sodium bicarbonate. The ether was evaporated, and the residue was crystallized from hexane; yield 6 g. (50%); m.p. 60–63°. A sample crystallized three additional times from hexane melted at 63.5–64.5°.

Anal. Calcd. for $C_{21}H_{27}O_6Cl_3$: C, 52.34; H, 5.65. Found: C, 52.46, 52.39; H, 5.70, 5.76.

1,2-Dibenzyl-3,4,5,6-tetrachlorobenzene. 1,2-Bis(bromomethyl)-3,4,5,6-tetrachlorobenzene (40.1 g., 0.1 mole) in benzene (200 cc.) was added dropwise at room temperature to a stirred suspension of aluminum chloride (0.5 g.) in benzene (200 cc.). Stirring was continued 6 hr., and the reaction mixture was then left standing overnight. The crude product was isolated in the usual manner. Distillation at 0.09 mm. gave a middle fraction, b.p. 170–220°, 24 g. Crystallization of this fraction from ethanol-benzene gave 21 g. (53%); m.p. 161–164°. Two recrystallizations raised the m.p. to 164–165.5°.

Anal. Calcd. for $C_{20}H_{14}Cl_4$: C, 60.68; H, 3.56. Found: C, 60.79, 60.94; H, 2.94, 3.06.

1-Methyl-2-benzyl-3,4,5,6-tetrachlorobenzene. 1-Methyl-2-bromomethyl-3,4,5,6-tetrachlorobenzene, treated with benzene and aluminum chloride as above, gave the product in 78% yield; b.p. 155° at 0.9 mm.; m.p. 87–88° from benzene-ethanol (1:1). Recrystallization raised the m.p. to 87.5–89°.

Anal. Calcd. for $C_{14}H_{10}Cl_4$: C, 52.58; H, 3.15. Found: C, 52.60, 52.41; H, 3.02, 3.16.

1,2-Bis(n-propoxymethyl)-3,4,5,6-tetrachlorobenzene. A solution of sodium propoxide was prepared by treating sodium (27.6 g., 1.2 moles) with 1-propanol (750 cc.). To this was added 1,2-bis(bromomethyl)-3,4,5,6-tetrachlorobenzene (201 g., 0.5 mole), and the mixture was refluxed overnight. Water was added, and the organic layer was separated, washed with saturated sodium chloride solution, dried over magnesium sulfate, and filtered. The 1-propanol was removed by distillation, and the crude product was distilled at 0.3 mm. to yield 157 g. (87%) of the diether; b.p. 145–149°. A small sample redistilled for analysis boiled at 143.5° at 0.2 mm. and n_D^{25} 1.5378.

Anal. Calcd. for $C_{14}H_{18}O_2Cl_4$: C, 46.69; H, 5.04. Found: C, 46.74, 46.92; H, 5.00, 4.84.

1-Methyl-2-n-propoxymethyl-3,4,5,6-tetrachlorobenzene. Treatment of 1-methyl-2-bromomethyl-3,4,5,6-tetrachlorobenzene with sodium propoxide in 1-propanol as above gave the ether contaminated with some tetrachloro-*o*-xylene, which was probably present as an impurity in the starting bromide. The crude product was distilled at 7 mm. (b.p. 180–181°). The distillate was crystallized from ethanol containing a little trichloroethylene. The tetrachloro-*o*-xylene crystallized first, and concentration of the mother liquors gave the ether; yield, 58%; m.p. 38–40°. A sample crystallized for analysis four times from 95% ethanol melted from 42–43°.

Anal. Calcd. for $C_{11}H_{12}OCl_4$: C, 43.73; H, 4.00. Found: C, 43.08, 43.19; H, 3.80, 3.72.

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NORTH ADAMS, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Synthesis of 5-Ketopipecolic Acid from Glutamic Acid

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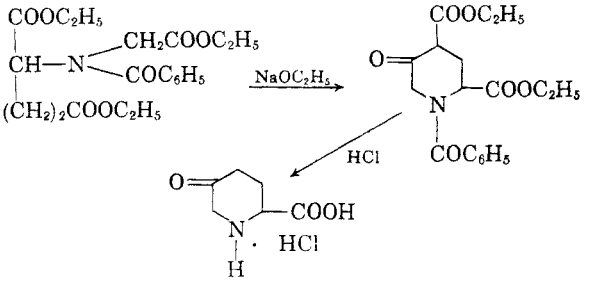
The synthesis of 5-keto-2-piperidinecarboxylic acid has been studied. It has been shown that an important by-product of this synthesis is diethyl 1-carboxymethylpyroglutamate. It was shown that the latter may be obtained in good yields from triethyl *N*-carboxymethylglutamate.

The synthesis of 5-ketopipecolic acid (5-keto-2-piperidinecarboxylic acid) from L-glutamic acid was first reported by King, King, and Warwick.[1] These workers isolated this compound as its hydrochloride salt containing one mole of methanol and one mole of acetone of crystallization. The over-all yield was rather low and they reported the formation of a by-product which they apparently did not identify.

These workers alkylated diethyl glutamate with ethyl bromoacetate to form diethyl *N*-carbethoxymethylglutamate. The latter compound was benzoylated in pyridine solution and the resulting *N*-benzoyl derivative treated with sodium ethoxide to form diethyl-1-benzoyl-5-ketopiperidine-2,4-dicarboxylate. In the last step, hydrolysis with hydrochloric acid gave 5-ketopipecolic acid.

5-Ketopipecolic acid was of interest to us for two reasons: (1) it appeared to be a useful starting material for the synthesis of other heterocyclic ring systems; and (2) it has been postulated that it might arise *in vivo* by intramolecular cyclization from 6-diazo-5-oxonorleucine.[2] It was decided, therefore, to study the reactions reported by the previous workers,[1] to study the properties of 5-ketopipecolic acid and to determine the nature of the by-product.

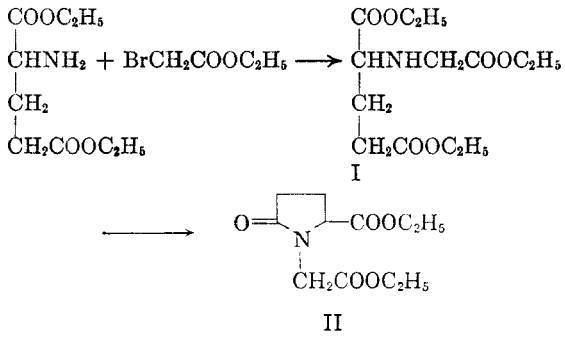


(1) F. E. King, T. J. King, and A. J. Warwick, *J. Chem. Soc.*, 3590 (1950).

(2) A. A. Patchett and B. Witkop, *J. Am. Chem. Soc.*, 79, 192 (1957).

The preparation of 5-ketopipecolic acid by King and co-workers, in about 10% over-all yield, could not be materially improved. Efforts to carry out this synthesis on a larger scale led to lower yields of 5-ketopipecolic acid with the by-product becoming a major product. Since in the original synthesis, a series of reactions from glutamic acid to triethyl *N*-benzoyl-*N*-carboxymethylglutamate was carried out without final purification of the intermediates, it was not immediately apparent at which stage in the reaction sequence the by-product was formed. It was reported that it was difficult to obtain a good analysis for triethyl *N*-carboxymethylglutamate, which suggested that it was at this point that their nonbasic by-product was formed.

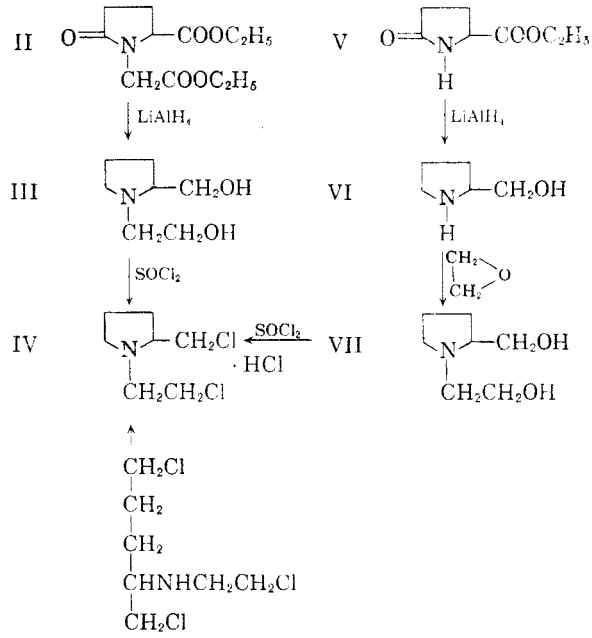
A study of the reactions which were involved in the synthesis suggested to us that the by-product was diethyl 1-carboxymethylpyroglutamate (II). Subsequent work showed this assumption to be correct. Such a product could be formed from triethyl *N*-carboxymethylglutamate (I) by way of an intramolecular aminolysis.



When the preparation of 5-ketopipecolic acid was attempted on a large scale (from two kilograms of glutamic acid), the major product, following the benzoylation step, was a product which boiled much lower than triethyl *N*-benzoyl-*N* carboxymethylglutamate. It had an analysis corresponding to $C_{11}H_{17}NO_5$ and had absorption bands in the infrared at 1747 cm.$^{-1}$ and 1715 cm.$^{-1}$ indicating the presence of both γ-lactam and ester groups. Confirmation of the identity of the suspected diethyl 1-carboxymethylpyroglutamate was obtained by the following series of reactions:

The new amino alcohol (III) was identical with VII which was prepared from the known compound ethyl pyroglutamate (V). Both III and VII, when treated with thionyl chloride, formed 1-β-chloroethyl-2-chloromethylpyrrolidine hydrochloride (m.p. 232–233°). The latter compound had been previously prepared from 1,5-dichloro-2-β-chloroethylaminopentane (VIII).[3]

A search of the literature revealed that diethyl 1-carboxymethylpyroglutamate had been prepared inadvertently during an attempted synthesis



of *N*-methylglutamic acid.[4] Only the boiling point of the product was reported, 156° at 2–3 mm. This did not quite agree with the value found in the present study, 163–166° at 2 mm.

It has not been possible to isolate the free 5-ketopipecolic acid in pure form. The dihydrate of the free acid was obtained in pure form fairly easily. Preliminary experiments designed to gain experience in working with this keto acid were not very encouraging. Attempts to benzoylate the 1-position under various conditions failed. Efforts to methylate with methyl iodine or formic acid–formaldehyde also failed. The extreme ease with which 5-ketopipecolic is oxidized was demonstrated by its reaction with copper sulfate solution at *p*H 6. Instead of obtaining the expected copper chelate the copper sulfate was reduced to cuprous oxide and from the organic residue only glutamic acid could be identified by paper chromatography.

Ethyl 5-ketopipecolate was obtained by allowing 5-ketopipecolic acid hydrochloride in dry ethanol, containing 10% of dry hydrogen chloride, to stand for two days at 15–20°. A monobenzal derivative of 5-ketopipecolic acid was obtained by treating the acid with benzaldehyde in glacial acetic acid containing dry hydrogen chloride. In general these experiments served to confirm the known instability of 5-ketopipecolic acid[2] and the related 4-ketoproline.[5]

EXPERIMENTAL

The melting points which are reported were determined by the capillary tube method in a Hoover-Thomas apparatus. The melting point values are uncorrected.

Diethyl glutamate. This ester was prepared from L-(+)-glutamic acid by a previously described procedure.[6] The

(3) O. M. Friedman and E. J. Boger, *J. Am. Chem. Soc.*, **78**, 4659 (1956).

(4) S. Sugasawa, *J. Pharm. Soc. Japan*, **543**, 359 (1927).

(5) R. Kuhn and G. Osswald, *Ber.*, **89**, 1423 (1956).

(6) H. M. Chiles and W. A. Nayes, *J. Am. Chem. Soc.*, **44**, 1798 (1922).

yield of the hydrochloride was 54%. It melted at 117–118° after recrystallization from chloroform-ether.

Triethyl N-carboxymethylglutamate. This was prepared from diethyl glutamate and ethyl bromoacetate by the method of King and co-workers.[1] The yield was 62%, b.p. 150–152°/0.5 mm.

Triethyl N-benzoyl-N-carboxymethylglutamate. The benzoyl derivative of triethyl *N*-carboxymethylglutamate was prepared by the procedure of King, King, and Warwick.[1] The yield was 51%, b.p. 205–210°/0.3 mm.

Diethyl 1-benzoyl-5-ketopiperidine-2,4-dicarboxylate. This compound was prepared by a modification of the previously described method.[1] A solution of 38.9 g. (0.1 mole) of triethyl *N*-benzoyl-*N*-carboxymethylglutamate and 5.6 ml. of dry ethanol in 50 ml. of dry benzene was added dropwise, with stirring, to 4.6 g. of 50% sodium dispersion (0.1 mole) suspended in 125 ml. of dry benzene. The reaction was exothermic and the benzene soon refluxed gently. After 1 hr., heat was applied and the mixture was refluxed for 5 hr. The benzene was removed under reduced pressure and the residue extracted with 200 ml. of cold water. The water solution was extracted with ether and the water layer then acidified to *p*H 2.5–3. The oil which formed was separated and dissolved in chloroform. After washing the extract with water it was dried over anhydrous sodium sulfate. The chloroform was removed by distillation leaving a residue of 27 g. (78%) of crude diethyl 1-benzoyl-5-ketopiperidine-2,4-dicarboxylate.

5-Ketopipecolic acid. The crude diethyl 1-benzoyl-5-ketopiperidine-2,4-dicarboxylate (27 g., 0.077 mole) was suspended in 250 ml. of 18% hydrochloric acid and the mixture refluxed for 8 hr. Benzoic acid separated on cooling. It was removed by filtration and the filtrate extracted several times with ether. The aqueous solution was then evaporated to dryness under reduced pressure. The residue was dissolved in the least amount of methanol and acetone added until the solution became cloudy. After cooling overnight the product was removed, washed with acetone, and dried. A sample recrystallized from methanol-acetone melted at 135–136° and had an analysis corresponding fairly well to the hydrochloride with 1 mole of methanol of crystallization.

Anal. Calcd. for $C_6H_{10}ClNO_3 \cdot CH_3OH$: C, 39.78; H, 6.66; N, 6.63; Cl, 16.77. Found: C, 40.28; H, 6.83; N, 6.85; Cl, 16.46.

The solvated hydrochloride (9 g.) was dissolved in 25 ml. of warm water, treated with decolorizing carbon, and the solution filtered. The filtrate was warmed to 35° and the *p*H adjusted to 4.5–5.0 by the careful addition of ammonium hydroxide. On cooling colorless crystals formed which were removed, washed with 5 ml. of ice-water, then with absolute ethanol, and dried over phosphorus pentoxide. The yield of 5-ketopipecolic acid dihydrate was 5.3 g. (39%) m.p. > 300°.

Anal. Calcd. for $C_6H_9NO_3 \cdot 2H_2O$: C, 40.25; H, 7.27; N, 7.84; H_2O, 20.5. Found: C, 40.22; H, 7.33; N, 7.79; H_2O, 20.60 (K. Fischer).

Diethyl 1-carboxymethylpyroglutamate. Triethyl *N*-carboxymethylglutamate (80 g., 0.33 mole) was refluxed in 100 ml. of toluene. Ethanol was allowed to distill until the temperature reached the boiling point of toluene. The toluene was then removed *in vacuo* (30 mm.) and the residue distilled at 2 mm. The yield was 56 g. (83%), b.p. 163–166°/2 mm., n_D^{24} 1.4670, $[\alpha]_D^{23}$ −25.63° (1.2% in 95% ethanol).

Anal. Calcd. for $C_{11}H_{17}NO_5$: C, 54.48; H, 7.07; N, 6.00. Found: C, 54.66; H, 7.14; N, 5.74.

Reactions used in establishing identity of diethyl 1-carboxymethylpyroglutamate. 1-β-Hydroxyethyl-2-hydroxymethylpyrrolidine. A solution of 180 g. of diethyl 1-carboxymethylpyroglutamate (0.73 mole) in 250 ml. of dry ether was added dropwise with stirring to a stirred suspension of 70 g. (1.84 moles) of lithium aluminum hydride in 1500 ml. of dry ether, cooled in ice. After the addition was completed, the reaction mixture was stirred overnight at room temperature. The complex was then decomposed by the cautious addition, with cooling, of 300 ml. of water and 200 ml. of 2-propanol. The mixture was stirred for 2 hr. and filtered. The precipitate was dissolved in 15% sodium hydroxide solution and the resulting solution extracted with 1-butanol. The butanol extract was combined with the initial filtrate, washed with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. After removing the solvents, the residue was distilled *in vacuo*. The yield was 47 g. (44%) b.p. 105–108°/0.2 mm., n_D^{25} 1.4944, $[\alpha]_D^{23}$ −55.69° (1% in 95% ethanol).

Anal. Calcd. for $C_7H_{15}NO_2$: C, 57.55; H, 10.40; N, 9.59. Found: C, 57.50; H, 10.14; N, 9.60.

1-β-Hydroxyethyl-2-hydroxymethylpyrrolidine from 2-hydroxymethylpyrrolidine. A solution of 29 g. (0.29 mole) of 2-hydroxymethylpyrrolidine in 50 ml. of dry methanol was placed in a flask fitted with a Dry Ice condenser. The solution was stirred while a solution of 13.2 g. (0.3 mole) of ethylene oxide in 30 ml. of methanol was slowly added. Occasional cooling was necessary to keep the temperature below 45°. After standing at room temperature overnight, the methanol was removed on a steam bath and the residue distilled *in vacuo*. The yield was 87%. The physical constants and analyses for this product were identical with those for the compound obtained from diethyl 1-carboxymethylpyroglutamate.

1-β-Chloroethyl-2-chloromethylpyrrolidine. To a solution of 120 g. (1 mole) of thionyl chloride in 500 ml. of dichloromethane was slowly added, with stirring, 60 g. (0.41 mole) of 1-β-hydroxyethyl-2-hydroxymethylpyrrolidine in 500 ml. of dichloromethane. When the addition was completed, the solution was refluxed for 4 hr. and then stirred overnight at room temperature. The solution was concentrated to 400 ml. and diluted with an equal volume of ethyl acetate. After cooling and standing for several hours, the product was removed by filtration, washed with ethyl acetate, and dried. The yield was 84 g. (92%). After one recrystallization from dichloromethane–ethyl acetate, the product melted at 232–234°, $[\alpha]_D^{22}$ −11.64 (1% in water).

Anal. Calcd. for $C_7H_{14}Cl_2N$: N, 6.40; Cl, 48.65. Found: N, 6.60; Cl, 48.85.

A sample was converted to the free base and distilled. The base was a colorless liquid, b.p. 70–72°/1 mm.

Anal. Calcd. for $C_7H_{13}Cl_2N$: C, 46.10; H, 7.20; N, 7.70; Cl, 38.90. Found: C, 46.33; H, 7.18; N, 7.75; Cl, 38.71.

Derivatives of 5-ketopipecolic acid, ethyl 5-ketopipecolate. 5-Ketopipecolic acid dihydrate (12 g.) was dissolved in 30 ml. of cold absolute ethanol containing about 16% of hydrogen chloride. After standing at room temperature for 4 hr., 40 g. of anhydrous calcium sulfate was added and the mixture allowed to stand at room temperature for 16 hr. The solution was filtered and the filtrate concentrated *in vacuo*, at room temperature, to a sirup. The latter was dissolved in 100 ml. of dry ethanol and concentrated as before. The solid so obtained was recrystallized from dichloromethane-ether. There was obtained 9.5 g. (69%) of ethyl-5-ketopipecolate hydrochloride, m.p. 154–155°.

Anal. Calcd. for $C_8H_{14}ClNO_3$: C, 46.45; H, 6.82; N, 6.75; Cl, 17.15. Found: C, 46.45; H, 7.01; N, 6.62; Cl, 16.91.

4-Benzal-5-ketopipecolic acid hydrochloride. 5-Ketopipecolic acid hydrochloride (0.5 g.) was dissolved in 100 ml. of glacial acetic acid saturated with hydrogen chloride. To this was added 0.8 g. of benzaldehyde and the reaction mixture was allowed to stand for 16 hr. at room temperature. The solid which formed was removed, washed with ethanol, and dried. The yield was 50%, m.p. 181–182°.

Anal. Calcd. for $C_{13}H_{14}ClNO_3$: C, 58.30; H, 5.28; N, 5.23; Cl, 13.28. Found: C, 58.46; H, 5.21; N, 5.24; Cl, 13.28.

PHILADELPHIA 4, PA.