quinoline has been described in the literature.[3] Our yields and melting points agreed essentially with those reported.

Derivatives of Dimethylquinolines.—The compounds described in Table I were prepared by refluxing the chloro compound with an excess of the appropriate amine as the solvent. The reflux time was eight to ten hours. The reaction mixture was then poured on ice. The 4-diethylamino-1-methylbutylamino derivative was extracted from the water with ether and was purified by distillation; whereas the solid piperidino, morpholino and 1-hydroxymethylpropylamino derivatives were filtered off and crystallized.

Summary

1. 2-Chloro-4,8-dimethylquinoline has been prepared.

2. Some derivatives of 2-amino-4,8-dimethylaminoquinoline and 4-amino-3,8-dimethylquinoline are described.

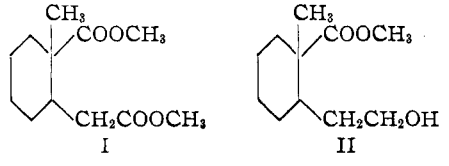
WICHITA, KANSAS RECEIVED APRIL 12, 1949

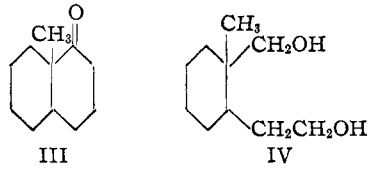
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

Reduction of a Diester to a Hydroxyester by Lithium Aluminum Hydride. Application to the Construction of Rings

BY W. E. BACHMANN AND ANDRE S. DREIDING[1]

No instance of the reduction of one of two ester groups by lithium aluminum hydride has been reported. Nystrom and Brown were unable to reduce one of the two primary carboxy groups of sebacic acid and its half ester at the boiling point of ether and suggested experimentation at lower temperatures.[2] We were interested in reducing selectively the primary ester group of the dimethyl ester of *cis*-2-methyl-2-carboxycyclohexaneacetic acid (I) to the alcohol (II) from which, after a malonic ester synthesis and cyclization, *cis*-9-methyl-1-decalone (III) could be obtained.





Accordingly we examined the reduction of the diester (I) with an amount of lithium aluminum hydride sufficient to reduce only one ester group at low temperatures. Below −15° no visible change occurred. When the reaction mixture was kept near −15° the reagent was used up in reducing the primary carbomethoxy group to yield *cis*-β-2-methyl-2-carbomethoxycyclohexaneëthanol (II). The crude product was converted to the bromoester by the action of phosphorus tribromide. Condensation with sodiomalonic ester followed by hydrolysis and decarboxylation yielded *cis*-γ-2-methyl-2-carboxycyclohexanebutyric acid. Its dimethyl ester underwent the Dieckmann cyclization, hydrolysis, and decarboxylation to give *cis*-9-methyl-1-decalone (III) in a 15% over-all yield from I. These reactions represent a new synthesis of the bicyclic ketone (III) from the diester (I) and the procedure may prove to be generally applicable for the construction of rings since the starting acetic esters are frequently available through the Reformatsky reaction or malonic ester synthesis. Recently we described the preparation of the ketone (III) from the ester (I) through two successive Arndt–Eistert reactions followed by cyclization.[3]

Reduction of the diester (I) with sufficient lithium aluminum hydride to reduce both ester groups yielded *cis*-β-2-methyl-2-hydroxymethylcyclohexaneëthanol (IV). The same product (IV) was obtained when the diester (I) was treated with an excess of sodium in boiling ethanol.

Experimental

Reduction of the Diester (I) to the Hydroxyester (II).—A 0.15-g. piece of lithium aluminum hydride (Metal Hydrides Inc., Beverly, Massachusetts) was softened by allowing it to rest in 15 cc. of boiling anhydrous ether for twenty minutes, while excluding moisture and carbon dioxide. It was broken up with a stirring rod and the resulting supension was refluxed again for twenty minutes. The remaining undissolved particles were crushed and brought into solution almost completely by boiling for another twenty minutes. To the solution, cooled to −60° in a Dry Ice–acetone-bath, a solution of 1.8 g. of the dimethyl ester of *cis*-2-methyl-2-carboxycyclohexaneacetic acid (I, made from the corresponding diacid[4] by esterification with diazomethane) in 10 cc. of ether was added in small portions so that the temperature did not rise above −40°. The colorless solution, which contained only a small amount of undissolved solids, stood at −60° for five hours and was allowed to warm up slowly. At −15° a colorless gelatinous precipitate appeared. The mixture was kept at −15 to −10° for twenty minutes by reinserting the flask in the cold bath from time to time with swirling. After standing at room temperature for three hours, a small amount of 10% sodium hydroxide and then excess hydrochloric acid was added. The ethereal layer was washed with a saturated sodium chloride solution and concentrated, and the crude residue was evaporatively distilled. The colorless camphoraceous oil (0.83 g. or 53%, presumably *cis*-β-2-methyl-2-carbomethoxycyclohexaneethanol, II), which was collected at 70–80° (0.4 mm.), was

(1) Alfred H. Lloyd Postdoctoral Fellow in the Horace H. Rackham School of Graduate Studies 1947/1948.

(2) Nystrom and Brown, THIS JOURNAL, **69**, 2548 (1947).

(3) Bachmann and Dreiding, *J. Org. Chem.*, **13**, 317 (1948).

(4) Chuang, Tien and Huang, *Ber.*, **68**, 866 (1935); Bachmann and Kushner, THIS JOURNAL, **65**, 1963 (1943).

treated in the cold with 0.13 cc. of phosphorus tribromide in 10 cc. of benzene. After standing for four hours at 0° and fifteen hours at room temperature, the mixture was diluted with ether, washed with 10% sodium hydroxide and water, and concentrated. The residue, which had a fruity odor, was evaporatively distilled, and the bromoester (0.73 g. or 71%), which was collected at 75–95° (0.3 mm.), was added to a suspension of the sodium salt of diethyl malonate (made from 0.11 g. of sodium, 1.5 cc. of ethanol, and 0.88 g. of diethyl malonate) in 7 cc. of benzene. The mixture was refluxed for fifteen hours, cooled, and treated with dilute hydrochloric acid. The organic layer was separated and concentrated and the residue saponified in 20% aqueous methanolic potassium hydroxide for eight hours. The clear yellow solution was concentrated, washed with ether, and acidified in the cold. The oily malonic acid derivative, isolated by means of ether, was decarboxylated at 180–210° for eight minutes. A solution of the melt in 10% sodium hydroxide was washed with ether and acidified. The precipitated *cis*-γ-2-methyl-2-carboxycyclohexanebutyric acid was taken up in ether, washed with water, and esterified with diazomethane. The ethereal solution was extracted with 5% sodium hydroxide, the solvent evaporated and the residual diester was evaporatively distilled at 90–115° (0.2 mm.); yield, 0.47 g. (66%). The distillate was subjected to a Dieckmann cyclization, hydrolysis, and decarboxylation according to the described method.[3] Evaporative distillation of the product at 60–80° (0.4 mm.) gave *cis*-9-methyl-1-decalone (III) as a colorless camphoraceous liquid; yield, 0.2 g. (66%). The 2,4-dinitrophenylhydrazone, crystallized twice from an ethanol–ethyl acetate mixture, melted at 158–163° alone and when mixed with an authentic sample (m. p. 164–165°).[3] The oxime crystallized from methanol as colorless prisms, m. p. 110–112° alone and when mixed with an authentic sample (m. p. 114–115°).[3]

Reduction of the Diester (I) to the Glycol (IV). (a) By Lithium Aluminum Hydride.—To a solution of 88 mg. of lithium aluminum hydride in 18 cc. of anhydrous ether (prepared as described above) was added in small portions a solution of 0.45 g. of the dimethyl ester of *cis*-2-methyl-2-carboxycyclohexaneacetic acid (I, prepared by esterification of the acid[4]) at room temperature over a period of fifteen minutes; a colorless gelatinous precipitate appeared immediately. After standing at room temperature for twenty minutes, 10% aqueous sodium hydroxide was added, followed by solution of the salts in excess hydrochloric acid. Evaporation of the ethereal layer gave ***cis*-β-2-methyl-2-hydroxymethylcyclohexaneëthanol (IV)**, which crystallized from ether–petroleum ether (b. p. 30–60°) in colorless needles; yield, 0.27 g. (80%), m. p. 112–116°; after another recrystallization, 116–117°.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.71. Found: C, 69.55; H, 11.80.

(b) **By Sodium and Alcohol.**—To a boiling solution of the diester (I) in 50 cc. of dry ethanol was added 5 g. of sodium in small slices over a period of fifteen minutes. The mixture was kept refluxing for three hours, when all the sodium had reacted. The cooled mixture was treated with ice and water and the product was extracted with ether. The ethereal solution was washed with a saturated sodium chloride solution, dried over magnesium sulfate, and concentrated. Evaporative distillation of the residue at 120–140° (0.4 mm.) gave 3.5 g. (95%) of a colorless glass which crystallized when covered with a small amount of ether, m. p. 114–116°. On recrystallization from 1:1 ether–petroleum ether (b. p. 30–60°) the glycol (IV) melted at 116–117°.

Summary

The selective reduction of the primary carbomethoxy group in the dimethyl ester of *cis*-2-methyl-2-carboxycyclohexaneacetic acid (I) by lithium aluminum hydride and its application to a synthesis of *cis*-9-methyl-1-decalone (III) is described.

ANN ARBOR, MICHIGAN RECEIVED APRIL 29, 1949

[A CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

Alkylamine Esters of 7-Aminofluorenone-2-carboxylic Acid

BY H. F. OEHLSCHLAEGER[1] AND IAN R. MACGREGOR

Alkylamine esters of fluorene and fluorenone carboxylic acids have been reported to possess local anesthetic action. For example, the alkylamine esters of fluorene-9-carboxylic acid have been investigated and patented as local anesthetics.[2,3]

Ray and Rieveschl[4,5] prepared the β-diethylaminoethyl ester of fluorene-2-carboxylic acid as well as a series of alkylamine esters of fluorenone-1, -2 and -4 carboxylic acids. Of the series, the esters of fluorenone-2-carboxylic acid proved to be the most active as local anesthetics and as antispasmodics. The water solubility of these esters, however, is low. Subsequent attempts by Ray and MacGregor[6] to produce more soluble anesthetics based on the fluorene nucleus and using a ketone linkage rather than the ester linkage did not appreciably alter the water solubilities.

In this investigation we hoped to increase the effectiveness of the alkylamine esters of fluorenone-2-carboxylic acid by the introduction of an amino group in the 7-position of the fluorenone molecule. Generally the presence of a free amino group in a position para to the ester linkage in compounds of the procaine type has an advantageous effect. There is a noticeable increase in activity with no apparent increase in toxicity in compounds containing the para-amino group over compounds devoid of this group.[7] A series of alkylamine esters of 7-nitrofluorenone-2-carboxylic acid, and 7-aminofluorenone-2-carboxylic acid were prepared.

A modification of a Friedel–Crafts reaction used by Broisman and MacGregor[8] gave 60–65%

(1) Abstracted from a thesis presented to the Graduate School, University of Cincinnati, by H. F. Oehlschlaeger in partial fulfillment of the requirements for the degree of Master of Science, 1948.

(2) Burtner, U. S. Patent 2,262,754 (1941).

(3) Lehmann and Knoefel, *J. Pharmacol.*, **74**, 217, 274 (1942); **76**, 194 (1942).

(4) F. E. Ray and G. Rieveschl, THIS JOURNAL, **65**, 836 (1943).

(5) F. E. Ray and G. Rieveschl, U. S. Patent, 2,377,040.

(6) F. E. Ray and I. R. MacGregor, THIS JOURNAL, **69**, 587 (1947).

(7) Gilman and Pickens, *ibid.*, **47**, 245 (1925).

(8) R. Broisman, Master of Science thesis, University of Cincinnati, 1947.