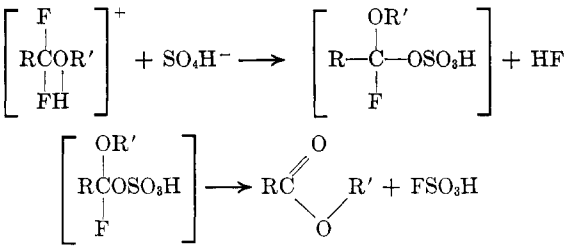
the addition of two moles of 96% sulfuric acid for each mole of ether at 10°, preferably in glass equipment. Yields vary from 55 to 83% and higher temperatures are reported to give undesirable side reactions with correspondingly lower yields.

We have found that α,α-difluoro ethers react with glass or silica gel, at temperatures of 70 to 160° to give the corresponding ester and silicon tetrafluoride, in yields of greater than 90% with no apparent side reactions.[3] The reaction is autocatalytic when the ether is heated in sealed glass ampoules without an added acid catalyst, but the addition of small amounts of sulfuric acid eliminates a prolonged induction period. Phosphoric acid (85%) and 2,2,3,3,3-pentafluoropropionic acid were ineffective as catalysts.

For preparative purposes the reaction is best carried out by refluxing[4] the ether along with approximately four mole percent of concentrated sulfuric acid in the presence of crushed glass until the reaction temperature becomes constant.

No satisfactory mechanism for the replacement of the fluorine atoms has been proposed. The mechanism for the hydrolysis of alkyl ethers suggested by Hammett[5] involving the formation of an alcohol and a carbonium ion is not applicable, since hydrolysis takes place without rupture of the C—O—C bond.[1a] It is suggested that the reaction may take place according to the following scheme.



The hydrogen fluoride and fluorosulfonic acid formed can react with silica to produce silicon tetrafluoride and regenerate the sulfuric acid. A direct reaction of the protonated ether with silica cannot, however, be ruled out.

Experimental

Methyl Bromofluoroacetate.—2-Bromo-1,1,2-trifluoroethyl methyl ether (200 g.) and 95.5% sulfuric acid (1 ml.) were charged to a 300-ml. flask containing silica gel (128 g., 6–12 mesh) and equipped with a reflux condenser and thermometer. The mixture was heated at reflux until the reaction temperature reached 133°, about 6 hr. The crude ester was extracted with diethyl ether. Rectification of the ethereal solution gave 19 g. of the starting ether, b.p. 88°, and 138 g. (78%) of methyl bromofluoroacetate, b.p. 130–134°, n^{25}D 1.4195. The conversion of ether was 81% and the over-all yield 90%.[6]

Anal. Calcd. for $C_3H_4BrFO_2$: C, 21.05; H, 2.36; Br, 46.74. Found: C, 21.05; H, 2.83; Br, 45.88.

Methyl Dichloroacetate.—2,2-Dichloro-1,1-difluoroethyl methyl ether (342 g.) was refluxed with silica gel (141 g., 6–12 mesh) and 95.5% sulfuric acid (1 ml.). The reaction was terminated when the temperature reached 142°. The crude ester was distilled away from the silica gel under vacuum. Distillation of the crude ester through a 4-in. Heli-Pak filled column gave 268 g. (91%) of methyl dichloroacetate, b.p. 62–63° (4 mm.), n^{25}D 1.4425. No unchanged ether was found. Redistillation of a portion of the product gave a center cut boiling at 143°, n^{25}D 1.4414 [lit.,[7] b.p. 142.79° (760 mm.), n^{25}D 1.4405].

Methyl Chlorofluoroacetate.—2-Chloro-1,1,2-trifluoroethyl methyl ether (138 g.) was heated with crushed "Pyrex" glass (157 g.) and 95.5% sulfuric acid (2 ml.) at 80–83° for 7.5 hr., and then allowed to stand overnight at room temperature. The crude ester was distilled from the glass under vacuum. Distillation gave 20 g. of starting ether, b.p. 66–72°, 7 g. of intercut, b.p. 72–113°, 86 g. (73%) of methyl chlorofluoroacetate, b.p. 113–116°, n^{25}D 1.3905 (lit.,[1a] b.p. 116°, n^{25}D 1.3903), and 3 g. of residue. A material balance gave an organic recovery of 95%, conversion of ether of 77%, and yield of 93%.

(3) E. R. Larsen, Abstracts, 140th National Meeting of the American Chemical Society, September 3–8, 1961, p. 30-M.

(4) The use of a nickel condenser is recommended, since with glass extensive etching, which weakens the condenser, takes place just below the cooling jacket.

(5) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1949, p. 300.

(6) A similar reaction using the procedure of Young and Tarrant[1a] gave a 61% crude yield of ester with no recovered starting ether.

(7) R. R. Driesbach, "Physical Properties of Pure Compounds," Vol. III, Advances in Chemistry Series, no. 29, R. F. Gould, ed., American Chemical Society, Washington, D. C., 1961, p. 446.

New Simple Cyclization of 2-Anilinopropionic Acids to 4-Keto-1,2,3,4-tetrahydroquinolines with Polyphosphoric Acid

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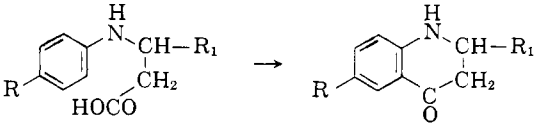
The cyclization of 2-anilinopropionic acids to 4-keto-1,2,3,4-tetrahydroquinolines was first investigated by Clemo and Perkin[1,2] and later by Backeberg.[3] More recently, this subject was thoroughly studied simultaneously by Elderfield[4,5] and by Johnson[6,7] with their collaborators. They concluded that protection of the free hydrogen on the nitrogen of the anilinopropionic acid was a necessary condition for the ring closure. This was accomplished by two separate steps of tosylation prior to ring closure and detosylation afterwards. The cyclization procedure itself, which was carried out with a variety of reagents under various conditions, appeared also quite laborious. The recent report[8] that 2-(2,5-dimethoxyanilino)butyric acid was directly cyclized to the corresponding dihydroquinolone with polyphosphoric acid led to the present investigation of its general applicability.



I. R = Cl; R_1 = H
II. R = Cl; R_1 = CH_3
III. R = CH_3O; R_1 = H

In a preliminary study, three anilino acids which previously were cyclized by Elderfield and Johnson were chosen for our experiments. It was found that these acids could be cyclized readily with polyphosphoric acid to 4-keto-1,2,3,4-tetrahydroquinolines, I, II, and III, in approximately 55% to 65% yield by modification of

(1) G. R. Clemo and W. H. Perkin, *J. Chem. Soc.*, **125**, 1608 (1924).
(2) G. R. Clemo and W. H. Perkin, *ibid.*, **127**, 2297 (1925).
(3) O. G. Backeberg, *ibid.*, 618 (1933).
(4) R. C. Elderfield, *et al.*, *J. Am. Chem. Soc.*, **68**, 1259 (1946).
(5) R. C. Elderfield and A. Maggiolo, *ibid.*, **71**, 1906 (1949).
(6) W. S. Johnson, *et al.*, *ibid.*, **71**, 1901 (1949).
(7) W. S. Johnson and B. G. Buell, *ibid.*, **74**, 4513 (1952).
(8) J. Koo, *J. Org. Chem.*, **26**, 2440 (1961).

the general polyphosphoric acid cyclization directions.[9] Procedure described in Experimental was typical and appeared to be general for this type of cyclization.

In view of elimination of the two extra steps of tosylation and detosylation and the simplicity of the experimental procedure, this new method offers clear advantages over those previously reported and provides a convenient synthetic route for the preparation of quinoline derivatives.

This study is currently being extended to isoquinolones, oxindoles and 5-ketotetrahydrobenzazepines. Additional findings will be reported later.

Experimental

4-Keto-6-chloro-1,2,3,4-tetrahydroquinoline (I).—A mixture of 6 g. of 2-(*p*-chloroanilino)propionic acid[10] and 100 g. of polyphosphoric acid in a 150-ml. beaker was heated on a hot plate with hand stirring until the temperature reached 120° (around 20 min.,) and was then kept between 120–125° for 20 min. After cooling to 80° the cherry-red reaction mixture was poured into 300 ml. of ice–water with stirring. After a few hours, the yellow precipitate was filtered and washed with water to provide 2.1 g. of pure chloroquinolone (I), m.p. 124–126°. The filtrate was saturated with sodium chloride and extracted with ether, from which another 1.5 g. of material was isolated, m.p. 116–120°. The combined yield of nearly pure product was 3.6 g. (66%). Recrystallization from benzene–petroleum ether gave canary yellow crystals, m.p. 124–126° (reported m.p. 112°[5] and 125–126°[11]).

Similarly, after 10 min. at 130°, II was obtained in 60% yield without the necessity of extraction of the aqueous solution. It seems of interest to point out that I and II did not form phosphoric acid salts. However, compound III was sufficiently basic to necessitate neutralization in order to isolate the yellow product in 55% yield. I, II, and III all gave positive dinitrophenylhydrazine tests and exhibited a strong carbonyl absorption band in the infrared spectrum at 1650 cm.$^{-1}$.

(9) J. Koo, *J. Am. Chem. Soc.*, **75**, 1891 (1953).
(10) C. D. Hurd and S. Hayao, *ibid.*, **74**, 5889 (1952).
(11) C. D. Hurd and S. Hayao, *ibid.*, **76**, 5056 (1954).

A Simple Preparation of Nipecotic Acid

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A straightforward catalytic reduction of nicotinic acid uncomplicated by decarboxylation has never been reported. While successful hydrogenation of the isomeric 2- and 4-acids in neutral solution has been carried out with ruthenium dioxide,[1] with 5% rhodium on carbon,[2] and more recently with platinum oxide,[3] the same conditions cannot be applied to the 3-acid. Extensive decarboxylation occurred in each attempt. Some success was achieved with rhodium on carbon[2] but extensive decarboxylation did occur. A 44% yield of nipecotic acid was obtained but the result was not reproducible.

Decarboxylation can be prevented by hydrogenation of the hydrochloride salt according to the general method of Hamilton and Adams[4] for the reduction of pyridines, or by conversion in the form of the sodium salt.[5] However, isolation of the free acid in each instance leaves much to be desired. Decarboxylation has been observed by Sorm[6] even under acidic conditions. He reported that when nicotinic acid was hydrogenated in acetic acid solution, 50% of piperidine was obtained while reduction in dilute hydrochloric acid gave about 10% of piperidine as a result of decarboxylation.

It occurred to us that the resultant piperidine nitrogen should be basic enough to displace ammonia if a solution of ammonium nicotinate would be hydrogenated and that free nipecotic acid should be obtained. We were led to anticipate success by some work, still incomplete, on the reduction of some pyridylalkanoic acids.

Actual work-up, after hydrogenation, proved to be very simple. It was only necessary to concentrate the solution, after removal of catalyst, to obtain nipecotic acid in very good yield.

Experimental

Nipecotic Acid.—A suspension of 6.15 g. (0.05 mole) of nicotinic acid in 50 cc. of water was treated with 5–6 cc. of concentrated aqueous ammonia and hydrogenated in the presence of 2.4 g. of 5% rhodium on alumina at room temperature and 2 atm. Uptake of hydrogen was complete in 4 hr. or less. The solution was filtered and concentrated to dryness under reduced pressure. To ensure complete removal of water the residue was treated with pure anhydrous benzol and reconcentrated. The yield of product melting at 260–261° was 5.7 g. (88.5%). Infrared examination[7] shows that it is identical to a known standard. A mixed melting point with an authentic sample showed no depression. For further proof, the product was submitted for analysis.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.79; H, 8.58; N, 10.84; O, 24.77. Found: C, 55.64; H, 8.54; N, 10.91; O, 24.88.[8]

(5) M. S. Raasch, *J. Org. Chem.*, **27**, 1406 (1962).
(6) F. Sorm, *Collection Czech. Chem. Commun.*, **13**, 57 (1948).
(7) Infrared examination carried out by A. Kammer and W. Washburn of this laboratory.
(8) Microanalyses carried out by E. F. Shelberg and O. Kolsto and their associates of this laboratory. Oxygen analysis carried out by a modification of the Unterzaucher method described by V. A. Aluise, R. T. Hall, F. C. Staats, and W. W. Becker, *Anal. Chem.*, **19**, 347 (1947).

Quinoxaline Studies. XI. Unequivocal Syntheses of *cis*- and *trans-dl*-Decahydroquinoxalines. Resolution of *trans-dl*-Decahydroquinoxalines[1–3]

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In 1952, Beck, Hamlin, and Weston[4] reported the preparation of *trans*-decahydroquinoxaline (m.p. 150–151°) by the cyclization of 2-(β-aminoethylamino)-cyclohexanol. Four years later Christie, Rohde, and Schultz[5] reported that the reduction of an ethanolic

(1) Abstracted in part from the Ph.D. thesis at the University of Miami, June, 1962, of Earl Brill, who thanks the National Science Foundation and the University of Miami for research assistantships during the summer, 1961, and during the academic year, 1961–1962, respectively.
(2) Presented before the Division of Organic Chemistry at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September 12, 1962.
(3) Paper X of this series: W. Blackburn, M. Danzig, H. Hubinger D. Soisson, and H. P. Schultz, *J. Org. Chem.*, **26**, 2805 (1961).
(4) K. M. Beck, *et al.*, *J. Am. Chem. Soc.*, **74**, 607 (1952).
(5) W. Christie, *et al.*, *J. Org. Chem.*, **21**, 243 (1956).

(1) M. Freifelder and G. R. Stone, *J. Org. Chem.*, **26**, 3805 (1961).
(2) M. Freifelder, R. M. Robinson, and G. R. Stone, *ibid.*, **27**, 284 (1962).
(3) M. Freifelder, *ibid.*, **28**, 602 (1963).
(4) T. S. Hamilton and R. Adams, *J. Am. Chem. Soc.*, **50**, 2260 (1928).