"Hantzsch-Type" Dihydropyridines. IV (1). Carboxylic Acids

Bernard Loev and Marjorie M. Goodman*

Research and Development Division, Smith Kline and French Laboratories, Philadelphia, PA 19101

Received August 23, 1974

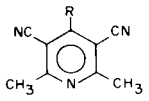
The synthesis and hypotensive structure-activity relationships of dihydropyridines have been described (1,2) and one of these compounds, Ib, is currently undergoing clinical trial. Continuing interest in these compounds led us to investigate the synthesis of the acids II in order to assist in the ultimate identification of such compounds as potential metabolites, and as part of an investigation of analogs of I capable of forming water-soluble salts.

Lachowicz (3) claimed (1896) that the *N*-*p*-tolyl derivatives of Ia could be hydrolyzed in high yield to the monoacid. However, Eisner and Kuthan (4), in their excellent review of dihydropyridines concluded that "the ester groups (in such compounds) could not be hydrolyzed without decomposition of the molecule".

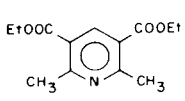
After an extensive study of hydrolytic conditions we finally isolated IIa, but only in 2% yield. More rigorous conditions did not improve the yield nor lead to any diacid, nor could Ib be hydrolysed under any conditions; therefore an alternate route to these compounds was investigated.

Oxidation of I readily gave the pyridines III in good yield; alkaline hydrolysis with a limited amount of potassium hydroxide gave the monoacids IV, and excess base gave the diacids V in fair yields.

The next step required reduction of the pyridines back to the desired dihydropyridines. While reduction of *quaternary* pyridinium salts is well known and proceeds readily with a variety of reducing agents (4), and biological reduction of pyridines is routinely carried out in the body by the coenzyme NADH (5), there are very few examples of reduction of *non*-quaternized pyridines containing strong electron-withdrawing groups as present in Hantzsch-type products (4). Thus, the nitrile VII (6) and the esters VIII (7) have been reduced to mixture of 1,2 and 1,4-



VII
R = H, Me, Et



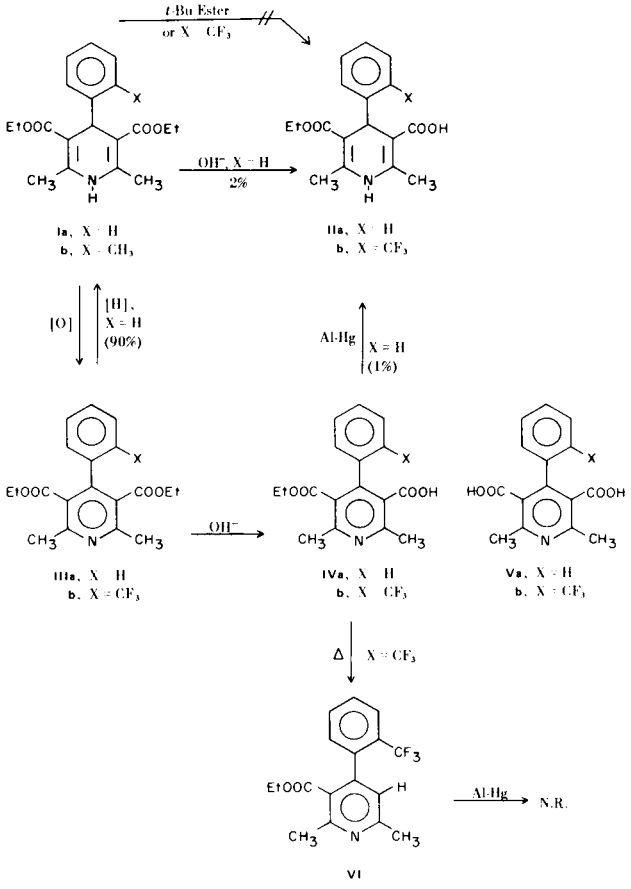
VIII

dihydropyridines in yields varying from 12 to 90% by sodium borohydride, and IIIa was reduced (yields unspecified, 8) to Ia with aluminum in alcohol.

Compound IIIa could not be reduced with sodium hydrosulfite, lithium aluminum hydride or sodium borohydride, but aluminum-amalgam in ethanol or moist ether gave the reduced product Ia in 90 and 45% yields respectively. Sodium-lead alloy gave only a trace of reduction product.

When the aluminum-amalgam reduction was applied to IVa, only a 1% yield of the dihydropyridine monoacid IIa was obtained using moist ether, and no product in ethanol; other reducing agents were ineffective. Neither the diacid Va, nor any of the trifloromethyl-containing compounds IIIb or IVb could be reduced. On heating, the trifloromethyl-containing acid IVb decarboxylated to VI; this also resisted reduction.

Scheme I



The acid IIa had hypotensive activity, although of a much reduced potency (producing a significant drop in blood pressure in the anesthetised dog at 16.5 mg./kg. iv; Ia is active at 0.1 mg./kg., 1).

Attempts to prepare dihydropyridine carboxylic acids by acid-catalysed "hydrolysis" of the *t*-butyl esters (I) failed.

EXPERIMENTAL

The cardiovascular activity was determined as previously described (1,9).

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Boiling points and melting points are uncorrected. Elemental analyses were performed by the Analytical Department of Smith Kline and French Laboratories. Ir and nmr spectra of all compounds were consistent with the assigned structures.

4-Phenyl-3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydropyridine (Ia).

A.

Aluminum amalgam (10), prepared from 5 g. of aluminum turnings and 0.5% mercuric chloride solution, 1 g. of IIIa (1) and 100 ml. of ether which had been saturated with water by shaking in a separatory funnel, were heated at reflux with stirring for 3 hours. After 1/2 hour several drops of water were added to the mixture. The mixture was filtered and the filtrate evaporated to dryness. The residue was stirred with a small amount of hexane and the resulting precipitate (0.3 g.) filtered, m.p. 144-153°. From the filtrate was obtained 0.45 g. of recovered starting material. The higher melting solid was recrystallized from ethanol-water to give Ia, m.p. 157-158° (40% conversion) identical with authentic materials (1,12).

B.

Aluminum amalgam (10) prepared from 5 g. of aluminum turnings, and 1 g. of IIIa (1) were heated in 100 ml. of ethanol. Vigorous hydrogen evolution occurred. The mixture was heated for 18 hours although hydrogen evolution became very slow after 1/2 hour. The mixture was poured into a large volume of dilute hydrochloric acid and extracted with chloroform. The chloroform solution was dried (magnesium sulfate) and concentrated giving an oil that crystallized, 0.9 g. of Ia, m.p. 157-158°, identical with material prepared above.

4-Phenyl-5-carbethoxy-2,6-dimethyl-1,4-dihydropyridine-3-carboxylic Acid (IIa).

A. By Hydrolysis of Ia.

To a solution of 8.5 g. (0.152 mole) of crushed potassium hydroxide pellets in 400 ml. of ethanol was added 50 g. (0.152 mole) of Ia (11). The solution was refluxed overnight then the mixture was concentrated *in vacuo* to give a tan gummy residue. This was dissolved in warm water and filtered from insoluble starting material (43 g.). The filtrate was acidified with dilute hydrochloric acid and the precipitated solid was collected and recrystallized from acetonitrile to give a 2% yield of IIa, white solid, m.p. 192-194° dec.

B. By Reduction of IVa.

Aluminum amalgam (10), prepared from 5 g. of aluminum turnings, was placed in a flask and to it was added 1 g. of IIIa in moist ether. The mixture was stirred and refluxed and small amounts of water were added three times at one hour intervals. Refluxing was continued overnight. The mixture was filtered from aluminum salts and the aluminum salts were extracted with boiling ether and chloroform. The combined extract and filtrate were concentrated to dryness and the residue mixed with dilute sodium hydroxide, extracted with chloroform and the aqueous layer acidified with dilute hydrochloric acid. The solid that separated was collected by filtration and recrystallized from acetonitrile to give a 1% yield of IIa as a white solid, m.p. 191-192° identical to that prepared above.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 66.87; H, 6.38; N, 4.74.

4-Phenyl-2,6-dimethyl-5-carbethoxypyridine-3-carboxylic Acid (IVa).

To 25 g. (0.0446 mole) of potassium hydroxide pellets dissolved in 20 ml. of ethanol was added 14.6 g. (0.0446 mole) of IIIa (11). The dark mixture was stirred and heated at reflux for three days, by which time everything was in solution. The solution was concentrated to dryness and the residue was stirred with water and filtered from 3.1 g. of unreacted starting material. The filtrate was acidified with dilute hydrochloric acid, extracted with chloroform and the organic extracts were dried (magnesium sulfate) and concentrated to give an oil. The oil was dissolved in hot acetonitrile and chilled and the solid product separated and was collected. Concentration of the filtrates to a small volume gave additional product. A total of 6.6 g. of IVa was obtained, m.p. 178.5-180°, Lit. (13) m.p. 179-180°

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 67.89; H, 5.59; N, 4.81.

4-(2-Trifluoromethylphenyl)-2,6-dimethyl-5-carbethoxypyridine-3-carboxylic Acid (IVb).

Compound IIIb (1) was hydrolyzed in a similar fashion to give IVb, m.p. 204.5-206.5° (acetonitrile) in 61% yield.

Anal. Calcd. for $C_{18}H_{16}F_3NO_4$: C, 58.86; H, 4.39; N, 3.81. Found: C, 58.84; H, 4.56; N, 3.78.

4-Phenyl-2,6-dimethylpyridine-3,5-dicarboxylic Acid (Va).

To 21.8 g. (0.39 mole) of potassium hydroxide in 100 ml. of ethanol was added 51 g. (0.156 mole) of IIIa. The dark solution was refluxed overnight, cooled, concentrated to dryness and the residue dissolved in a small amount of water and filtered from insoluble material. On acidification of the filtrate the product precipitates. On heating with methanol it first dissolves and then precipitates. The product (21.5 g.) melted at about 300° with decomposition, Lit. (14) m.p. 296° (anhydrous).

Anal. Calcd. for $C_{15}H_{13}NO_4 \cdot 1/4\ H_2O$: C, 65.32; H, 4.93; N, 5.08. Found: C, 65.29; H, 5.03; N, 4.98.

Compound Vb was prepared in the identical manner, 65%, m.p. 337° (ethanol-hexane).

Anal. Calcd. for $C_{16}H_{12}F_3NO_4$: C, 56.65; H, 3.57; N, 4.13. Found: C, 56.71; H, 3.88; N, 4.11.

Ethyl 4-2(Trifluoromethylphenyl)-2,6-dimethylpyridine-3-carboxylate (VI).

A suspension of 5 g. (0.0136 mole) of IVb in 50 ml. of Dowtherm was stirred and heated to boiling. At 245°, carbon dioxide began evolving. The solution was kept at 245° until carbon dioxide evolution ceased (30 minutes); it was then cooled and distilled under reduced pressure (0.05 mm). The first fraction, b.p. to 94° was discarded (Dowtherm); a second fraction was collected from 94-104°, and a third fraction was collected from 112-120°. Each of the fractions was dissolved in ether and

extracted with dilute hydrochloric acid then the aqueous solution was made basic with dilute sodium hydroxide, extracted with ether, dried (magnesium sulfate) and concentrated. The resulting oils crystallized on standing. The lower boiling fraction gave 0.5 g. of product, m.p. 61-63.5°, the higher boiling fraction gave 2 g. of the same material, for a combined yield of 53%.

Anal. Calcd. for $C_{17}H_{16}F_3NO_2$: C, 63.15; H, 4.99; N, 4.33. Found: C, 63.23; H, 5.05; N, 4.08.

REFERENCES

(1) For Part III see B. Loev, M. M. Goodman, K. M. Snader, R. Tedeschi, and E. Macko, *J. Med. Chem.*, **17**, 956 (1974).

(2) B. Loev, S. Ehrreich, and R. Tedeschi, *J. Pharm. Pharmacol.*, **24**, 917 (1972).

(3) B. Lachowicz, *Monatsh. Chem.*, **17**, 343 (1896).

(4) U. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972).

(5) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 2, W. A. Benjamin, Inc., New York, N. Y. (1966), p. 301; M. Florkin and E. H. Stotz (Ed.) "Comprehensive Biochemistry," Vol. 14, Elsevier, Amsterdam, 1966.

(6) J. Kuthan and E. Janeckova, *Collect. Czech. Chem. Commun.*, **29**, 1654 (1964).

(7) S. Yamada and Y. Kikugawa, *Chem. Ind.* (London), 2169 (1966).

(8) O. Mumm and W. Beth, *Ber.*, **54**, 1591 (1921).

(9) E. Macko, B. Douglas, J. A. Weisbach and D. T. Watz, *Arch. Intern. Pharmacodyn. Ther.*, **197**, 265 (1972).

(10) H. Wisclicenus and L. Kaufman, *Ber.*, **28**, 1323 (1895).

(11) S. Skraup, *Ann. Chem.*, **419**, 1 (1919).

(12) R. Schiff and J. Puliti, *Ber.*, **16**, 1607 (1883).

(13) A. Hantzsch, *ibid.*, 17, 2903 (1884).

(14) W. H. Mills, W. H. Palmer, and M. G. Tomkinson, *J. Chem. Soc.*, 2365 (1924).