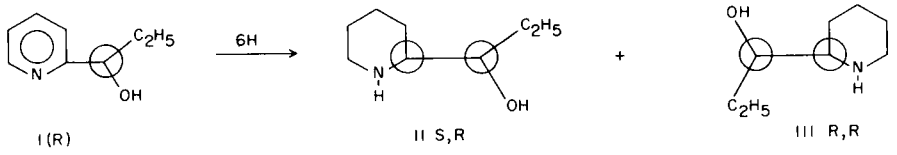
A Direct, Stereoselective Synthesis of Optically Active Conhydrines

Gabor Fodor and Eberhard Bauerschmidt

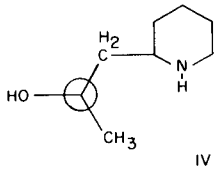
Department of Chemistry, Université Laval

2-Pyridylethylcarbinol (I) has been resolved and the antipodes hydrogenated as free bases. The (+) form gave (+) conhydrine (II) while the (-) form afforded the levorotatory base stereoselectively with minor contamination of the other epimer. Hydrogenation of *racemic* I as well as of 2-pyridyl ethyl ketone in acid solution led formerly to the mixture of both racemates.

Synthesis (1) of ϵ-coniceine (2) 1,2-piperido-4-methyl-1,2-azetidine involved hydrogenation of optically active 2-picolylmethylcarbinol (1) into (+) or (-) *threo*-2-pipecolylmethylcarbinol (IV) with complete stereospecifity. This fact coupled with our aim to repeat the conversion of conhydrine into ϵ-coniceine reported by Löffler (2) prompted us to disclose a practical synthesis of (+) conhydrine (II). The sole synthesis of the alkaloid I was achieved by H. Galinovsky and H. Mulley (3) by reducing 2-pyridyl ethyl ketone catalytically to the mixture of the two racemates of II, followed by separation of the latter by fractional crystallization and resolving the higher melting racemate with (+) and (-) 6,6′-dinitro-2,2′-diphenic acid. Instead of following this rather tedious procedure, we extended our previous investigations to the hydrogenation of 2-pyridylethylcarbinol (I). According to our recent experience (4) stepwise formation of the four stereoisomers was preferable. We prepared 2-pyridylethylcarbinol (I) either by reduction of the ketone with sodium borohydride or by Polonovski rearrangement of 2-ethylpyridine *N*-oxide as reported by Govindachari and Rajappa (5). The carbinol was then resolved, for the first time, using D(-) -dibenzoyl tartaric acid (DBTA). The (-) base (-)DBTA diastereoisomer (m.p. 150°, $[\alpha]_D^{20}$ -117°) separated first and was purified easily by three repeated recrystallizations. The impure dextrorotatory base from the mother liquors was then liberated and the salt treated with L (+) DBTA in the same way as the racemate was resolved with the D(-) acid. This technique afforded a 36% yield of each base, $[\alpha]_D^{20}$ -68° and +68° respectively. Fig. 1 (curve I) shows the ORD curve of (-) I. It was further characterized by its IR and UV spectra (see Experimental). The n.m.r. spectrum (scale δ) is given in Fig. 2. Three protons appear as a triplet 0.97 p.p.m. (C-methyl); 2 protons at 1.57-2.07 p.p.m. (CH_2); a singlet for 1 proton δ 4.38 which is exchanged by deuterium oxide (OH); a clear triplet (1 proton) at 4.7 p.p.m. (methine). Aromatic protons resonate 6.0-7.85 p.p.m. (3 protons) and a doublet at 8.53 (1 proton) corresponding to H-6.



I (R) II S,R III R,R



IV

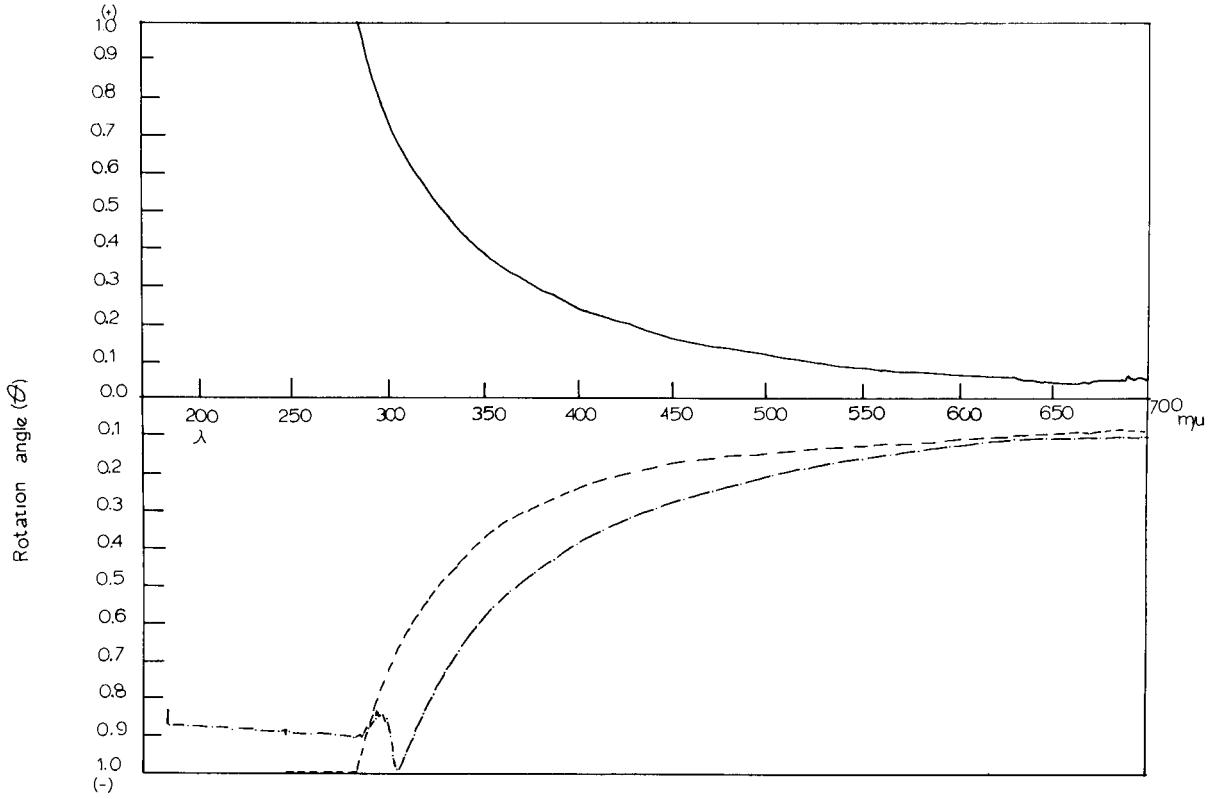


Figure 1

ORD curves: 1 –·–·–·– (–) pyridylethylcarbinol
2 – – – – (broken line) (–) conhydrine
3 ——— (full line) (+) conhydrine

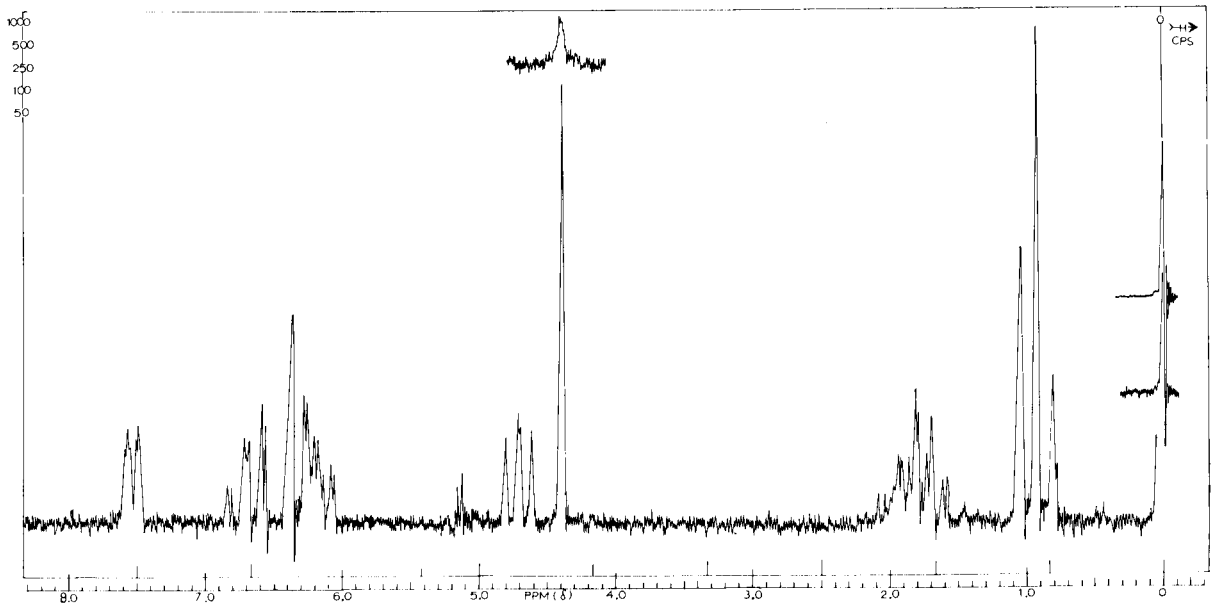


Figure 2

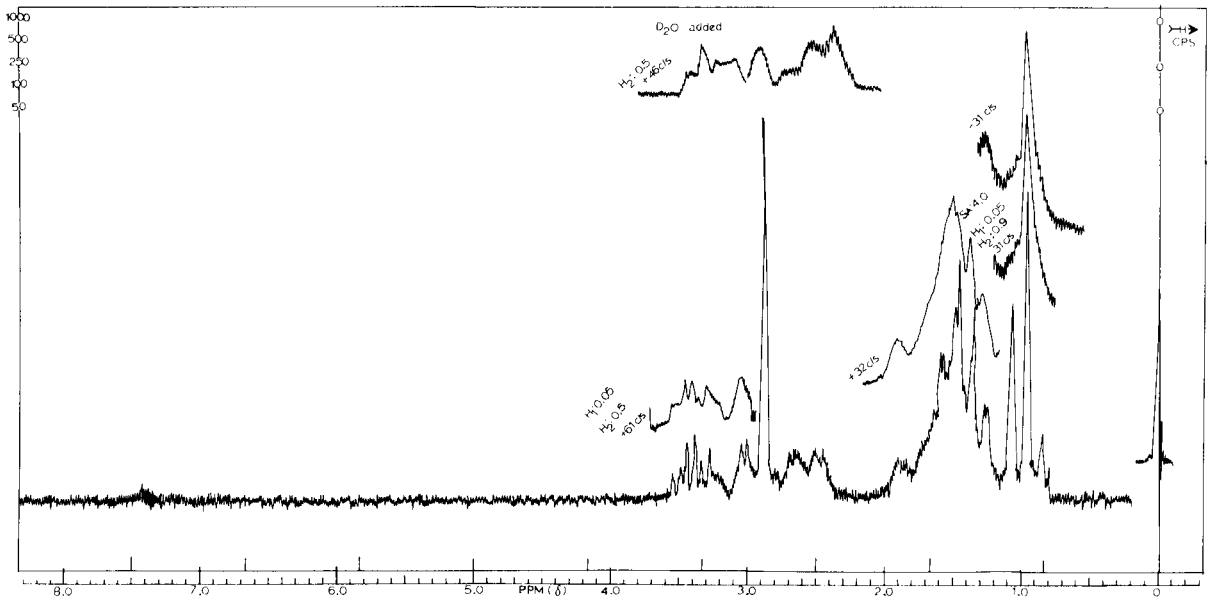


Figure 3

Levorotatory I-base was then hydrogenated in alcohol, *i.e.*, in slightly basic solution (4). In case of hydrogenating the active picolylmethylcarbinol stereospecificity was merely achieved by keeping the intramolecular hydrogen bridge (4) intact. This lends to the system a rather rigid geometry allowing preferential approach of hydrogens from one side on the surface of the catalyst. The result was, as predicted, a 60% yield of an optically pure (-) conhydrine, $[\alpha]_D^{20}$-9.3°and another 35% having a somewhat lower rotation (-8.4°). The antimers (-) II and (+) II were characterized by their optical rotatory dispersion (curves 2 and 3 in Fig. 1). The 60 Mc n.m.r. spectrum in chloroform-d (Fig. 3) showed the following δ-values (p.p.m. from T.M.S.): the triplet centered at 0.97 due to C-methyl (3 protons) collapses to a singlet by saturating the adjacent protons 31 c.p.s. downfield. Hence, the adjacent methylene protons have the chemical shift 1.47 p.p.m. Inversely, double-irradiation of the methyl protons at 32 c.p.s. upfield changes the multiplet pattern at δ 1.12 to 2.05 p.p.m. for the 8 protons (C-3, C-4, and C-2′). It was also shown that the C-2′ protons couple strongly with the C-1′ proton (hydroxyl bearing carbon) which appear as a six-line pattern (J = 3.3 c.p.s.) centered at δ 3.25 by spin-decoupling technique. The singlet at δ 2.8 (2 protons) disappears on the addition of deuterium oxide, thus showing the labile OH and NH protons. Further, 2 protons resonate at 2.3-2.65 p.p.m. corresponding to H-6, adjacent to nitrogen. The broad triplet δ 2.7-3.2 has to be assigned to the C-1 (methine) proton, adjacent to oxygen.

The epimers of conhydrine have never been obtained in optically active form so it cannot be determined how much of (+) *epi*-conhydrine (III) is contaminating this third crop. However, *threo* forms usually have higher optical rotations (6,7) than *erythro* isomers and since *erythro* configuration was allotted (8,9) to (±) conhydrine, then *threo* (*epi*) conhydrine should have a somewhat higher rotation. Assuming $[\alpha]_D^{20}$ value no higher than +10° for this *threo* epimer (III), then the crop having $[\alpha]_D^{20}$ -8.4° cannot contain more than 6% of this isomer. This means that the method described here is practical and stereoselective. The same series of reactions when carried out with dextrorotatory I gave natural (+) conhydrine (II) in about the same yield, m.p. 121°, $[\alpha]_D^{20}$ +9.6°. Galinovsky (3) reported the same data.

Unfortunately, the *threo* epimer III present in minor amount as optically active form could not be isolated, neither by g.l.c. and t.l.c. nor preparative paper chromatography. This might, however, be achieved by a non-stereoselective reduction (*e.g.*, in acid solution) of the optically active carbinol (I) as reported for the (±) I (10,11) or of the (inactive) ketone (3), followed by separation of two epimers. This would make the use of an optically unstable resolving agent such as dinitrodiphenic acid unnecessary.

There is an apparent parallelism in the steric selectivity of the hydrogenation of optically active 2-picolylmethylcarbinol to (+) or (-) sedridine (IV) and of (+) and (-) I to

(+) and (-) conhydrine (II), respectively. However, for (±) sedridine, the *threo* relative configuration was deduced (12) and (-) sedridine was correlated indeed (13) by us with *R*(-)2-octanol recently while (±) conhydrine should be *erythro*, based on the steric course of its Hofmann degradation (8,9) to an epoxide. There is no explanation we could offer for the striking discrepancy of the selective steric course in hydrogenation of the pyridine ring in two closely related carbinols.

(+) Conhydrine was already degraded to *R*(-)pipecolic acid, hence its absolute configuration as being *R* at C-2 has been proven definitely. Similar direct correlation of the carbinol carbon comparable to that we applied in case of sedridine seems, however, desirable. This work is now in progress.

EXPERIMENTAL

Melting points were determined in open capillary tubes using the electrothermal melting point apparatus and are uncorrected. The IR spectra were run on a Beckman-IR4 spectrometer as films on sodium chloride cells or as potassium bromide pellets and UV spectra were taken on Beckman DK-IA recording spectrometer. Specific rotations were obtained with Schmidt-Haensch Polarimeter, model No. 16479 and Carl Zeiss 369417 Polarimeter, and the values given are for the sodium D line. ORD curves were taken on JASCO ORD/UV-5 Optical Rotatory Dispersion recorder. The n.m.r. spectra were recorded by Varian A-60 spectrometer and the decoupling experiments were carried out using Varian Model V-6058A spin decoupler. TMS was used as an internal standard. Microanalyses were performed by Miss I. Beetz (Kronach, Germany).

Resolution of 2-Pyridylethylcarbinol (I).

A solution of (±) 2-pyridylethylcarbinol (117 g.) with D(-)-dibenzoyl tartaric acid (306 g.) in acetone (1000 ml.) gave 251 g. of the salt in two subsequent crops. Recrystallization five times from acetone (or methyl ethyl ketone) produced 78 g. (36.5%) of pure salt (-) I. (-)DBTA, m.p. 150°, $[\alpha]_D^{20}$ -117° (c 4 DMF).

Anal. Calcd. for $C_{26}H_{25}NO_9$: C, 63.02; H, 5.09. Found: C, 62.94; H, 4.95.

The pure salt (30 g.) was suspended in anhydrous acetone (30 ml.) and treated with ethereal hydrogen chloride until a clear solution persisted. The hydrochloride of the base (-) I was precipitated with anhydrous ether (300 ml.) and after standing for 5 hours, the ethereal solution was decanted. Finally the solid was washed twice with ether and treated with a slurry of aqueous potassium carbonate. The base was extracted thoroughly with chloroform and evaporation of the solvent gave the free (-) base, yield, 8.0 g. (95%), $[\alpha]_D^{20}$ -65.2° (c 2 EtOH). This was further purified by distillation (bath temp. 90-100°, 0.1 mm) to give (-) base (I) as a colorless oil, film max: 3350 (bonded OH) 2950 (C-H), 1600 and 1580 (pyridine C=N-), 1330 (OH), 1480, 1440, 1100, 1050 and 760 cm^{-1} (aromatic ring and skeletal vibrations). UV λ max, 250 mμ (EtOH).

The ethereal solution was evaporated after the (-) base-hydrochloride had been filtered off to yield 18.0 g. of (+)-DMTA.

From the mother liquors, of the isolation of the (-)base(-)-DBTA salt, the free base was obtained following the same experimental procedure as described above, yield: 18.5 g., $[\alpha]_D^{20}$ +26.8° (c 2 EtOH). This consisted of 70% *dextrorotatory* base and 30% *levorotatory* base. To this in 170 ml. of acetone, 34.5 g. of (+)-DBTA was added to give 51.2 g. (calcd., 47 g.) of the *salt* which was recrystallized 5 times from five volumes acetone, yield 9.0 g. (19%) of the pure (-) I base-(+)DBTA antimer; m.p. 150°; $[\alpha]_D^{20}$ +117° (c 4 DMF).

Anal. Calcd. for $C_{26}H_{25}NO_9$: C, 63.02; H, 5.09; O, 29.06. Found: C, 63.82; H, 5.51; O, 28.78.

The free (+)-base (I) was liberated in 90% yield following the aforementioned basification procedure, $[\alpha]_D^{20}$ +67° (c 2 EtOH). Better yields were achieved when methyl ethyl ketone was employed as a solvent.

Hydrogenation of 2-Pyridylethylcarbinol.

(a) Preparation of (-)Conhydrine (II).

A solution of 6.9 g. of pure (-)-carbinol (I) in 300 ml. of ethanol was submitted to hydrogenation over 400 mg. of platinum oxide in the PARR apparatus for 2 days. The catalyst was filtered off. Evaporation of ethanol gave a crystalline material which was purified by sublimation at 65° (bath temp.) under 10^{-3} mm, yield, 6.7 g. of (-) conhydrine. Further purification by sublimation and recrystallization from ether gave an optically pure alkaloid in the form of delicate crystals 3.3 g., m.p. 120-122°, $[\alpha]_D^{20}$ -9.3 (c 4 EtOH). Further, 3.2 g. of the (-)-conhydrine was obtained from the mother liquors; m.p. 85-110°, $[\alpha]_D^{20}$ -8.4 (c 4 EtOH).

Anal. Calcd. for $C_8H_{17}NO$: C, 67.07; H, 11.96; N, 9.78. Found: C, 67.20; H, 11.87; N, 9.78.

(b) Preparation of (+)Conhydrine (II).

Following the above hydrogenation procedure the *dextrorotatory* carbinol (I) (4.8 g.) ($[\alpha]_D^{20}$ +63°) (slightly contaminated with the other epimer) was reduced to yield 4.7 g. of the crude product. This has been purified by sublimation from a bath of 65° under 10^{-3} mm, yield, 2.35 g. of colorless crystals, m.p. 120-122°, $[\alpha]_D^{20}$ +7.3° (c 4 EtOH). Further, 2.3 g. of a mixture, m.p. 85-105°, $[\alpha]_D^{20}$ +5.5°, was also obtained. One recrystallization of the first crop from ether gave pure (+) conhydrine identical with the natural product, m.p. 120-122°, undepressed in an admixture with an authentic (14) specimen. The IR spectrum showed the following main peaks: 3290 (NH stretching), 3120 (bonded OH), 2950, 2820 (CH stretching), 1480, 1455 (CH deformation), 1110, 1060 (OH, C-O stretching, OH in-plane deformation), 980, 895 cm^{-1} (skeletal vibrations). The curve is superimposable to that of natural conhydrine, $[\alpha]_D^{20}$ +9.6° (c 4 EtOH); Galinovsky (3) reported +9.76°.

Anal. Found: C, 67.05; H, 11.67; N, 10.02.

Attempts to separate the diastereoisomer by g. l. c., t. l. c. or paper chromatography failed.

Acknowledgment.

This work was supported by National Research Council of Canada under a Grant No. A 2839. Thanks are due to Dr. Nagahushanam Mandava for his help in decoupling experiments.

REFERENCES

(1) G. Fodor and G. A. Cooke, *Tetrahedron Suppl*, 8, 113 (1966).

(2) K. Löffler, *Ber.*, 42, 948 (1910).

(3) F. Galinovsky and H. Mulley, *Monatsh. Chem.*, 79, 426 (1948).
(4) G. A. Cooke and G. Fodor, *Can. J. Chem.* (in press).
(5) T. R. Govindachari and S. Rajappa, *J. Chem. Soc.*, 1306 (1958).
(6) M. C. Rebstock, H. M. Crooks, J. Controulis and Q. R. Bartz, *J. Am. Chem. Soc.*, 71, 2458 (1949).
(7) G. Fodor, J. Stefanovski and B. I. Kurtev, *Chem. Ber.*, 98, 705 (1965).
(8) J. Sicher and M. Tichy, *Collection Czech. Chem. Commun.*, 23, 1081 (1958).
(9) R. K. Hill, *J. Am. Chem. Soc.*, **80**, 1611 (1958).
(10) L. Lautenschlager and A. G. T. Onsager, *Ber.*, **51**, 604 (1918).
(11) K. Hess and R. Grau, *Ann. Chem.*, **441**, 101 (1925).
(12) H. C. Beyerman, L. Maat, A. van Veen, A. Zweistra and W. von Philipsborn, *Rec. Trav. Chim.*, **84**, 1367 (1965).
(13) G. Fodor and D. Butruille, *J. Am. Chem. Soc.*, (in press)
(14) A sample of natural (+) conhydrine was obtained from Professor E. Leete, for which the authors express their gratitude.

Received January 2, 1968 Quebec 10e, Canada