The Action of Ammonia and Other Bases on γ-Methyl and γ-Ethyl L-Glutamate

BY A. F. BEECHAM

RECEIVED MARCH 31, 1954

Ammonolysis of the γ half-esters of glutamic acid might be expected to provide a convenient synthesis of glutamine. However, aqueous ammonia has been shown[1,2] to convert γ-ethyl L-glutamate to L-pyrrolidonecarboxylic acid. A study of the effect of ammonia, under various conditions, and of other bases on γ-methyl and γ-ethyl L-glutamate is reported here.

The esters were treated with methanolic, ethanolic, aqueous or liquid ammonia, and progress of the reactions followed by paper chromatography. From both compounds the main product was always L-pyrrolidonecarboxylic acid, isolated in 70–90% yield. Minor amounts of glutamine were formed also but, in every case, the cyclization appeared to be far more rapid than the competing ammonolysis. An indication of the relative rates of the two reactions is given by the following comparison. A solution of γ-methyl L-glutamate in methanolic ammonia contained only a trace of uncyclized ester after standing for four hours, whereas complete conversion to the amide of the homologous β-methyl, L-aspartate under the same conditions required over 40 hours. In the latter case cyclization does not occur.

The formation of glutamine from the γ-half esters of L-glutamic acid appeared most pronounced when liquid ammonia was used. A 3% yield of the compound was isolated after liquid ammonia treatment of γ-methyl L-glutamate. No evidence of selective catalysis of the glutamine-producing reaction could be obtained when either sodium amide or various ammono acids were added to the medium.

Other experiments showed that conversion of the γ-half esters to L-pyrrolidonecarboxylic acid is readily effected by bases other than ammonia[3] and that cyclization occurs even under mildly alkaline conditions.

Experimental

γ-Methyl L-Glutamate.—To γ-methyl L-glutamate hydrochloride[2] (19.75 g., 0.1 mole) dissolved in methanol (150 cc.) was added with stirring 10 *N* ammonia (10 cc., 0.1 mole) to give, after recrystallization from aqueous ethanol, the free ester, 14.7 g. (92%), m.p. 175° dec.

Cyclization of γ-Methyl L-Glutamate.—The ester, 5 g., dissolved readily in methanol (150 cc.) saturated with dry ammonia. Samples of the solution withdrawn at intervals examined by paper chromatography showed, after four hours, only a trace of unreacted ester. The solution was evaporated, ethanol added, evaporated again and the residue taken up in *N* aqueous hydrochloric acid (31 cc.). Addition of 300 cc. of acetone precipitated ammonium chloride. The filtrate was evaporated, the residue taken up in hot methyl ethyl ketone and carbon tetrachloride added until precipitation was complete. The crystalline product, 3.89 g., had m.p. 157–159°. Recrystallization by the same procedure gave L-pyrrolidonecarboxylic acid, 3.82 g. (95%), m.p. 159–160.5°, $[\alpha]^{20}D$ −11.7° (*c* 4 in water), R_f 0.71 (phenol/water).

The same compound was isolated (yields in parentheses) after dissolution of γ-methyl L-glutamate in the following: ammonia-saturated ethanol (72%), 0.88 sp. gr. aqueous ammonia (80%)[4]; anhydrous liquid ammonia (76%), the equivalent amount of *N* aqueous sodium hydroxide (87%), the equivalent amount of 0.52 *N* methanolic sodium methoxide (80%).

An aqueous solution of γ-methyl L-glutamate continually brought to *p*H 9 by the addition of *N* aqueous ammonia, dropped to lower *p*H values after each addition until, after six hours, one equivalent of the base had been consumed.

Cyclization of γ-Ethyl L-Glutamate.—The ester, prepared according to Coleman,[2] was treated with ammonia under the conditions described for γ-methyl L-glutamate. Reaction was somewhat slower, but in each case the product was identical and the yield similar to that obtained using the methyl ester.

L-Glutamine.—Paper chromatography gave evidence of glutamine formation from both esters in the presence of ammonia, liquid ammonia treatment producing the strongest spot with the R_f value of the amide. γ-Methyl L-glutamate, 1.61 g., was dissolved in 30 cc. of liquid ammonia, and the solvent allowed to evaporate overnight. The residue, dissolved in 5 cc. of water, was run onto an alumina column, 10 × 1.8 cm., developed with water, and the eluate collected in 10-cc. fractions. These were examined by paper chromatography. Fractions 5–13 contained only glutamine. Evaporation over sulfuric acid gave 0.05 g. (3%) of L-glutamine, m.p. 180–181°. A mixture with a sample isolated from red beet[5] melted at 180–182°.

Reaction with liquid ammonia in the presence of sodium amide, ammonium chloride, ammonium bromide, ammonium nitrate and ammonium acetate gave no evidence of enhanced glutamine formation.

The Reaction of Ammonia with β-Methyl L-Aspartate.—β-Methyl L-aspartate hydrochloride,[2] 5 g., was dissolved in 100 cc. of ammonia-saturated ethanol, and the solution examined at intervals by paper chromatography. After three hours only the ester was detectable, after 18 hours both the ester and asparagine were present and after 42 hours only asparagine. Removal of the solvent, dissolution in 30 cc. of hot water and addition of 150 cc. of methanol gave asparagine monohydrate, 2.94 g. (72%), R_f 0.41 (phenol/water).

Paper Chromatography.—Paper chromatograms were run using aqueous phenol as the mobile phase. The developing agents were ninhydrin (0.1% w./v. in *n*-butyl alcohol) and brom phenol blue (0.4% w./v. in water made just alkaline with sodium hydroxide).

(1) M. Bergmann and L. Zervas, *Z. physiol. Chem.*, **221**, 51 (1933).

(2) D. Coleman, *J. Chem. Soc.*, 2294 (1951).

(3) However, the γ-acid hydrazide of glutamic acid has been prepared from γ-ethyl L-glutamate by the action of aqueous hydrazine; *cf.* J. A. Roper and H. McIlwain, *Biochem. J.*, **42**, 485 (1948).

(4) The appearance of glutamic acid on paper chromatograms of the ammonia solution indicated some hydrolysis of the ester.

(5) H. B. Vickery and G. W. Pucher in H. E. Carter's "Biochemical Preparations," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 44.

CHEMICAL PHYSICS SECTION
DIVISION OF INDUSTRIAL CHEMISTRY
COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANIZATION
MELBOURNE, AUSTRALIA

Analogs of Benadryl

BY F. F. BLICKE AND G. R. TOY[1]

RECEIVED APRIL 7, 1954

This paper describes the preparation of basic ethers of the general formula $(C_6H_5)_2C(R)OCH_2CH_2X$ in which R represents hydrogen, methoxy or β-diethylaminoethoxy, and in which the basic radical (X) is diethylamino, morpholino, piperidino, 1-hexamethylenimino or 4-methyl-1-hexamethylenimino. In addition, α-phenyl-α-(2-pyridyl)-β′-(1-hexamethylenimino)-diethyl ether and the corresponding β′-(4-methyl-1-hexamethylenimino) compound were obtained.

Diphenylbromomethane reacted with β-(1-hexa-

(1) The Wm. S. Merrell Company Fellow.

methylenimino)-ethanol and with β-(4-methyl-1-hexamethylenimino)-ethanol to form benzhydryl β-(1-hexamethylenimino)-ethyl ether and benzhydryl β-(4-methyl-1-hexamethylenimino)-ethyl ether, respectively.

Dimethoxydiphenylmethane reacted with one molecular equivalent of ethylene bromohydrin to form α-methoxybenzhydryl β′-bromoethyl ether. Interaction of this substance with morpholine yielded α-methoxybenzhydryl β′-morpholinoethyl ether, and with piperidine α-methoxybenzhydryl β′-piperidinoethyl ether was obtained.

When dimethoxydiphenylmethane was allowed to react with two molecular equivalents of ethylene bromohydrin, and the di-(β-bromoethoxy)-diphenylmethane (not isolated) produced was heated with diethylamine, the reaction product was di-(β-diethylaminoethoxy)-diphenylmethane.

A toluene solution of α-methyl-α-phenyl-2-pyridinemethanol[2] was allowed to react with sodium, and β-(1-hexamethylenimino)-ethyl chloride was then added; α-phenyl-α-(2-pyridyl)-β′-(1-hexamethylenimino)-diethyl ether was formed. The same reaction was carried out with the use of β-(4-methyl-1-hexamethylenimino)-ethyl chloride.

The compounds prepared are of interest since they are analogs of the antihistaminic Benadryl (benzhydryl β-dimethylaminoethyl ether).

Experimental

Benzhydryl β-(1-Hexamethylenimino)-ethyl Ether.—A mixture of 18.5 g. of β-(1-hexamethylenimino)ethanol,[3] 37.1 g. of bromodiphenylmethane[4] and 16.6 g. of anhydrous potassium carbonate was stirred and heated at 150–160° for 4 hours in a nitrogen atmosphere. Water (100 cc.) was added to the cold mixture which was then extracted with ether. The extract was shaken with three 60-cc. portions of 5% hydrochloric acid. The acidic solution was made alkaline and extracted with ether. The ether solution was dried over potassium carbonate. The product boiled at 158–160° (0.01 mm.), yield 22.3 g. (56%).

An ethereal solution of the base was treated with the calculated amount of ethereal hydrogen chloride; the hydrochloride melted at 144–146° after recrystallization from dioxane.

Anal. Calcd. for $C_{21}H_{28}ONCl$: N, 4.05; Cl, 10.25. Found: N, 3.90; Cl, 10.25.

An excess of methyl bromide was added to an ether–ethanol solution of the base; the precipitated methobromide was recrystallized from ethyl acetate–ethanol; m.p. 156–158°.

Anal. Calcd. for $C_{22}H_{30}ONBr$: N, 3.46; Br, 19.76. Found: N, 3.35; Br, 19.59.

Benzhydryl β-(4-Methyl-1-hexamethylenimino)-ethyl Ether.—By the method described above, 15.7 g. of β-(4-methyl-1-hexamethylenimino)-ethanol,[3] 24.7 g. of bromodiphenylmethane and 13.8 g. of anhydrous potassium carbonate yielded 18.7 g. (57.8%) of product; b.p. 164–165° (0.01 mm.).

The hydrochloride melted at 97–99° dec. after recrystallization from toluene.

Anal. Calcd. for $C_{22}H_{30}ONCl$: N, 3.89; Cl, 9.85. Found: N, 3.83; Cl, 9.80.

The methiodide was recrystallized from absolute ethanol; m.p. 189–190° dec.

Anal. Calcd. for $C_{23}H_{32}ONI$: N, 3.01; I, 27.27. Found: N, 2.98; I, 26.97.

α-Methoxybenzhydryl β′-Bromoethyl Ether.—A mixture of 56.7 g. of diphenyldimethoxymethane[5] and 31.6 g. of ethylene bromohydrin was placed in a small distillation flask and heated for 5 hours at 120–130°. During this time 6.6 g. (83%) of the calculated amount of methanol distilled from the mixture. Upon fractionation of the residue, 47.0 g. (59%) of product was obtained; b.p. 169–170° (3 mm.).

Anal. Calcd. for $C_{16}H_{17}O_2Br$: Br, 24.88. Found: Br, 24.80.

α-Methoxybenzhydryl β′-Piperidinoethyl Ether.—A mixture of 35.7 g. of α-methoxybenzhydryl β′-bromoethyl ether, 94.6 g. of piperidine and 50 cc. of benzene was heated in a pressure bottle at 60° for 5 days. The mixture was washed with 20% sodium hydroxide solution and then with water. The benzene layer was distilled; the product boiled at 145–147° (36%).

The hydrochloride was recrystallized from chloroform–ether; m.p. 179–180° dec.

Anal. Calcd. for $C_{21}H_{28}O_2NCl$: N, 3.88; Cl, 9.80. Found: N, 3.77; Cl, 9.78.

α-Methoxybenzhydryl β′-Morpholinoethyl Ether.—By the method described above, 35.7 g. of α-methoxybenzhydryl β′-bromoethyl ether, 50 cc. of benzene and 96.9 g. of morpholine yielded 11.5 g. (32%) of product, b.p. 153–156° (0.01 mm.).

The hydrochloride was recrystallized from chloroform–ether; m.p. 162–163° dec.

Anal. Calcd. for $C_{20}H_{26}O_3NCl$: N, 3.86; Cl, 9.76. Found: N, 3.65; Cl, 9.73.

Di-(β-diethylaminoethoxy)-diphenylmethane.—A mixture of 22.8 g. of diphenyldimethoxymethane and 25.5 g. of ethylene bromohydrin was heated in a small distillation flask at 135° for 24 hours. The methanol which distilled from the mixture weighed 4.9 g. (76.6%). Unchanged bromohydrin was removed from the residue by distillation under reduced pressure and the residual oil was transferred to a pressure bottle which contained a solution of 54.9 g. of diethylamine in 50 cc. of benzene. The mixture was heated at 60° for 3 days. After treatment with a solution of 10 g. of sodium hydroxide in 25 cc. of water, the organic layer was separated and washed thoroughly with water. Upon distillation, 12.7 g. (32%) of product was obtained; b.p. 148–150° (0.05 mm.).[6]

The dihydrochloride was prepared by treatment of the base with the calculated amount of ethereal hydrogen chloride; m.p. 178–179° dec. after recrystallization from chloroform–ether.

Anal. Calcd. for $C_{25}H_{40}O_2N_2Cl_2$: N, 5.94; Cl, 15.04. Found: N, 5.85; Cl, 14.87.

The α-Phenyl-α-(2-pyridyl)-β′-(1-hexamethylenimino)-diethyl Ether.—α-Methyl-α-phenyl-2-pyridinemethanol[2] (24.0 g.), dissolved in 150 cc. of toluene, was allowed to react with 2.7 g. of sodium. The mixture was then treated with the chloride obtained by the addition of 11.2 g. of potassium hydroxide, 100 cc. of water and 150 cc. of toluene to 27.8 g. of β-(1-hexamethylenimino)-ethyl chloride hydrochloride.[3] The process employed was the same as the "general procedure" described by Tilford, *et al.*[7] The product boiled at 164–165° (0.05 mm.), yield 22.5 g. (57.7%).

The methobromide melted at 222–224° dec. after recrystallization from ethanol.

Anal. Calcd. for $C_{22}H_{31}ON_2Br$: N, 6.68; Br, 19.06. Found: N, 6.73; Br, 19.06.

α-Phenyl-α-(2-pyridyl)-β′-(4-methyl-1-hexamethylenimino)-diethyl Ether.—From 24.0 g. of α-methyl-α-phenyl-2-pyridinemethanol, 2.7 g. of sodium, 34.0 g. of β-(4-methyl-1-hexamethylenimino)-ethyl chloride hydrochloride[3] and 300 cc. of toluene, 25.8 g. (63.5%) of product was obtained b.p. 157–159° (0.05 mm.).

The hydrochloride melted at 143–145° dec. after recrystallization from methyl ethyl ketone.

Anal. Calcd. for $C_{22}H_{31}ON_2Cl$: N, 7.47; Cl, 9.46. Found: N, 7.55.; Cl, 9.59.

COLLEGE OF PHARMACY
UNIVERSITY OF MICHIGAN
ANN ARBOR, MICHIGAN

(2) N. Sperber, D. Papa, E. Schwenk and M. Sherlock, THIS JOURNAL, **71**, 887 (1949).

(3) G. R. Toy, Dissertation, University of Michigan, 1951.

(4) C. Courtot, *Ann. chim. phys.*, [9] **5**, 80 (1916).

(5) J. E. Mackenzie, *J. Chem. Soc.*, **69**, 987 (1896).

(6) P. Truitt and W. D. Compton, THIS JOURNAL, **72**, 2300 (1950), reported b.p. 217–223° (5 mm.).

(7) C. H. Tilford, R. S. Shelton and M. G. Van Campen, Jr., *ibid.*, **70**, 4007 (1948).