ethanolic picric acid and was recrystallized from absolute ethanol, m.p. 102–103°.

Anal. Calcd. for $C_{19}H_{24}O_8N_4$: C, 52.3; H, 5.5; N, 12.8. Found: C, 52.5; H, 5.7; N, 13.0.

2-*n*-Heptyl-6-methylpyridine.—Following the general procedure of Leonard and Ryder,[7] 12 g. (0.058 mole) of 1-(6′-methyl-2′-pyridyl)-1-heptanol in 100 ml. of benzene was treated with 7.7 g. (0.065 mole) of thionyl chloride. At the end of the reaction period, the solution was cooled, made alkaline with concd. sodium hydroxide and extracted with two 50-ml. portions of benzene after removing the original organic layer. Evaporation of the combined benzene extracts left an oil which was dissolved in 75 ml. of glacial acetic acid and treated with 9.3 g. of zinc dust, added in small portions over a 40-minute period with stirring. The mixture, after being stirred on the steam-bath overnight, was filtered, the filtrate was concentrated *in vacuo* and the residue was made alkaline and extracted with four 50-ml. portions of ether. Distillation of the combined and dried ether extracts gave 6.3 g. (57% yield) of 2-*n*-heptyl-6-methylpyridine, b.p. 124–125.5° (9 mm.), $n^{25}D$ 1.4830.

Anal. Calcd. for $C_{13}H_{21}N$: C, 81.6; H, 11.1. Found: C, 81.8; H, 11.4.

The picrate was prepared with ethanolic picric acid and recrystallized from absolute ethanol, m.p. 60–62°.

Anal. Calcd. for $C_{19}H_{24}O_7N_4$: C, 54.3; H, 5.8. Found: C, 54.2; H, 5.8.

Methyl hydrogen suberate (VI) was prepared by heating a mixture of dimethyl suberate, suberic acid, methanol, di-*n*-butyl ether and hydrochloric acid[18] and was isolated by fractional distillation, b.p. 164–166° (5 mm.) (reported[19] b.p. 185–189° (17 mm.)).

Methyl 7-Formylheptanoate (VI).—Methyl hydrogen suberate (43 g., 0.23 mole) was converted to the acid chloride by heating under reflux for 2.5 hours with thionyl chloride (69 g., 0.58 mole). The reaction mixture was then distilled and the 7-carbomethoxyheptanoyl chloride (47 g., 94% yield) was collected from 138–143° (12 mm.) (reported[19] b.p. 164° (34 mm.)). Hydrogen was bubbled through a rapidly stirred and refluxing solution of 41 g. (0.2 mole) of the acid chloride in 250 ml. of xylene containing 10 g. of 5% palladized barium sulfate and 0.6 ml. of Rosenmund poison.[20] After about 5 hours, hydrogen chloride evolution ceased and the reaction mixture was cooled, filtered and distilled. Methyl 7-formylheptanoate was collected at 80° (0.2 mm.), $n^{25}D$ 1.4494.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.8; H, 9.4; OCH_3, 18.0. Found: C, 62.9; H, 9.6; OCH_3, 18.2.

The 2,4-dinitrophenylhydrazone, prepared in the usual manner, melted at 76–78°.

Anal. Calcd. for $C_{15}H_{20}O_6N_4$: C, 51.1; H, 5.7; N, 15.9. Found: C, 50.9; H, 5.8; N, 16.0.

Methyl η-Hydroxy-6-methyl-2-pyridineoctanoate (VII).—The decarboxylation of 30 g. of 6-methylpicolinic acid in the presence of 30 g. of methyl 7-formylheptanoate was carried out in the same manner as the previous Hammick reaction and the reaction mixture was extracted with six 100-ml. portions of *p*H 2.4 phosphate buffer. The combined aqueous extracts were adjusted to *p*H 10.5 and extracted with six 100-ml. portions of ether which were then combined, washed with water, dried and evaporated. Fractionation of the residual liquid gave 4.2 g. (9%) of the pyridylcarbinol VII, b.p. 172–173.5° (1.3 mm.), $n^{25}D$ 1.5013.

Anal. Calcd. for $C_{15}H_{23}O_3N$: C, 67.9; H, 8.7; N, 5.3; OCH_3, 11.7. Found: C, 67.6; H, 8.5; N, 5.4; OCH_3, 12.0.

Methyl 6-Methyl-2-pyridineoctanoate (Methyl Desoxycarpyrinate).—Replacement of the hydroxyl group of the pyridylcarbinol VII by hydrogen was carried out in the same manner as in the preparation of 2-*n*-heptyl-6-methylpyridine above except that all additions of sodium hydroxide were made in the cold and to a *p*H of 10.5. In the final extraction, a voluminous precipitate of zinc hydroxide formed but this did not interfere with the ether extraction, made in eight portions. The methyl 6-methyl-2-pyridineoctanoate boiled at 152.5–155° (3.5 mm.), $n^{25}D$ 1.4883. Its infrared spectrum was identical with that of a sample prepared from desoxycarpyrinic acid[3] by esterification with diazomethane.

Anal. Calcd. for $C_{15}H_{23}O_2N$: C, 72.3; H, 9.3; N, 5.6; OCH_3, 12.4. Found: C, 72.4; H, 9.2; N, 5.7; OCH_3, 12.1.

(15) V. Prey, *Ber.*, **74**, 1219 (1941).

(16) After this work had been practically completed, a general study of the ammonolysis of α-furyl ketones appeared by W. Gruber [*Ber.*, **88**, 178 (1955)]. Among the β-hydroxypyridines he prepared by this independent method were the compounds corresponding to ethyl carpyrinate and carpyrinic acid hydrochloride. Although no direct comparison was made with material from natural sources, similarity of physical properties (see Experimental) leaves little doubt as to their identity.

(17) 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.

(18) S. Swann, Jr., R. Oehler and R. J. Buswell, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 276.

(19) G. T. Morgan and E. Walton, *J. Chem. Soc.*, 290 (1935).

(20) E. B. Hershberg and J. Cason, *Org. Syntheses*, **21**, 84 (1941).

6-Methyl-2-pyridineoctanoic Acid (Desoxycarpyrinic Acid) (II).—After being heated under reflux for 15 hours, a solution of methyl desoxycarpyrinate (2 g., 8 mmoles) in 100 ml. of 1.2 *N* methanolic potassium hydroxide was evaporated under a nitrogen stream, and the residue was dissolved in 40 ml. of water and acidified to congo red with hydrochloric acid. Evaporation of this solution followed by digestion with four 100-ml. portions of chloroform and removal of the chloroform *in vacuo* left a crystalline residue. Recrystallization from acetone by rapid cooling and partial evaporation gave material of m.p. 71–72° whereas slower crystallization and drying *in vacuo* at 60° resulted in crystals melting at 95–97°. This dimorphic behavior parallels that found for authentic desoxycarpyrinic acid hydrochloride (m.p. 72–73° and 94.6–96.4°[3,21]) and on mixing with the synthetic material there was no change in melting point.

2-Methyl-3-hydroxypyridine (IX).—A mixture of 85 g. (0.77 mole) of 2-acetylfuran (prepared by the reaction of furan and acetic anhydride in the presence of phosphoric acid[22] (b.p. 101–102° (12 mm.)), $n^{25}D$ 1.5038, reported[22] b.p. 45–48° (5 mm.), and two liters of 11 *N* aqueous ammonia was heated with rocking for 17 hours at 150° in a large hydrogenation bomb (void, 3.35 liters). After being cooled, the reaction mixture was filtered (gravity), the filtrate was evaporated to dryness on the steam-bath under an air stream and the residue was distilled, b.p. 185–195° (70 mm.). Crystallization of the distillate (57 g., 66%) from ethanol gave 38 g. (45% yield) of 2-methyl-3-hydroxypyridine, m.p. 170–171°. From the mother liquors a second crop was obtained bringing the yield to 56% of material melting above 168° (reported[8] m.p. 168–170°); **picrate**, from ethanol, m.p. 206–207° (reported[8] m.p. 202°).

5-Hydroxy-6-methylpicolinic Acid (X).—The dry potassium salt of 2-methyl-3-hydroxypyridine was prepared dissolving this compound in an equivalent amount of 2.5 *N* aqueous potassium hydroxide, concentrating this solution to a thick glass on the steam-bath under a nitrogen stream and completing the drying at 70° in a vacuum oven. A mixture of 27 g. (0.18 mole) of this potassium salt and 38 g. (0.28 mole) of anhydrous potassium carbonate was thoroughly ground in a ball mill for 1 hr. The resulting fine powder was quickly transferred to a hydrogenation bomb which was charged to a pressure of 500 p.s.i. with carbon dioxide and heated with rocking at 250° for 9 hr. Rocking was continued as the bomb was allowed to cool to room temperature. In a series of experiments, the pressure drop always amounted to 80–100% of that calculated for the absorption of 1 mole of carbon dioxide per mole of 2-methyl-3-hydroxypyridine. Using 350 ml. of boiling water in portions, the contents of the bomb were removed, the mixture was heated to boiling and filtered hot and the filtrate was acidified to *p*H 2 with sulfuric acid. The carbon dioxide was driven off by boiling and the mixture, cooled to room temperature, was rapidly adjusted to *p*H 7.3–7.4 with concd. sodium hydroxide solution. Filtration at this point gave 23 g. of 5-hydroxy-6-methylpicolinic acid, and continuous extraction of the filtrate with methylene chloride, maintaining the *p*H at 7.3, led to a recovery of 3 g. of 2-methyl-3-hydroxypyridine. The aqueous phase then was acidified to *p*H 3 with sulfuric acid and thoroughly extracted with *n*-butyl alcohol. Concentration of the *n*-butyl alcohol extracts gave an additional 4 g. of the picolinic acid, bringing the total to 27 g. of material (93% yield, based on consumed 2-methyl-3-hydroxypyridine) melting above 240° dec. An analytical sample was obtained by crystallization from a dilute solution in isopropyl alcohol and sublimation at 150° (5 μ), m.p. 246–247° dec., pK'_1 5.13, pK'_2 9.49.[11]

Anal. Calcd. for $C_7H_7O_3N$: C, 54.9; H, 4.6; N, 9.2. Found: C, 54.9; H, 4.6; N, 9.5.

5-Methoxy-6-methylpicolinic Acid (XI).—Four successive 30-ml. portions of dimethyl sulfate were added to a solution of 50 g. of crude 5-hydroxy-6-methylpicolinic acid and 40 g. of sodium hydroxide in 250 ml. of water. Each addition was accompanied by shaking and cooling so that the internal temperature remained between 30–35°, and the subsequent addition was not made until the mixture became homogeneous and the reaction was no longer exothermic. A solution of 13.5 g. of sodium hydroxide in 25 ml. of water was added along with each of the last two dimethyl sulfate portions, and finally 27 g. of sodium hydroxide in 50 ml. of water was added and the solution was heated under reflux for 4 hr. The *p*H was adjusted to 7, with sulfuric acid, the mixture was allowed to stand for 0.5 hr. and then filtered and the filtrate was acidified to *p*H 3. Some unreacted hydroxy acid was recovered by filtration, and the filtrate was exhaustively and continuously extracted with methylene chloride. The methylene chloride was evaporated and the residue was very slowly sublimed at 95° (5 μ). By this procedure the hydroxy acid remained as the residue and 5-methoxy-6-methylpicolinic acid was obtained as a crystalline sublimate in 40% yield, m.p. 172–174°.

Anal. Calcd. for $C_8H_9O_3N$: C, 57.5; H, 5.4; OCH_3, 18.5; equiv. wt., 167. Found: C, 57.7; H, 5.5; OCH_3, 18.3[23]; equiv. wt., 168.

Methyl η-Hydroxy-5-methoxy-6-methyl-2-pyridineoctanoate (XII).—The decarboxylation of 10 g. (60 mmoles) of 5-methoxy-6-methylpicolinic acid in the presence of 10 g. (58 mmoles) of methyl 7-formylheptanoate and 70 ml. of *p*-cymene proceeded as in the previous Hammick reactions except that carbon dioxide evolution ceased after 10 hr. The reaction mixture was cooled and filtered to remove a small amount (7%) of unreacted 5-methoxy-6-methylpicolinic acid and the filtrate was fractionally distilled after being washed with sodium bicarbonate and dried. A 25% yield (4.1 g.) of the pyridylcarbinol was obtained as an oil which solidified in the ice-box, b.p. 181.5–182.5° (0.7 mm.), $n^{25}D$ 1.5053, $n^{20}D$ 1.5068; λ_{max}^{EtOH} 282 (ϵ 5,670), 224 (ϵ 8,830), $\lambda_{min.}$ 245 (ϵ 1,330) mμ.

Anal. Calcd. for $C_{16}H_{25}O_4N$: C, 65.1; H, 8.5; OCH_3, 21.0. Found: C, 65.4; H, 8.9; OCH_3, 21.4.

Methyl η-Oxo-5-methoxy-6-methyl-2-pyridineoctanoate (XIII).—A solution of 512 mg. (1.73 mmoles) of the pyridylcarbinol XII in 50 ml. of chloroform was shaken for 23 hr. with 5 g. of manganese dioxide.[24] After filtering, the chloroform solution was evaporated to dryness and the residue was crystallized from hexane. A total of 360 mg. (71%) of the pyridyl ketone XIII was obtained, m.p. 56.2–57.6°; $\lambda_{max.}^{EtOH}$ 288 (ϵ 13,570), 270 (ϵ 11,620), $\lambda_{min.}$ 273 (ϵ 11,600), 227 (ϵ 1,000) mμ.

Anal. Calcd. for $C_{16}H_{23}O_4N$: C, 65.5; H, 7.9; OCH_3, 21.2. Found: C, 65.3; H, 7.9; OCH_3, 20.6.

5-Methoxy-6-methyl-2-pyridineoctanoic Acid (XIV).—To a solution of sodium ethoxide (from 310 mg., 13.5 mmoles of sodium) in 4.5 ml. of absolute ethanol was added 0.6 g. (2 mmoles) of the pyridyl ketone and 0.5 ml. of 85% hydrazine hydrate. The solution was heated in a bomb tube for 6 hr. at 175° after which it was cooled and the contents were removed using an ethanol wash. Most of the ethanol was removed under a nitrogen stream, 10 ml. of water was added, the solution was heated under reflux for 3 hr., and after acidifying to *p*H 2 with concd. hydrochloric acid, the solution was evaporated to dryness on the steam-bath with an air stream. Repeated digestion of the residue with chloroform, evaporation of the chloroform digests and crystallization of the residue gave 320 mg. (52%) of 5-methoxy-6-methyl-2-pyridineoctanoic acid hydrochloride, m.p. 134–136°.

Anal. Calcd. for $C_{15}H_{24}O_3NCl$: C, 59.7; H, 8.0; Cl, 11.8. Found: C, 59.2; H, 8.0; Cl, 11.7.

Methyl 5-Hydroxy-6-methyl-2-pyridineoctanoate (Methyl Carpyrinate).—Pyridine hydrochloride (500 mg., 4.3 mmoles) was mixed with 5-methoxy-6-methyl-2-pyridineoctanoic acid (XIV) hydrochloride (168 mg., 0.6 mmole) and the mixture was heated at 200° for 1 hr. and then under reflux for 2.5 hr. after adding 1 ml. of methanol and 0.01 ml. of concd. sulfuric acid. Cold, 1 *M* bicarbonate solution (15 ml.) was added, the *p*H was adjusted to 8 with sodium hydroxide and the aqueous phase was extracted with three 20-ml. portions of ether. Evaporation of the combined and

(21) H. D. Baldridge, Jr., Ph.D. Thesis, University of California, Berkeley, 1950.

(22) H. D. Hartough and A. I. Kosak, THIS JOURNAL, **68**, 2639 (1946).

(23) Zeisel determinations made in the customary manner led to methoxyl values of 7–13%, and only on raising the temperature and extending the heating time did checks for the calculated value result. This difficulty with low methoxyl values for some methoxypyridines has also been observed by E. T. Stiller, J. C. Keresztesy and J. R. Stevens, THIS JOURNAL, **61**, 1237 (1939).

(24) O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

dried ether extracts and two crystallizations of the residue from benzene gave 72 mg. (49%) of methyl 5-hydroxy-6-methyl-2-pyridineoctanoate, m.p. 125–126°. On mixing with methyl carpyrinate of m.p. 125–126° (prepared below), the m.p. was unchanged, and the two compounds had identical infrared and ultraviolet spectra.

Anal. Calcd. for $C_{15}H_{23}O_3N$: C, 67.9; H, 8.7. Found: C, 67.6; H, 8.7.

5-Hydroxy-6-methyl-2-pyridineoctanoic Acid (Carpyrinic Acid) (III).—A mixture of 45 mg. of the methyl ester, 2.5 ml. of water, 4 ml. of 95% ethanol and 410 mg. of potassium hydroxide was heated under reflux for 4 hr. and then the solution was concentrated to a gel by heating on the steam-bath under a nitrogen stream. After being acidified to *p*H 2 with hydrochloric acid, the solution was concentrated to dryness and the residue was digested repeatedly with dry acetone. Concentration of the acetone digests gave carpyrinic acid hydrochloride which was crystallized from dry acetone. It partially melted at 78–83°, resolidified and melted at 110°. A sample dried at 80° (0.2 mm.) for 22 hr. melted at 110–111° (reported[4] m.p. 85–86.5°) and synthetic material was identical with that derived from carpaine.

Anal. Calcd. for $C_{14}H_{22}O_3NCl$: C, 58.4; H, 7.7. Found: C, 58.5; H, 7.5.

Methyl Carpyrinate from Carpaine.—Carpamic acid hydrochloride,[3] suspended in methanol, was treated with excess ethereal diazomethane overnight. The solution was concentrated to a small volume, ether and water were added and the ether phase was separated and washed with aqueous carbonate solution. Evaporation of the ether left a quantitative yield of methyl carpamate as an oil. This material was dehydrogenated following the procedure previously described[4] with the addition of magnetic stirring in the dehydrogenation vessel. Hydrogen evolution ceased after five hours (2.5 moles of hydrogen evolved) and the reaction mixture was filtered hot. The catalyst was digested with benzene and cooling the combined filtrate and digests gave a 68% yield of methyl carpyrinate, m.p. 125–126°; $\lambda_{max.}^{EtOH}$ 288 (ε 6,010), 224 (ε 8,210), $\lambda_{min.}$ 246 (ε 740) mμ; in 0.01 *N* potassium hydroxide in ethanol, $\lambda_{max.}$ 310 (ε 6,460), 245 (ε 11,540), 211 (ε 13,210), $\lambda_{min.}$ 271 (ε 720), 224 (ε 4,530) mμ [reported[4] for ethyl carpyrinate, λ^{EtOH} 287 (ε 6,030), 247 (ε 563), 223 (ε 8,140), $\lambda^{KOH-EtOH}$ 310 (ε 6,170), 272 (ε 603), 247 (ε 10,000) mμ].

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The Mutarotation of Isocolchicine

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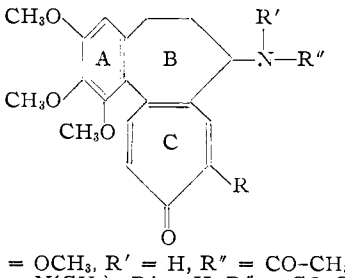
Solutions of isocolchicine and some of its derivatives mutarotate in a number of non-polar solvents but not in ethanol. This phenomenon is not exhibited by colchicine and also disappears when the acetamido group is deacetylated or N-methylated. Crystallization of mutarotated isocolchicine restores the rotation to its initial value, and throughout the change the ultraviolet and infrared spectra remain constant. The reaction is first order with an activation energy of 23.7 kcal. Hypotheses involving solvent-complexing and change in state of aggregation in solution have been considered and discarded in favor of hindered rotation between rings A and C as the best explanation for mutarotation.

During work on the preparation of isocolchicine derivatives, it was decided to use the specific rotation of the starting isocolchicine as a reliable and rapidly determined criterion of purity. However, seemingly similar samples (based on m.p. behavior) gave considerably different specific rotations, and duplicate determinations on the same sample frequently differed widely. This lack of consistency finally was found to be due to a change in specific rotation with time. Since it was quite unexpected that isocolchicine solutions should mutarotate, a detailed investigation was made and forms the substance of this report. An independent and prior observation of this phenomenon with isocolchicine has been reported recently,[2] and it also has been observed to occur with methylthioisocolchicide.[3]

Generally, mutarotation has been the result of a structural change or, more frequently, the result of diastereomer formation in solution.[4] Another and quite different type is that observed in the reversible denaturation of proteins[5] in which mutarotation is caused by the change in state of aggregation of the species in solution. Presumably then any change slow enough to be followed polarimetrically of the species in solution—either intramolecular or intermolecular, or even interaction with the solvent—might be a cause of mutarotation. In examining the isocolchicine structure[6] (I) with its single asymmetric carbon atom, it certainly is not obvious how this molecule fits into these categories for mutarotation. Therefore, an explanation was sought in a detailed study of the various factors that might be involved.



I, R = OCH_3, R′ = H, R″ = CO-CH_3
II, R = $N(CH_3)_2$, R′ = H, R″ = CO-CH_3
III, R = $NHCH_3$, R′ = H, R″ = CO-CH_3
IV, R = OCH_3, R′ = H, R″ = H
V, R = OCH_3, R′ = CH_3, R″ = CO-CH_3

It was first necessary to exclude possible extraneous factors. That a trace of acid in the solvent chloroform might be the cause was eliminated by

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

(2) R. F. Raffauf, E. F. Bumbier and G. E. Ullyot, THIS JOURNAL, **76**, 1707 (1954).

(3) L. Velluz and G. Muller, *Bull. soc. chim. France*, 198 (1955).

(4) R. L. Shriner, R. Adams and C. S. Marvel in "Organic Chemistry," Vol. I, edited by H. Gilman, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 305.

(5) R. B. Simpson and W. Kauzmann, THIS JOURNAL, **75**, 5139 (1953), and references therein.

(6) See H. Rapoport, A. R. Williams, J. E. Campion and D. E. Pack, *ibid.*, **76**, 3693 (1954), for a review of the evidence leading to general acceptance of this structure.