561. *Optically Active Forms of* 1-*Methyl*-2-2′-*pyridylethylamine.*

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1-Methyl-2-2′-pyridylethyl toluene-*p*-sulphonate has been resolved through its hydrogen tartrate. Each enantiomer has been converted into the corresponding optically active form of 1-methyl-2-2′-pyridylethylamine, and these two enantiomers have been submitted for pharmacological test, especially for histamine-like action. Benzyl *N*-(±)-1-methyl-2-2′-pyridylethylcarbamate, and *N*-(−)-menthyl-*N*′-(±)-1-methyl-2-2′-pyridylethylurea are also described. A note on the resolution of racemic acid with cinchonine is included.

Several compounds which simulate the physiological action of histamine are capable of optical activity (cf. Alles, Weissburger, and Shull, *J. Pharmacol.*, 1943, **77**, 54; Lee and Jones, *ibid.*, 1949, **97**, 71). The object of the present work was to investigate the physiological activity of the enantiomers of one of the more accessible of these compounds. We chose 1-methyl-2-2′-pyridylethylamine on grounds of accessibility (Burger and Ullyott, *J. Org. Chem.*, 1947, **12**, 342), despite the fact that this base was reported not to yield crystalline salts even with mineral acids, for clearly optical resolution presented problems of intrinsic chemical interest here.

In the event we have been unable to resolve the base by formation of diastereoisomeric salts, only the hydrogen tartrate being crystalline, but very hygroscopic and not separable into diastereoisomers by crystallisation. In order to reduce the number of possibilities of salt formation we converted the base into an acyl derivative capable of reconversion into the base by a process unlikely to cause racemisation, *viz.*, the *N*-substituted benzyl carbamate. This proved to be unstable to acids even at 0° and could not be resolved. We next prepared *N*-(−)-menthyl-*N*′-(±)-1-methyl-2-2′-pyridylethylurea, but this could not

be resolved by crystallisation or by chromatography on alumina, nor could its salts with optically active acids be separated. However, we were able to resolve a precursor of the required amine, (±)-1-methyl-2-2′-pyridylethyl toluene-*p*-sulphonate, through its hydrogen tartrate, and obtain both (+)- and (−)-1-methyl-2-2′-pyridylethyl toluene-*p*-sulphonate optically pure. The (+)- and the (−)-enantiomer were converted into (−)- and (+)-1-methyl-2-2′-pyridylethylamine respectively by the action of an excess of anhydrous ammonia at 50—60°. A more feebly basic substance formed at the same time was probably 2-propenylpyridine. We have no explicit evidence that the two enantiomers are optically pure. Partial racemisation in the amination stage is possible, though in our opinion unlikely, but because of the properties of the base it has not been possible to settle this point experimentally. The enantiomers had nearly equal optical rotations, *viz.*, $[\alpha]_D^{15}$ +20·7° ± 0·5° and −22·2° ± 0·5°, the difference being perhaps due to the ready absorption of water and carbon dioxide from the air.

Preliminary pharmacological examination (unpublished) shows that (±)-1-methyl-2-2′-pyridylethylamine has histamine-like activity but is less potent than histamine, and that there is a difference in potency between the (−)- and the (+)-isomer.

Experimental

Unless otherwise stated optical rotations were measured in methanol with $c = 1{\cdot}0$.

(±)-1-Methyl-2-2′-pyridylethylamine, prepared by Burger and Ullyott's method (*loc. cit.*), gave a *toluene*-p-*sulphonyl* derivative, m. p. 133·5—134·5° (Found: C, 61·6; H, 6·4; N, 9·9. $C_{15}H_{18}O_2N_2S$ requires C, 62·0; H, 6·2; N, 9·7%), but no crystalline salts with mineral acids (cf. Löffler and Kirschner, *Ber.*, 1905, **38**, 3329) or with (+)-camphor-10-sulphonic or (+)-camphoric acid. (+)-Tartaric acid gave a very hygroscopic salt which could be recrystallised only from dry methanol–ether.

Benzyl N-(±)-1-*Methyl*-2-2′-*pyridylethylcarbamate*. Benzyl chloroformate (7·65 g., 0·045 mole; Bergmann and Servas, *Ber.*, 1932, **65**, 1192) in a little acetone at 0° was added during 0·5 hr. to the foregoing amine (3·15 g., 0·023 mole) in acetone containing a trace of aqueous sodium hydroxide, the temperature being kept below 5° and the pH just alkaline by addition of aqueous sodium hydroxide. The product was brought to pH 7, acetone removed at 15 mm., 4·5N-sodium hydroxide added, and the oil formed was extracted with ether, dried (Na_2SO_4), and, after removal of ether, purified by extraction of neutral material from a solution in 2N-hydrochloric acid with methylene dichloride. Benzyl *N*-(±)-1-methyl-2-2′-pyridylethylcarbamate was liberated, extracted with acetone–ether (1 : 1), dried (Na_2SO_4), and after removal of solvents distilled (b. p. 110°/0·1 mm.); it gave a *picrate*, m. p. 136—137° (rapid heating) (Found: C, 53·0; H, 4·4; N, 13·8. $C_{22}H_{21}O_9N_5$ requires C, 53·0; H, 4·2; N, 14·0%), by the action of ethanolic picric acid on the base in ethanol at 40°.

N-(−)-*Menthyl*-N′-(±)-1-*methyl*-2-2′-*pyridylethylurea*.—(−)-Menthyl *iso*cyanate (Hardy, *J.*, 1934, 2011), b. p. 100°/14 mm., $[\alpha]_D^{20}$ −61·2° (*c.*, 4·0 in C_6H_6), when added (7·03 g., 0·04 mole) in dry (Na) ether slowly to (±)-1-methyl-2-2′-pyridylethylamine (5·4 g., 0·04 mole) in dry ether gave N-(−)-*menthyl*-N′-(±)-1-*methyl*-2-2′-*pyridylethylurea* (89%), m. p. 123—126·5°, $[\alpha]_D^{20}$ −60·9° (*c*, 1·0 in EtOH) (Found: N, 13·0. $C_{19}H_{30}ON_3$ requires N, 13·3%). The urea was not resolved by fractional crystallisation from dry ether–acetone (1 : 4), the only solvent from which it was found to crystallise readily. The diastereoisomers were not separated by chromatography on alumina from light petroleum (b. p. 60—80°). No crystalline salts were obtained with (+)-tartaric or (+)-camphor-10-sulphonic acid.

(+)- *and* (−)-1-*Methyl*-2-2′-*pyridylethyl Toluene*-p-*sulphonate*.—(±)-1-Methyl-2-2′-pyridylethanol, b. p. 121—123°/14 mm. (*Org. Synth.*, **23**, 83) gave no crystalline salt with (+)-camphor-10-sulphonic acid, and its (+)-hydrogen tartrate was very hygroscopic. To toluene-*p*-sulphonyl chloride (7·4 g., 0·039 mole) in cold pyridine (25 g.) (±)-1-methyl-2-2′-pyridylethanol (5·2 g., 0·039 mole) was added at 0°, and the mixture was kept at *ca.* 0° for 48 hr. Sodium hydrogen carbonate (3·7 g.) was added and the mixture was stirred at 0° for 2 hr. and filtered. After removal of pyridine at 30°/15 mm., the residue was poured into water (60 c.c.), and an excess of 1·8N-sodium carbonate added. (±)-1-*Methyl*-2-2′-*pyridylethyl toluene*-p-*sulphonate* (98%) was obtained, and after recrystallisation from aqueous methanol by slow evaporation at room temperature had m. p. 83·5—85° (Found: C, 61·6; H, 5·9; N, 4·8. $C_{15}H_{17}O_3NS$ requires C, 61·8; H, 5·9; N, 4·8; S, 11·0%). It gave no crystalline salts with (+)-mandelic or (+)-camphor-10-sulphonic acid. Dissolving (+)-tartaric acid (61·6 g., 0·41

mole) in a warm solution of the racemic toluene-*p*-sulphonate (120 g., 0·41 mole) in dry (Na_2SO_4) acetone (4710 c.c.) gave initially a clear solution; a salt crystallised steadily during 2 hr. and (+)-1-*methyl*-2-2′-*pyridylethyl toluene*-p-*sulphonate hydrogen* (+)-*tartrate* (68·3 g.), $[\alpha]_D^{18}$ +21·7°, was obtained. Recrystallisation from dry acetone (2500 c.c.) or absolute ethanol gave material (24%) with m. p. 139—140° and $[\alpha]_D^{17}$ +35·5 ± 0·5°, unchanged by further crystallisation (Found: C, 52·0; H, 5·2; N, 2·8; S, 7·2. $C_{19}H_{23}O_9NS$ requires C, 51·7; H, 5·8; N, 3·2; S, 7·3%). Adding an excess of 1·8N-sodium carbonate to a solution of the pure hydrogen tartrate (75 g.) in 4*N*-hydrochloric acid (250 c.c.) gave (+)-1-*methyl*-2-2′-*pyridyelthyl toluene*-p-*sulphonate* (100%), m. p. 70·5—71·5°, $[\alpha]_D^{18}$ +54·7 ± 0·5° (Found: C, 61·9; H, 5·8; N, 4·9; S, 10·8%). After one recrystallisation from aqueous methanol it had m. p. 70·5—72°. (−)-1-*Methyl*-2-2′-*pyridylethyl toluene*-p-*sulphonate* was obtained by a similar process with (−)-tartaric acid and a specimen of the toluene-*p*-sulphonate enriched in (−)-enantiomer, obtained as a residue in the preparation of the (+)-isomer, and had m. p. 69·5—71·5°, $[\alpha]_D^{15}$ −54·9 ± 0·5° (Found: C, 62·0; H, 5·9; N, 4·7; S, 11·1%); it gave a *hydrogen* (−)-*tartrate*, m. p. 140°, $[\alpha]_D^{15}$ −35·6 ± 0·5° (Found: C, 51·7; H, 5·1; N, 2·9; S, 7·2%). In this case an excess of aqueous ammonia (*d*, 0·88) was used to liberate the toluene-*p*-sulphonate from its hydrogen tartrate.

(+)- *and* (−)-1-*Methyl*-2-2′-*pyridylethylamine*.—An excess of dry (CaO) ammonia was condensed into a glass bulb containing (+)-1-methyl-2-2′-pyridylethyl toluene-*p*-sulphonate (21 g.), and the bulb was sealed and heated in a stainless steel autoclave at 45—50° for 60 hr. After ammonia had been allowed to evaporate from the cooled product, 4·5N-sodium hydroxide was added and sodium toluene-*p*-sulphonate was filtered off. An oil was extracted from the filtrate with ether, the extract dried (KOH), and the ether removed in a stream of carbon dioxide-free nitrogen, affording an oil (7·5 g.), n_D 1·5280, $[\alpha]_D^{18}$ +17°, which gave a low nitrogen analysis. The amine was not purified by chromatography on ion-exchange resins or by distillation. The oil was dissolved in sufficient dilute (~0·1N) hydrochloric acid to bring the pH to 8·48, previous electrometric titration (pH meter) having established the necessary volume of acid. Feebly basic impurities were removed by four-fold extraction with an equal volume of methylene dichloride, and an excess of potassium hydroxide was added to the aqueous solution. The liberated oil was extracted with ether, the extract dried (KOH), the ether removed, and the base distilled in an atmosphere of nitrogen free from carbon dioxide, giving (−)-1-*methyl*-2-2′-*pyridylethylamine* (50%), b. p. 49°/0·016 mm., n_D^{16} 1·5212, $[\alpha]_D^{15}$ −22·2° (*c*, 0·85), $[\alpha]_D^{15}$ −8·3° (*c*, 0·6 in 0·0987N-hydrochloric acid) (Found: C, 70·5; H, 8·9; N, 19·0%; neutralisation equiv. 137·2 at first neutralisation point. $C_8H_{12}N_2$ requires C, 70·6; H, 8·9; N, 20·6%; equiv. 136·2 for a monoacid base).

(+)-1-*Methyl*-2-2′-*pyridylethylamine*, b. p. 75°/0·5 mm., $[\alpha]_D^{15}$ +20·7 ± 0·5°, was similarly prepared (20%) (Found: C, 70·7; H, 8·8; N, 20·3%).

(−)-*Tartaric Acid*.—In the preparation of this by Read and Reid's method (*J. Soc. Chem. Ind.*, 1928, **47**, 9T) from racemic acid and (−)-cinchonine (from the British Drug Houses Ltd.), satisfactory yields were obtained only if the (−)-cinchonine was purified by Andrews's method (*Ind. Eng. Chem. Anal.*, 1922, **14**, 543), so that it had m. p. 254—257°, and the racemic acid was crystallised until it had m. p. 203—204°. The (−)-tartaric acid was isolated through its lead salt (Haskins and Hudson, *J. Amer. Chem. Soc.*, 1939, **61**, 1266).

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