Synthesis of α-Substituted Glutarimides via Michael Condensation

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A useful approach to the synthesis of certain α-substituted glutarimides required as intermediates in the synthesis of potential hypnotic compounds appeared to be the Michael condensation of appropriate donors to various nitrogen containing acceptors.

Cyanoethylation of dibenzyl methyl malonate in the presence of sodium hydride gave the appropriate Michael condensation adduct I whose conversion into α-methylglutarimide(III) proved inefficient. However, it was found that when acrylamide was used as acceptor, a glutarimide derivative II was isolated directly upon workup of the Michael reaction mixture. The α-methyl-α-carbobenzoxy-glutarimide (II) thus obtained could be debenzylated either by catalytic hydrogenolysis using palladized carbon or by treatment with hydrogen bromide in acetic acid[2], affording α-methyl-glutarimide (III). The structure of the latter was proven by hydrolysis to yield the known α-methylglutaric acid and by lithium aluminium hydride reduction to yield the known 3-methylpiperidine. These reactions are summarized in reaction scheme 1.

Similarly, cyanoethylation of diphenylacetonitrile in the presence of methanolic potassium hydroxide gave α,α-diphenylglutarodinitrile (IV). The transformations of this product into α,α-diphenylglutarimide (V) and intermediate products are summarized in reaction scheme 2.

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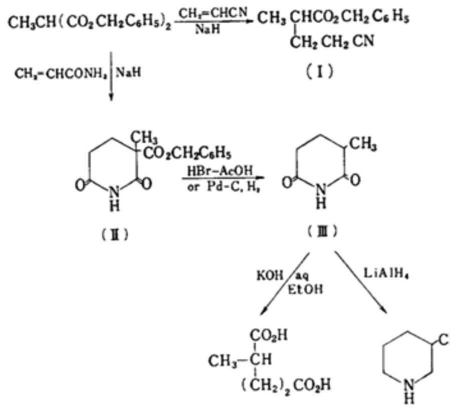
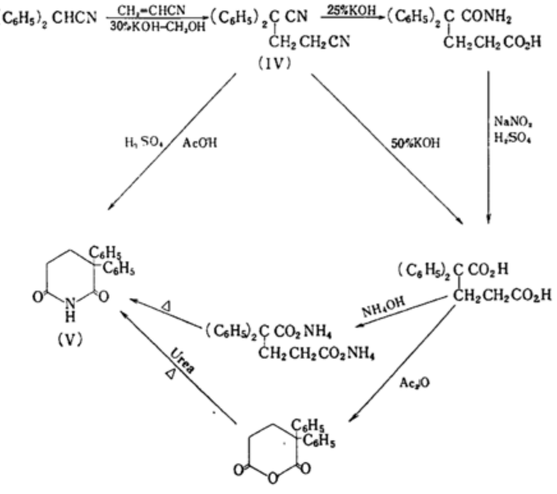
[2] D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

Reaction Scheme 1.



Reaction Scheme 2.



Experimental

Dibenzyl methylmalonate.—This was prepared analogously to the preparation of dibenzyl malonate[3] by transesterification of diethyl methylmalonate[4] (58 g.; 0.33 mole) with benzyl alcohol (72 g.; 0.67 mole) in dry benzene (660 ml.) in the presence of sodium methoxide (1.7 g.). The ester had b. p. 164~167°C/0.04 mm.Hg (71 g.; 72%).

Benzyl α-(2′-cyanoethyl)-propionate (I).—The sodio-derivative was prepared by heating under reflux dibenzyl methylmalonate (37 g.) and sodium hydride (3.8 g.) in dry benzene (300 ml.) for 6 hr. The reaction mixture was cooled and a solution of acrylonitrile (8 g.) in dry benzene (50 ml.) was added and the whole was again refluxed for 6 hr. The benzene was removed at the water pump and the residue was poured into water containing sufficient acetic acid for neutralization. The oily precipitate was extracted with ethyl acetate, the extract was dried, and the solvent was evaporated. Ether was added to the residue (46 g.) and the extract was filtered to remove yellow polymeric material. The ether-soluble material (33 g.) solidified after long standing and was recrystallized from benzene-petroleum ether, m. p. 79~80°C.

Anal. Found: C, 76.85; H, 6.37; N, 4.43. Calcd. for $C_{13}H_{15}O_2N \cdot C_6H_6$: C, 77.28; H, 7.11; N, 4.74%.

3-Carbobenzoxy-3-methylglutarimide (II).—A mixture of dibenzyl methylmalonate (4 g.), sodium hydride (0.33 g.) and dry benzene was refluxed for 2 hr. After cooling, acrylamide[5] (0.33 g.) was added and the mixture was refluxed for 4~5 hr. A clear solution was finally obtained. The benzene was removed under reduced pressure and the residue was poured into ice water containing the calculated quantity of acetic acid required for neutralization. Scratching the precipitated oil after the addition of a small amount of ethanol induced crystallization. The crude solid (3 g.) was filtered, m. p. 93~94°C (from aqueous ethanol).

Anal. Found: C, 64.53; H, 5.61; N, 5.10. Calcd. for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79; N, 4.36%.

3-Methylglutarimide (III).—*a*) The imide-ester II (36.9 g.) was refluxed with 30% hydrogen bromide in acetic acid (200 ml.) for 6 hr. After evaporation to dryness, the residue was treated with aqueous sodium bicarbonate and ether. The ether layer was evaporated in vacuo to remove the solvent and benzyl bromide. A small amount of imide (0.6 g.) crystallized in the residue. The bicarbonate solution was acidified with dilute hydrochloric acid. The imide was extracted with ether and afforded more crystalline material on evaporation (4.1 g.). Continuous extraction of the acidified solution with ether afforded more of the imide (6.7 g.). Total yield, 62%, m. p. 101~102°C (from ethanol-ether). The imide can be sublimed in a vacuum.

Anal. Found: C, 56.40; H, 7.24; N, 11.10. Calcd. for $C_6H_9O_2N$: C, 56.68; H, 7.14; N, 11.02%.

b) The imide can also be obtained by hydrogenolysis of the imide-ester II (5 g.) in ethyl acetate (100 ml.) in the presence of 10% palladized carbon (0.5 g.) at an initial pressure of 48 lbs./sq. in metric system. Hydrogen uptake (1 mole) was complete within 30 min. The catalyst was removed by filtration and the solvent was removed by distillation. The residue soon solidified, m. p. 94~95°C. Recrystallization from ethanol-ether gave the imide III, m. p. 101~102°C, identical with that described above.

Proof of Structure of 3-Methylglutarimide.—*a*) The imide III (100 mg.) was saponified by refluxing for 7 hr. with potassium hydroxide (0.52 g.) in 50% ethanol (4.5 ml.). Ammonia was evolved. The mixture was evaporated to dryness and the residue was taken up in a little water and the solution was acidified and extracted with ether. The ether was removed from the

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[3] D. Ginsburg and R. Pappo, *J. Am. Chem. Soc.*, **75**, 1094 (1953).

[4] "Organic Syntheses", Coll. Vol. II, Wiley, New York, (1946), p. 279.

[5] Cf. D. Elad and D. Ginsburg, *J. Chem. Soc.*, **1953**, 4137.

extract and the residual oil which soon solidified (100 mg.) was recrystallized from benzene-petroleum ether, m. p. 75°C. Lit.[6] m. p. 77~80°C for α-methylglutaric acid.

b) A solution of the imide III (1.27 g.) in dry dioxan (20 ml.) was added to a solution of lithium aluminium hydride (0.27 g.) in dry ether (30 ml.) during 20 min. The mixture was refluxed for 90 min. and was cooled and decomposed slowly with hydrochloric acid (10%). The mixture was evaporated to dryness under reduced pressure. Aqueous potassium hydroxide (50%) was added and the mixture was extracted with ether. Removal of the ether gave an oil (0.3 g.) of piperidine-like odor. The hydrochloride was prepared and had m. p. 171~172°C (from ether-benzene). Lit.[7] m. p. 171~172°C for 3-methylpiperidine.

α, α-Diphenylglutaronitrile (IV).—To a solution of diphenylacetonitrile (77.5 g.) in *tert*-butanol (120 ml.) and dioxan (30 ml.) was added methanolic potassium hydroxide (30%; 3 ml.). A solution of acrylonitrile (21.2 g.) in *tert*-butanol (200 ml.) was then added with stirring at 10~25°C during 30 min. Stirring at room temperature was continued for 2 hr. The emulsion deposited much crystalline material. The mixture was poured into ice-water and the solid was filtered and recrystallized from dilute methanol, m. p. 69~70°C (87 g.). The product depressed the m. p. of diphenylacetonitrile.

Anal. Found: C, 82.82; H, 5.72; N, 11.06. Calcd. for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37%.

γ-Carboxamido-γ, γ-diphenylbutyric acid.—This was obtained by refluxing the dinitrile (2.46 g.) with potassium hydroxide (2.46 g.) in aqueous (10 ml.) ethanol (10 ml.) for 17 hr. followed by the addition of more potassium hydroxide (5 g.) and continued reflux for 23 hr. longer. The ethanol was evaporated, dilute hydrochloric acid was added and the precipitate was recrystallized first from methanol, then from benzene, m. p. 153~154°C (1.19 g.).

Anal. Found: C, 72.13; H, 5.97; N, 5.04. Calcd. for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.05; N, 4.94%.

α, α-Diphenylglutaric acid.—*a*) The dinitrile (2.46 g.) was saponified by refluxing with aqueous potassium hydroxide (50%; 5.6 g.) for 4 hr. After dilution with water and hydrochloric acid the resinous solid which separated was recrystallized from aqueous methanol, m. p. 187~188°C (1.77 g.).

Anal. Found: C, 72.35; H, 6.15. Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67%.

b) The above amido-acid (0.14 g.) was dissolved in concentrated sulfuric acid (0.6 g.) and a saturated solution of sodium nitrite (0.4 g.) was added beneath the surface of the yellow acid solution. The mixture was warmed on the steam bath for 1 hr. It was poured into ice water and the precipitate was filtered. Recrystallization from aqueous methanol gave α, α-diphenylglutaric acid (30 mg.) identical with that described above.

α,α-Diphenylglutaric anhydride.—A solution of the above diacid (4.26 g.) and acetic anhydride (25 ml.) was refluxed for 90 min. The solvents were removed under reduced pressure and the residue was recrystallized from benzene-petroleum ether (3 g.; 2 crops), m. p. 134°C.

Anal. Found: C, 76.99; H, 5.38. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30%.

α, α-Diphenylglutarimide.—*a*) A mixture of the dinitrile IV (24.6 g.), concentrated sulfuric acid (50 g.), acetic acid (35 g.) and water (15 ml.) was refluxed for 3 hr. It was poured into ice-water and the viscous solid was triturated with a little methanol and then washed with a little water and filtered (18.2 g.), m. p. 169~170°C (sinters 160°C) (from methanol). The imide is soluble in potassium hydroxide solution, but not in sodium bicarbonate solution.

Anal. Found: C, 77.02; H, 5.76; N, 5.39. Calcd. for $C_{17}H_{15}O_2N$: C, 76.96; H, 5.70; N, 5.28%.

b) A mixture of the above anhydride (1.33 g.) and urea (3 g.) formed a clear melt when heated to 140~150°C in an oil bath. The temperature was raised to 200~210°C and the contents solidified after 1 hr. at this temperature. After cooling and extraction with water to remove excess urea, the undissolved residue was recrystallized from aqueous methanol, m. p. 169°C (sinters 161°C) (0.76 g.). This product was identical with the imide described above.

c) α, α-Diphenylglutaric acid was dissolved in excess ammonium hydroxide and the viscous ammonium salt (1.67 g.) was obtained by evaporation to dryness. This was heated in a distillation flask with a free flame and some material distilled at 190°C. Ether was added to the distillate and petroleum ether was then added, inducing crystallization of the imide (0.1 g.) identical with that described above, m. p. 168~169°C.

Summary

A method for the synthesis of α-monosubstituted and α, α-disubstituted glutarimides by Michael addition of active methylene and methine compounds to acrylonitrile or acrylamide, is described.

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[6] A. Franke and M. Kohn, *Monatsh.*, **23**, 740 (1920).

[7] A. Franke and M. Kohn, ibid., **23**, 884 (1902).