Hydrogenation of Some Pyridinealkanoic Acids

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In a recent publication, it was reported that pyridinecarboxylic acids could be hydrogenated with platinum oxide in the absence of an acidic agent,[1] in contrast to the usual method of reducing pyridines with this catalyst.[2] At that time the suggestion was made that the isomeric pyridineacetic acids could be hydrogenated just as readily under the same conditions.

In this study 3- and 4-pyridineacetic acids and 2-(2-, 3-, and 4-pyridine)propionic acids are covered. 2-Pyridineacetic acid was deliberately avoided because of its known propensity toward decarboxylation in aqueous solution.[3]

The reduction of 3-pyridineacetic acid in aqueous solution in the presence of platinum oxide was complete in twelve hours. Slightly better results were obtained with 5% rhodium on alumina or 5% rhodium on carbon (ten hours). Conversion of 2-(3- and 4-pyridine)propionic acids took a much longer time because of poor solubility of the starting materials. This made the procedure look less attractive, particularly if hydrogenation of longer chain and less soluble acids should be contemplated.

We had noted that the pH of aqueous solutions of the resultant piperidine acids was above 8.0. It occurred to us that two purposes would be served by carrying out hydrogenation of any pyridinealkanoic acid in aqueous solution containing a slight excess of ammonia. The hydrogen uptake would be speeded up considerably. More important, concentration of the solution after reduction should yield the desired free acid since the greater basicity of the piperidine nitrogen should cause displacement of ammonia.

Our expectations were realized when the hydrogenations were carried out in the presence of either rhodium on alumina or rhodium on carbon. Uptake of hydrogen was complete in one to three hours as compared to ten hours in the absence of ammonia, and high yields of pure product were obtained. However, in the presence of platinum oxide, uptake of hydrogen did not take place. This was not unexpected, since it is well known that the unshielded ring nitrogen will poison platinum catalysts.[2] In ammoniacal solution the effect of the carboxyl group[1] is nullified.

The results of this study suggest that most pyridinealkanoic acids could be readily hydrogenated in aqueous solution containing a slight excess of ammonia in the presence of rhodium catalysts. Indeed, it might be the method of choice for the preparation of piperidinealkanoic acids whenever the corresponding pyridine acids or ammonia salts are available. Its limitation appears to be the stability of the starting pyridine acids or the resultant piperidines.

Experimental

3-Piperidineacetic Acid.—A solution of 6.85 g. (0.05 mole) of 3-pyridineacetic acid[4] in 50 cc. of water was hydrogenated under 2.5 atm. pressure in the presence of 0.137 g. of platinum oxide. Uptake of hydrogen was complete in 12 hr. After reduction was complete, the solution was filtered from the catalyst and concentrated to dryness under reduced pressure. The residue was thoroughly dried. It weighed 6.8 g. (95%) and melted at 276–278°. Similar reductions with 1.6 g. of 5% rhodium on alumina or 5% rhodium on carbon were complete in 10 hr. or less. Yields and melting points were identical. The three lots were combined and a sample submitted for analysis.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.71; H, 9.15; N, 9.78. Found: C, 58.82; H, 9.30; N, 9.80.

2-(2-Pyridine)propionic Acid.—A solution of 24.0 g. (0.161 mole) of 2-(2-pyridine)acrylic acid[5] in 75 cc. of water containing 6.44 g. (0.161 mole) of sodium hyroxide was hydrogenated under 2 atm. pressure in the presence of 2.0 g. of 5% palladium on carbon. Uptake of hydrogen was complete in less than 2 hr. The solution, after removal of catalyst, was acidified to pH 5.0. The mixture was then cooled to 5–10°. The precipitated acid after filtration was recrystallized from hot 95% alcohol. Yield of product melting at 144.5–145°[6] was 11.6 g. (67.4%). 2-(3-Pyridine)acrylic acid[4] and 2-(4-pyridine)acrylic acid[4] were similarly converted to the corresponding saturated acids. 2-(3-Pyridine)propionic acid melting at 163–165°[7] was obtained in 63% yield after recrystallization from alcohol. 2-(4-Pyridine)-propionic acid was obtained in 80% yield after recrystallization from water, m.p. 225–227°.[8]

2-(3-Piperidine)propionic Acid.—A mixture of 7.55 g. (0.05 mole) 2-(3-pyridine)propionic acid, 100 cc. of water and 5 cc. of 29% aqueous ammonia was hydrogenated under 2.5 atm. pressure in the presence of 2.5 g. of 5% rhodium on carbon. Uptake of hydrogen was complete in 3 hr. or less. The solution was filtered and concentrated to dryness under reduced pressure, and the residue was thoroughly dried before analysis. The product weighed 7.4 g. (94% yield) and melted at 180–181°.[9]

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.11; H, 9.61; N, 8.91. Found: C, 60.75; H, 9.78; N, 8.78.

2-(4-Piperidine)propionic acid, m.p. 275–277°,[10] was obtained in 89% yield.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.11; H, 9.61; N, 8.91. Found: C, 60.94; H, 9.79; N, 9.15.

2-(2-Piperidine)propionic acid was prepared in a similar manner. However, it was necessary to concentrate the solution, after reduction, by freeze–drying technique at 0.005 mm. The product was obtained in 96.4% yield. It melted and completely disappeared at 185–187°.[11] The compound retained water tenaciously and was extremely difficult to dry. Before analysis it was placed in an Abderhalden drying pistol over boiling xylene for 8 hr. under 0.05-mm. pressure.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.11; H, 9.61; N, 8.91; O, 20.37. Found: C, 60.74; H, 10.00; N, 8.71; O, 20.58.

When the solution after reduction was concentrated at 100° (20 mm.) no residue was obtained. Apparently decarboxylation took place.

4-Piperidineacetic Acid.—A solution of 2.5 g. (0.0144 mole) of 4-pyridineacetic acid hydrochloride[12] in 200 cc. of water was absorbed on Amberlite resin IRA 120 acid form and was eluted with 2–5% aqueous ammonia. The eluate was concentrated to dryness by freeze drying technique to avoid decarboxylation. The residue was dissolved in water and 1 cc. of aqueous ammonia added. The solution was then hydrogenated with 5% rhodium

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(2) T. S. Hamilton and R. Adams, *J. Am. Chem. Soc.*, **50**, 2260 (1928).

(3) M. P. Oparina, *Khim. Farm. Prom.*, **2**, 109 (1935); *Chem. Zentr.*, **106**, 3240 (1935 II).

(4) Available from Aldrich Chemical Co., Milwaukee, Wis.

(5) J. A. King, V. Hofman, and F. H. McMillan, *J. Org. Chem.*, **16**, 1100 (1951).

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(10) Described, 275–276°. V. Prelog and E. Cerkovnikov, *Ann.*, **532**, 83 (1937).

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(12) R. L. Malan and P. M. Dean, *J. Am. Chem. Soc.*, **69**, 1797 (1947)

on carbon. After concentration of the solution 67.5% yield of free acid was obtained. It melted with gradual decomposition beginning at 255° and boiled out of the tube at 264°.[13]

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.71; H, 9.15; N, 9.78. Found: C, 58.37; H, 9.49; N, 9.95.

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[13] V. Prelog, D. Kohlbach, E. Cerkovnikov, A. Rezek, and M. Piantanida, *Ann.*, **532**, 69 (1937), give 237–238°. We found that, if samples were not thoroughly dried, the melting range was between 230–240°.

On the Preparation and Reactions of Dibenzyl Oximinomalonate and Its Sodium Complex[1]

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Kissman and Withop[2] have prepared dibenzyl oximinomalonate (I) for use as an intermediate in amino acid synthesis. These authors did not isolate I but employed it in solution as an intermediate in the preparation of tryptophan. Pure, crystalline I has now been obtained by acid hydrolysis of its sodium complex, dibenzyl sodiooximinomalonate acid salt (II).

The sodium complex (II) was discovered accidentally in an attempted large-scale reduction of crude I to dibenzyl aminomalonate according to the method of Kissman and Withop.[2] The reaction mixture, which contained mostly unchanged I, was washed with 10% aqueous sodium carbonate, whereupon a light yellow precipitate appeared. Recrystallization of this precipitate from toluene or from acetone–petroleum ether gave II as a white powder.

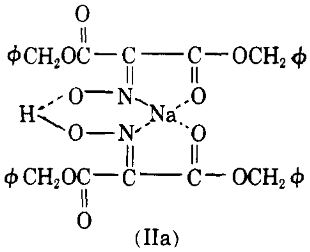
Treatment of II with dilute acid, followed by recrystallization from chloroform–cyclohexane, gave I as white crystals which melted at 65.5–67°. The sodium complex (II) could be regenerated from the oxime (I) in dilute aqueous ammonium hydroxide by addition of one-half molar equivalent of sodium chloride and allowing the solution to stand. Precipitation of II was complete in about fifteen minutes.

$$\mathrm{NaCl} + 2\mathrm{HON{=}C(CO_2CH_2C_6H_5)_2} \underset{\text{dil. HCl}}{\overset{\text{dil. NH}_4\text{OH}}{\rightleftharpoons}}$$

(I)

$$\mathrm{NaON{=}C(CO_2CH_2C_6H_5)_2{\cdot}HON{=}C(CO_2CH_2C_6H_5)}$$

(II)



(IIa)

The solubility of II in organic solvents suggests that II is a chelated complex of sodium. A probable structure for II is IIa. Nonpolar sodium complexes are well known. A similar complex of sodium with diethyl oximinomalonate has been prepared, in nonaqueous medium, by Shaw and Nolan[3] and by Bouveault and Wahl.[4] However, under conditions similar to those used in the preparation of II, diethyl oximinomalonate does not give any precipitate. Evidently, the presence of benzyl groups in II is responsible for the low solubility of II in dilute ammonium hydroxide.

When II is shaken repeatedly with water, the water becomes weakly alkaline, and the insoluble residue reverts to I. Therefore, since II can be both formed and destroyed in aqueous medium, particular importance must be attached to the pH of the reaction medium. Determination of conditions for optimum yield of II was beyond the scope of this study.

Attempts to prepare complexes of I with ions other than sodium met with little success, under conditions similar to those which favored the formation of II from sodium chloride. Use of potassium chloride or lithium chloride in place of sodium chloride in dilute aqueous ammonia resulted in clear solutions from which no solid separated even after several hours. Cupric, cobaltous, and nickel salts gave highly colored oils which could be solidified but not purified. Magnesium and calcium salts gave gummy yellow precipitates which could not be purified.

Since, under the stated conditions, sodium gives a complex with I, and potassium does not, an attempt was made to precipitate sodium selectively from a mixture with potassium. When an equimolar mixture of sodium chloride and potassium chloride was added to I in dilute ammonium hydroxide and the mixture allowed to stand for four hours, essentially pure II precipitated in 74% yield. On longer standing, the precipitate changed to an oil, perhaps because of a change in *p*H caused by slow evaporation of ammonia.

Experimental[5]

Dibenzyl Sodio Oximinomalonate Acid Salt (II).—To a solution of 0.3133 g. (0.001 mole) of dibenzyl oximinomalonate in 3 ml. of 5 *N* ammonium hydroxide was added 0.0292 g. (0.0005 mole) of sodium chloride. The solution was diluted with water to 5 ml. and allowed to stand for 30 min. The white precipitate, after filtration and air drying, weighed 0.270 g. (83%); m.p. 156.0–156.1° dec. An analytical sample was prepared by threefold recrystallization from dry toluene.

Anal. Calcd. for $C_{34}H_{29}O_{10}N_2Na$: C, 62.96; H, 4.50; N, 4.32; Na, 3.55. Found: C, 62.93; H, 4.51; N, 4.41; Na, 3.47.

Dibenzyl Oximinomalonate (I).—A solution of 10.00 g. (0.0154 mole) of II in 200 ml. of 0.1 *N* hydrochloric acid was shaken with 200 ml. of ether. The ether layer was separated, washed with 100 ml. of water in two portions, dried over magnesium sulfate, and evaporated *in vacuo;* the yellow, crystalline residue weighed

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[1] This work was supported by a grant [AT(11-1)-314] from the Atomic Energy Commission.

[2] H. M. Kissman and B. Withop, *J. Am. Chem. Soc.*, **75**, 1967 (1953).

[3] K. N. F. Shaw and C. Nolan, *J. Org. Chem.*, **22**, 1668 (1957).

[4] L. Bouveault and A. Wahl, *Bull. soc. chim. France*, [3] **29**, 628, 960 (1903); *Compt. rend.*, **137**, 196 (1903).

[5] Analyses were performed by Mr. Josef Nemeth and associates.