compounds and intermediates are described. Preliminary pharmacological data for the new tetra-substituted ethylenediamines is reported.

BLOOMFIELD, N. J. RECEIVED OCTOBER 7, 1949

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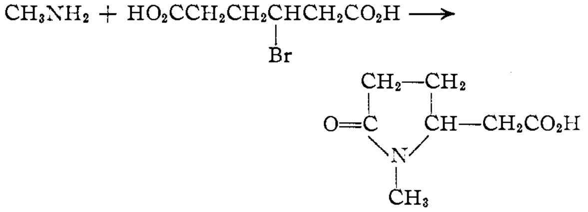
Synthesis of Ecgoninic Acid and Related Pyrrolidones

BY G. L. EVANS, H. W. GRAY AND H. W. JACOBSON

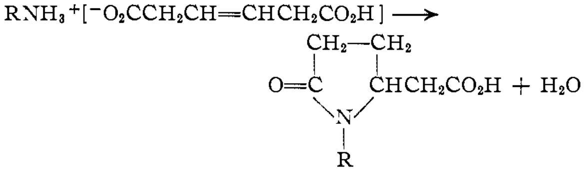
Ecgoninic acid, the end-product of the controlled oxidation of the alkaloids tropine and ecgonine, was shown to be 1-methyl-5-oxo-2-pyrrolidineacetic acid by Willstätter and Hollander[1] who synthesized it by the action of methylamine on β-bromoadipic acid.



$$CH_3NH_2 + HO_2CCH_2CH_2\underset{\displaystyle Br}{CH}CH_2CO_2H \longrightarrow$$

Compounds containing the ring system of ecgoninic acid have been prepared in a variety of ways, for example by heating the methyl ester of the lactone of γ-hydroxyadipic acid with ammonia,[2] by heating lactones with amines,[3,4,5] or by catalytic reduction of γ-nitrocarboxylic acids.[6]

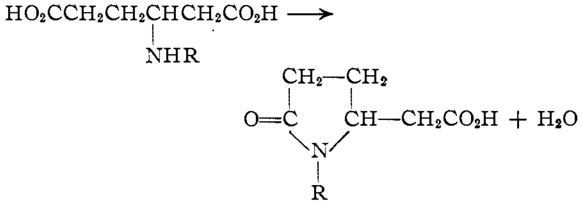
A convenient and general reaction for the synthesis in good yield of ecgoninic acid and related acids and their derivatives has been found in heating ammonium or amine salts of β-hydromuconic acid at elevated temperatures.



$$RNH_3^+[^-O_2CCH_2CH{=}CHCH_2CO_2H] \longrightarrow$$

If two moles of organic base for each mole of acid is employed, the corresponding amide is obtained. A plausible mechanism for this reaction involves a shift of the double bond of the β-hydromuconic acid to an α,β-position followed by addition of ammonia or amine to the unsaturated system and ring closure as indicated in the following scheme.

$$RNH_3^+[^-O_2CCH_2CH{=}CHCH_2CO_2H] \longrightarrow$$
$$RNH_3^+[HO_2CCH_2CH{=}CH^-CHCO_2H] \rightleftarrows$$
$$RNH_3^+[HO_2CCH_2{}^-CHCH{=}CHCO_2H] \longrightarrow$$
$$RNH_2 + HO_2CCH_2CH_2CH{=}CHCO_2H \longrightarrow$$



$$HO_2CCH_2CH_2\underset{\displaystyle NHR}{CH}CH_2CO_2H \longrightarrow$$

Experimental

β-Hydromuconic Acid.—Three hundred sixty-six grams of 1,4-dicyano-2-butene, prepared by the action of sodium cyanide on 1,4-dichloro-2-butene in acetonitrile solution with cuprous bromide catalyst,[7] was hydrolyzed by dissolving in a mixture of 1 l. of concentrated hydrochloric acid and 1 l. of water and refluxing the solution for five hours. The reaction mixture was cooled to 10°, filtered and the crude product was crystallized from 4 l. of water. There was obtained 418 g. of β-hydromuconic acid (84% yield), m. p. 196–197° (uncor.).

Ecgoninic Acid.—A mixture of 12 g. of methylamine (0.388 mole) and 55.8 g. of β-hydromuconic acid (0.388 mole) was heated in a sealed glass tube at 210° for two hours. After cooling to room temperature, the tube was opened and the pale yellow, viscous product was dissolved in 100 ml. of acetone. After drying the solution over anhydrous magnesium sulfate, it was concentrated to approximately one-half the original volume and cooled to induce crystallization. There was obtained 43 g. (71% yield) of ecgoninic acid which was recrystallized from acetone, m. p. 94–95°. *Anal.* Calcd. for $C_7H_{11}NO_3$: C, 53.50; H, 7.06; N, 8.92; neut. eq., 157.2. Found: C, 53.72; H, 7.17; N, 8.86; neut. eq., 158.0.

5-Oxo-2-pyrrolidineacetic Acid.—Fifty grams of ammonium acid β-hydromuconate, prepared by adding one mole of ammonia to one mole of β-hydromuconic acid in absolute methanol, was heated for three hours at 200–210° in a sealed tube. The viscous product was dissolved in 50 ml. of absolute ethanol. One hundred twenty-five ml. of benzene was added, and the solution dried by azeotropic distillation. After removal of water, the benzene was poured off the lower layer of viscous product (benzene insoluble) from which crystals weighing 20.9 g. (47% yield) were deposited. This crude product was purified by precipitation with ether from chloroform solution, and recrystallization from butanol, to give white, water-soluble crystals, m. p. 120.5–122.2°. *Anal.* Calcd. for $C_6H_9NO_3$: C, 50.34; H, 6.30; N, 9.79; neut. eq., 143. Found: C, 50.84; H, 6.49; N, 9.84; neut. eq., 142.8.

1-Butyl-5-oxo-2-pyrrolidineacetic Acid.—A mixture of 14.6 g. of butylamine (0.2 mole) and 28.8 g. of β-hydromuconic acid (0.2 mole) was heated as described for ecgoninic acid. There was obtained 30 g. (65% yield) of acid, b. p. 188–190° (5 mm.), m. p. 70–71°. *Anal.* Calcd. for $C_{10}H_{17}NO_3$: C, 60.30; H, 8.55; N, 7.04; neut. eq., 199.2. Found: C, 60.30; H, 8.78; N, 7.04; neut. eq., 199.9.

The methyl ester was prepared in 55% yield by the method of Newman,[8] b. p. 142–144° (2 mm.); n^{25}D

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(1) Willstätter and Hollander, *Ber.*, **34**, 1818 (1901).

(2) Leuchs and Möbis, *ibid.*, **42**, 1234 (1909).

(3) Zienty and Steahly, THIS JOURNAL, **69**, 715 (1947).

(4) Schuster and Seib, U. S. Patent 2,267,757 (Dec. 30, 1941).

(5) Meyer and Kissin, *Ber.*, **42**, 2837 (1909).

(6) French Patent 880,400 (Dec. 27, 1942).

(7) Hager, U. S. Patent 2,462,388 (Feb. 22, 1949).

(8) Newman, THIS JOURNAL, **63**, 2431 (1941).

1.4690. *Anal.* Calcd. for $C_{11}H_{19}NO_3$: C, 61.97; H, 8.92; N, 6.57. Found: C, 61.51; H, 9.02; N, 6.67.

The isopropyl ester was obtained in 63.3% yield by a conventional esterification using sulfuric acid catalyst, b. p. 155° (2.5 mm.); n^{25}D 1.4619. *Anal.* Calcd. for $C_{13}H_{23}NO_3$: C, 64.73; H, 9.54; N, 5.81; sapn. eq., 241. Found: C, 64.49; H, 9.79; N, 5.83; sapn. eq., 241.8.

1-Phenyl-5-oxo-2-pyrrolidineacetic Acid.—One hundred eighty grams of β-hydromuconic acid (1.25 moles) and 116 g. (1.26 moles) of distilled aniline were heated together in a glass-lined autoclave for three hours at 225°. There was obtained 285 g. of dark viscous sirup which was dried by azeotropic distillation with 200 ml. of absolute ethanol and 400 ml. of benzene. The dried solution deposited dark crystals which were filtered, wt. 93.5 g. The filtrate was concentrated on the steam-bath to a thick sirup which partially crystallized on cooling. The dark crystals so obtained were filtered to give 113.5 g. of crude material, thus bringing the total weight to 207 g. There was obtained 55.6 g. (19.7% yield) of 1-phenyl-5-oxo-2-pyrrolidineacetic acid after recrystallizing several times from water, m. p. 135–136°. *Anal.* Calcd. for $C_{12}H_{13}NO_3$: C, 65.76; H, 5.94; N, 6.39; neut. eq., 219. Found: C, 65.53; H, 5.99; N, 6.29; neut. eq., 215.6.

5-Oxo-2-pyrrolidineacetamide.—This compound, previously reported by Leuchs and Möbis,[2] was prepared by heating 232 g. of diammonium β-hydromuconate at 215° in a stainless steel Parr bomb for three hours. The crude product weighing 159 g. was purified by repeated crystallization from ethyl acetate. There was obtained 108 g. (59.5% yield) of pure amide, m. p. 147–148°. *Anal.* Calcd. for $C_6H_{10}N_2O_2$: C, 50.70; H, 7.04; N, 19.72. Found: C, 50.56; H, 7.03; N, 19.68.

N-1-Dibutyl-5-oxo-2-pyrrolidineacetamide.—Forty-eight grams of bis-(butylammonium) β-hydromuconate, prepared by adding two moles of butylamine to one mole of β-hydromuconic acid in absolute ethanol, was heated in a sealed tube for three hours at 210–215°. The water-white product thus obtained was dissolved in methanol, dried over anhydrous magnesium sulfate and distilled to give an essentially quantitative yield of the substituted pyrrolidone, b. p. 210–212° (2 mm.). *Anal.* Calcd. for $C_{14}H_{26}N_2O_2$: C, 66.14; H, 10.24; N, 11.02. Found: C, 65.38; H, 10.25; N, 11.31.

The corresponding linear diamide, N,N′-dibutyl-β-hydromuconamide of the same empirical formula, was prepared by the action of butylamine on the acid chloride of β-hydromuconic acid. It was a solid, m. p. 167–168°. *Anal.* Found: C, 66.38; H, 10.25; N, 10.62.

The substituted pyrrolidone was hydrolyzed with 6 *N* hydrochloric acid to give a 73% yield of 1-butyl-5-oxo-2-pyrrolidineacetic acid, m. p. 70.5–72.5°. *Anal.* Calcd. for $C_{10}H_{17}NO_3$: C, 60.30; H, 8.55; N, 7.04. Found: C, 60.57; H, 8.55; N, 7.33.

N,1-Dioctadecyl-5-oxo-2-pyrrolidineacetamide.—Forty-five grams of bis-(octadecylammonium) β-hydromuconate was heated at 225–230° for three hours in a sealed tube to give 38 g. (89% yield) of substituted pyrrolidone, m. p. 71–72.5° after crystallizing from ethanol. *Anal.* Calcd. for $C_{42}H_{82}N_2O_2$: C, 78.02; H, 12.69; N, 4.34. Found: C, 78.02; H, 12.71; N, 4.85.

N,1-Diphenyl-5-oxo-2-pyrrolidineacetamide.—A mixture of 33.8 g. of aniline (0.364 mole) and 26.2 g. of β-hydromuconic acid (0.182 mole) was heated in a sealed tube at 110° for twenty minutes. The temperature was raised to 210° and held for one hour. The product, obtained in essentially quantitative yield, was insoluble in benzene and ether and only slightly soluble in ethanol or dioxane. A small sample was crystallized from ethanol, m. p. 245° (dec.). *Anal.* Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.47; H, 6.13; N, 9.52. Found: C, 73.10; H, 6.31; N, 9.94.

N,1-Bis-(*p*-chlorophenyl)-5-oxo-2-pyrrolidineacetamide.—A mixture of 43.6 g. (0.302 mole) of β-hydromuconic acid and 77.1 g. (0.605 mole) of recrystallized *p*-chloroaniline was heated for one hour at 200° in a glass-lined autoclave. The resulting viscous red-colored product was dissolved in 150 ml. of methanol and to the solution (cold) was added 25 ml. of water. The crystals which separated (69.1 g.) were dissolved in methanol, treated with Darco (activated charcoal) and further recrystallized to give 52.1 g. (47.4% yield). A sample of this material was further recrystallized from aqueous methanol to give an analytical sample, m. p. 166.0–166.9°. *Anal.* Calcd. for $C_{18}H_{16}Cl_2N_2O_2$: Cl, 19.56; N, 7.71. Found: Cl, 19.09; N, 7.82.

N,1-Bis-(4-diethylaminocyclohexyl)-5-oxo-2-pyrrolidineacetamide.—The salt formed by adding 50 g. of β-hydromuconic acid (0.347 mole) to 118 g. (0.694 mole) of N,N-diethyl-1,4-cyclohexanediamine at 70–85° was heated for one hour at 200° in a glass-lined autoclave. The straw-colored, viscous product was dissolved in an equal volume of acetone and cooled to give 73 g. of crystals. By repeated crystallization, first from aqueous acetone and finally from ethyl acetate, a total of 50.4 g. (33.2% yield) of N,1-bis-(4-diethylaminocyclohexyl)-5-oxo-2-pyrrolidineacetamide was obtained, m. p. 163.5–165° (slight dec.). *Anal.* Calcd. for $C_{26}H_{48}N_4O_2$: C, 69.64; H, 10.71; N, 12.50. Found: C, 68.93; H, 10.84; N, 12.66.

Summary

A convenient and general method for the synthesis of ecgoninic acid and certain related acids and amides from β-hydromuconic acid is described.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Steric Effect of Methylene Groups. V

BY RICHARD T. ARNOLD AND PAUL N. CRAIG[1]

In view of the recent successful results obtained in the evaluation of absorption at certain characteristic wave lengths,[2,3] we have applied this elegant method to our current stereochemical studies.

Evidence has been presented[4,5] already which indicates strongly that methylene groups do not exhibit a constant steric effect and that the value in a particular case depends upon the type of structure in which the group is found. Previous work indicated that the magnitude of this steric influence decreases in the order $—CH_2—$ (in $CH_3—$) $>$ $—CH_2—$ (in a six-membered ring) $\gg$ $—CH_2—$ (in a five-membered ring).

Our earlier work has now been extended to include compounds II, III, V and VI, and the ultraviolet spectra of these are compared with I. Unfortunately, numerous attempts to prepare compound IV failed.

[1] Abstracted from the Ph.D. Thesis of Paul N. Craig; du Pont Fellow 1947–1948.

[2] Remington, THIS JOURNAL, **67**, 1838 (1945).

[3] Brown and Reagan, *ibid.*, **69**, 1032 (1947).

[4] Arnold and Craig, *ibid.*, **70**, 2791 (1948).

[5] Arnold and Richter, *ibid.*, **70**, 3505 (1948).