Pyrrolidine- and piperidine-alkanoic acid hydrochlorides. Synthesis by hydrogenation of pyrrolyl ester and pyridine-alkanoic acid hydrochlorides

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2-Pyrrolidylacetic acid and β-(2-pyrrolidyl)propionic acid hydrochloride have been prepared by hydrogenation of ethyl 2-pyrrolylacetate and diethyl 2-pyrrolylmethylenemalonate respectively, over rhodium on alumina in HCl solution, followed by acidic hydrolysis. Similarly, 1-methylnipecotic acid, 1-methylisonipecotic acid, 2- and 3-piperidine-acetic acid, and 3-piperidine-propionic acid hydrochlorides have been prepared by hydrogenation of the corresponding pyridine-alkanoic acid hydrochlorides over platinum oxide, rhodium on alumina, or palladium on carbon in water.

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On a préparé les chlorhydrates des acides pyrrolidyl-2 acétique et β(pyrollidyl-2) propionique par hydrogénation respectivement du pyrrolyl-2 acétate d'éthyle et du pyrrolyl-2 méthylènemalonate de diéthyle sur du rhodium sur l'alumine en solution HCl, suivie par une hydrolyse acide. De la même manière, on a préparé les chlorhydrates des acides méthyl-1 nipécotique, méthyl-1 isonipécotique, pipéridine-2 (et -3) acétique et pipéridine-3 propionique par hydrogénation des chlorhydrates des acides pyridine alcanoïques correspondants sur de l'oxyde de platine, du rhodium sur l'alumine ou du palladium sur du charbon dans l'eau.

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Introduction

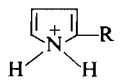
It is well established that γ-aminobutyric acid (GABA) is an important neurotransmitter in the mammalian central nervous system (1). Various structural analogues of this substance have been isolated or synthesized which affect its metabolism and function (2). Such compounds are of pharmacological interest as potential antiepileptics.

Recently, nipecotic acid **6***d* has been reported as a potent inhibitor of the uptake of GABA by slices of rat cerebral cortex (3) and we have found that 1-methylnipecotic acid **4***a* has similar effects (manuscript in preparation). As a result we became interested in the possibility of a rapid high-yield preparation of easily purifiable, water soluble, hydrochloride salts of related piperidine- and pyrroline-alkanoic acids by hydrogenation of the corresponding pyrrolyl ester and pyridine alkanoic acid hydrochlorides at medium to low pressure.

Discussion

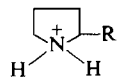
Hydrogenation was complete at 2.5 atm and at room temperature for all pyridines regardless of the catalyst used (platinum oxide, 5% rhodium on alumina, or 10% palladium on carbon); for pyrrolines, shorter times were required and less tar was found using 5% rhodium on alumina. Completeness of hydrogenation was more correctly assessed from the absence of any olefinic hydrogen in the ^{1}Hmr spectra of the products rather than from hydrogen uptake which may stop prematurely due to catalyst poisoning.

Compounds **2***a* and **2***b* were prepared by reduction of the esters **1***a* and **1***b* followed by hydrolysis, since hydrolysis of the starting pyrrolyl esters led to in-



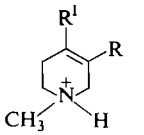
1

a R = CH_2CO_2Et
b R = $CH{=}C(CO_2Et)_2$



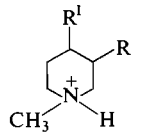
2

a R = CH_2COOH
b R = CH_2CH_2COOH



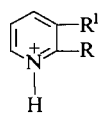
3

a R^1 = H, R = COOH
b R^1 = COOH, R = H



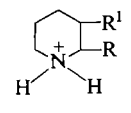
4

a R^1 = H, R = COOH
b R^1 = COOH, R = H



5

a R^1 = H, R = CH_2COOH
b R^1 = CH_2COOH, R = H
c R^1 = CH=CHCOOH, R = H
d R^1 = COOH, R = H



6

a R^1 = H, R = CH_2COOH
b R^1 = CH_2COOH, R = H
c R^1 = CH_2CH_2COOH, R = H
d R = COOH, R = H

(In all cases the anion was chloride)

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tractable tar formation. Hydrogenation was carried out in dilute HCl (0.05 *M*), the acid added being sufficient to promote hydrogenation but not enough to cause tar formation. Solution of starting material was incomplete at the beginning of the reaction but complete at the end. This route to **2***b* is simpler than the previous 2-step procedure (4).

Compounds **4***a* and **4***b* were obtained in high yields by direct hydrogenation of **3***a* and **3***b* respectively. Compound **4***a* had previously been prepared in good yield by the hydrogenation of the corresponding 1-methylnicotinic betaine with platinum but hydrogen pressure and temperature were not specified (5). Direct hydrogenation of **5***d* over PtO_2 has provided **6***d* in high yield (6).

Piperidines **6***a* and **6***b* were obtained in high yield from **5***a* and **5***b* respectively. Compound **6***a* had previously been assumed to be unstable under these hydrogenation conditions (7). Compound **6***c* was obtained, also in high yield, from **5***c*.

Attempts to use acetic acid in place of hydrochloric acid led to longer hydrogenation times and acetate salts which were difficult to purify. The direct reduction of the hydrochloride salts of the appropriate pyridine compound avoids the need for ester hydrolysis which is frequently accompanied by decarboxylation (8). In most cases the starting hydrochloride salt is commercially available or readily obtained by hydrolysis of the corresponding ester.

Experimental

Nuclear magnetic resonance spectra were measured on a Varian T60 spectrometer in D_2O with sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standard. Infrared spectra were recorded with KBr on Perkin Elmer or Beckman infrared spectrophotometers. Melting points were determined on a Mel-Temp hot stage apparatus. Elemental analyses were conducted by Mr. R. G. Teed, Department of Chemistry and Chemical Engineering, University of Saskatchewan.

Hydrogenation of Pyrrolyl Esters with 5% Rhodium on Alumina

General Procedure

A mixture of 1.0 g of freshly prepared pyrrolyl ester in 20 mL of 0.05 *M* HCl solution was hydrogenated with 0.4 g of 5% rhodium on alumina. After a period of 20 h, the mixture was filtered. The clear solution was added to 10 mL of 37% HCl and refluxed for 4 h. The solution was then treated with charcoal and dried *in vacuo*. The residue was recrystallized from ether–ethanol. The ^{1}Hmr spectrum of the crude products after acid hydrolysis showed that the hydrogenation was complete for both the following pyrrolyl esters **1***a* (9), **1***b* (10).

2-Pyrrolidylacetic Acid Hydrochloride **2**a

The yield was 45%; mp 170–171°C; ir ν_{max}: 3170–2400, 1730, 1400, and 1180 cm^{-1}; ^{1}Hmr δ: 1.40–2.52 (m, 4H), 2.75–3.10 (m, 2H), 3.15–3.57 (m, 2H), 3.80–4.15 (s b, 1H). *Anal.* calcd. for $C_6H_{12}ClNO_2$: C 43.51, H 7.31, N 8.46; found: C 43.62, H 7.36, N 8.33.

β-*(2-Pyrrolidyl)propionic Acid Hydrochloride* **2**b

The yield was 40%; mp 115–117°C (lit. (4) mp 115–118°C); ir ν_{max}: 3100–2450, 1700, 1420, and 1200 cm^{-1}; ^{1}Hmr δ: 1.50–2.18 (m, 6H), 2.30–2.85 (m, 2H), 3.20–3.95 (m, 3H). *Anal.* calcd. for $C_7H_{14}ClNO_2$: C 46.80, H 7.85, N 7.79; found: C 46.79, H 7.88, N 7.66.

Hydrogenation of Pyridine Alkanoic Acid Hydrochloride with Different Catalysts: Platinum Oxide, Rhodium on Alumina, or Palladium on Carbon

General Procedure

A solution of 0.55 g of pyridine alkanoic acid hydrochloride in 20 mL of water was hydrogenated with 0.05 g of platinum oxide (or 0.35 g of 5% rhodium on alumina, or 10% palladium on carbon). After a period of 10 h the solution was filtered and dried in a freezer–dryer at 0.01 Torr. Except where noted, purification of product was unnecessary. The ^{1}Hmr spectra of the crude products indicated that only in the case of hydrogenation of 2-pyridineacetic acid hydrochloride **5***a* with palladium on carbon was a reduction time in excess of 10 h required, the 10-h reduction period being sufficient to complete the hydrogenation of **3***a*, **3***b* (11), **5***b*, and **5***c* to form their respective products. The compounds synthesized by these hydrogenations follow.

1-Methylnipecotic Acid Hydrochloride **4**a

The yield was 75–85%; mp 173–174°C (ether–ethanol) (lit. (5) mp 174–175°C); ir ν_{max}: 3200–2500, 1730, 1470, and 1200 cm^{-1}; ^{1}Hmr δ: 1.38–2.40 (m, 4H), 2.55–3.85 (m, 5H), 2.90 (s, 3H). *Anal.* calcd. for $C_7H_{14}ClNO_2$: C 46.80, H 7.85, N 7.79; found: C 46.80, H 8.13, N 7.77.

1-Methylisonipecotic Acid Hydrochloride **4**b

The yield was 74–86%; mp 230–232°C (ether–ethanol); ir ν_{max}: 3070–2470, 1720, 1450, 1200 cm^{-1}; ^{1}Hmr δ: 1.45–2.55 (m, 4H), 2.6–3.85 (m, 5H), 2.9 (s, 3H). *Anal.* calcd. for $C_7H_{14}ClNO_2$: C 46.80, H 7.85, N 7.79; found: C 46.46, H 7.86, N 7.54.

2-Piperidineacetic Acid Hydrochloride **6**a

The yield was 60–70%; mp 180–182°C (ether–ethanol) (lit. (12) mp 180–182°C); ir ν_{max}: 3200–2770, 1730, 1380, and 1175 cm^{-1}; ^{1}Hmr δ: 1.22–2.20 (m, 6H), 2.80–3.82 (m, 3H), 2.80 (d, 2H). *Anal.* calcd. for $C_7H_{14}ClNO_2$: C 46.80, H 7.86, N 7.79; found: C 47.16, H 7.97, N 7.51.

3-Piperidineacetic Acid Hydrochloride **6**b

The yield was 85–90%; mp 202–204°C; ir ν_{max}: 3120–2750, 1720, 1400, and 1180 cm^{-1}; ^{1}Hmr δ: 1.20–2.21 (m, 4H), 2.52–3.62 (m, 5H), 2.39 (s b, 2H). *Anal.* calcd. for $C_7H_{14}ClNO_2$: C 46.80, H 7.85, N 7.79; found: C 46.21, H 7.93, N 7.63.

β-*(3-Piperidine)propionic Acid Hydrochloride* **6**c

The yield was 86–91%; mp 224–226°C; ir ν_{max}: 3170–2730, 1730, 1395, and 1180 cm^{-1}; ^{1}Hmr δ: 1.35–2.15 (m, 7H), 2.32–2.62 (t, 2H), 2.62–3.62 (m, 4H). *Anal.* calcd. for $C_8H_{16}ClNO_2$: C 49.61, H 8.33, N 7.23; found: C 49.53, H 8.30, N 7.19.

Acknowledgements

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1. K. KRNJEVIC. Physiol. Rev. **54**, 419 (1974).
2. G. A. R. JOHNSTON. Ann. Rev. Pharmacol. Toxicol. **18**, 269 (1978).
3. P. KROGSGAARD-LARSEN and G. A. R. JOHNSTON. J. Neurochem. **25**, 797 (1975).

4. C. CORONELLI, A. VIGEVANI, B. CAVALLERI, and G. G. GALLO. J. Antibiot. **24**, 497 (1971).
5. P. H. LIST and K. TERLINDEN. Pharm. Ind. **30**, 219 (1968).
6. S. M. MCELVAIN and R. ADAMS. J. Am. Chem. Soc. **45**, 2738 (1923).
7. M. FREIFELDER. Practical catalytic hydrogenation. John Wiley and Sons, Toronto, Ont. 1971. p. 588.
8. M. FREIFELDER. J. Org. Chem. **28**, 602 (1963).
9. L. MANDELL and E. C. ROBERTS. J. Heterocycl. Chem. **2**, 479 (1965).
10. G. R. CLEMO, N. FLETCHER, G. R. FULTON, and R. RAPER. J. Chem. Soc. 1140 (1950).
11. R. E. LYLE, E. F. PERLOWSKI, H. J. TROSCIANIEC, and G. G. LYLE. J. Org. Chem. **20**, 1761 (1955).
12. W. D. MARSHALL, T. T. NGUYEN, D. B. MACLEAN, and I. D. SPENSER. Can. J. Chem. **53**, 41 (1975).

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