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).

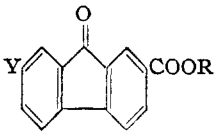
[5] F. E. Ray and G. Rieveschl, U. S. Patent, 2,377,040.

[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.

TABLE I



No.	Y	R	M. p., °C.[a]	Formula	Analyses, % Calcd.	Analyses, % Found
1	NO_2	β-Diethylaminoethyl[b,c]	134–136	$C_{20}H_{20}O_5N_2$	N, 7.61	7.67
2	NO_2	β-Diethylaminopropyl hydrochloride[d]	242–244	$C_{21}H_{23}O_5N_2Cl$	N, 6.68	6.91
					Cl, 8.48	8.41
3	NO_2	β-Di-*n*-butylaminoethyl[e,f]	206–207	$C_{24}H_{28}O_5N_2$	N, 6.60	6.31
4	NO_2	γ-Morpholino-β-dimethylaminopropyl[g,h]	166–167	$C_{23}H_{24}O_6N_2$	N, 6.61	6.63
5	NH_2	β-Diethylaminopropyl[i]	215–216	$C_{20}H_{22}O_3N_2$	N, 8.28	8.02
6	NH_2	β-Diethylaminopropyl[j]	91–93	$C_{21}H_{24}O_3N_2$	N, 7.96	8.24
7	NH_2	β-Di-*n*-butylaminoethyl	84–85	$C_{24}H_{30}O_3N_2$	N, 7.11	7.37
8	NH_2	γ-Morpholino-β-dimethylaminopropyl	176–177	$C_{23}H_{26}O_4N_2$	N, 7.11	7.14

[a] All melting points are uncorrected. [b] Hydrochloride m. p. 230–232°. [c] Nitrate m. p. 214–215°; anal. calcd. for N, 9.75; found N, 10.03. [d] Nitrate m. p. 175–176°. [e] Hydrochloride m. p. 209°. [f] Nitrate m. p. 156–157°. [g] Hydrochloride m. p. 232–233°. [h] Nitrate m. p. 165°. [i] Oxime m. p. 242–243°. [j] Oxime m. p. 139–140°.

yields of 7-nitro-2-acetylfluorene from 2-nitrofluorene, acetyl chloride, and aluminum chloride in nitrobenzene solvent. The purified 7-nitro-2-acetylfluorene was readily oxidized in glacial acetic acid by sodium dichromate to 7-nitrofluorenone-2-carboxylic acid, m. p. 324° (uncor.). Some controversy existed over the melting point of the acid since Stockton[9] had reported it as melting at 220°, while Broisman[8] had reported the melting point as 233°. Proof of structure of the 7-nitrofluorenone-2-carboxylic acid was established by reduction of the nitro group to the amine and deamination by diazotization and treatment with hypophosphorous acid to yield the known fluorenone-2-carboxylic acid. The nitrocarboxylic acid formed a reddish-orange phenylhydrazone when refluxed with phenylhydrazine in alcohol solution.

An intermediate compound in the oxidation of 7-nitro-2-acetylfluorene was 7-nitro-2-acetylfluorenone which was easily isolated from the 7-nitrofluorenone-2-carboxylic acid by virtue of the insolubility of the former in aqueous potassium hydroxide.

The carboxylic acid was converted to the corresponding 7-nitrofluorenone-2-carbonyl chloride, by reaction with thionyl chloride. Esterification of 7-nitrofluorenone-2-carbonyl chloride with several amino alcohols was carried out in very good yields using inert solvents such as chlorobenzene or toluene. The resulting 7-nitrofluorenone-2-carboxylates were reduced satsifactorily to the corresponding alkylamine esters of 7-aminofluorenone-2-carboxylic acid by means of ammonium hydroxide and hydrogen sulfide. The reaction was accompanied by some tar formation which accounted for the erratic yields. The esters of the nitro- and aminofluorenonecarboxylic acids that were prepared are listed in Table I.

Experimental

7-Nitro-2-acetylfluorene.—To a well-stirred suspension of 97 g. (0.46 mole) of crude 2-nitrofluorene[10] were added 500 cc. redistilled nitrobenzene and 113 g. (0.85 mole) of anhydrous aluminum chloride. A deep red color developed as the suspension was warmed to 40°. During a period of one-half hour, 40 cc. (0.56 mole) of acetyl chloride was added dropwise, the temperature being maintained between 40 and 50°. The mixture was stirred and warmed to 50–55° for an additional four hours. The dark green mixture was hydrolyzed by pouring it portionwise into a strongly stirred mixture of 20 cc. of hydrochloric acid, 200 g. of ice and 800 cc. of water. The water layer was poured off and the oily precipitate was extracted twice with 750 cc. of ether to remove the excess nitrobenzene. The residue was collected on a Büchner funnel, pressed dry, and recrystallized from glacial acetic acid. The straw colored needles melted at 228°; the yield was 62.8%.

Anal. Calcd. for $C_{15}H_{11}O_3N$: N, 5.53. Found: N, 5.50.

7-Nitrofluorenone-2-carboxylic Acid.—To a solution of 30 g. (0.12 mole) of 7-nitro-2-acetylfluorene in 2000 cc. of glacial acetic acid was added, in small quantities, 150 g. (0.50 mole) of powdered sodium dichromate. After refluxing the mixture for two hours, 100 cc. of acetic anhydride was added slowly after which refluxing was continued for four hours longer. The reaction mixture was poured into 2.5 gallons of hot water, into which was passed live steam to coagulate the oxidation products. The suspension was filtered, washed with very dilute acid and pressed dry. The entire solution was warmed with 1000 cc. of 0.5% potassium hydroxide and filtered while hot. The filtrate was acidified with an excess of 1:1 hydrochloric acid, and the heavy yellow flocculent precipitate of the carboxylic acid was isolated by filtration, washed with water and recrystallized from glacial acetic acid. The alkali insoluble material was reoxidized with 75 g. of sodium dichromate in 1200 cc. of glacial acetic acid, yielding an additional amount of the acid after treatment in the same manner as the first oxidation reaction solution. The total crude product obtained from the oxidation was 20 g. (62.5% theoretical). Two recrystallizations from glacial acetic acid yielded a yellow crystalline product which melted at 322–324°.

Anal. Calcd. for $C_{14}H_7O_5N$: N, 5.20. Found: N, 5.14.

A solution of 1.0 g. of 7-nitrofluorenone-2-carboxylic

---

(9) M. R. Stockton, Doctor of Philosophy thesis, University of Cincinnati, 1943.

(10) Kuhn, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Vol. XIII, 1943, p. 74.

acid in 100 cc. of ethyl alcohol was refluxed for fifteen minutes with 2.0 cc. (2.19 g., 0.02 mole) of phenylhydrazine. The mixture was cooled in an ice-bath and water was added dropwise to the solution until 100 cc. had deen added. The resulting precipitate was isolated by filtration and recrystallized from ethyl alcohol. The recrystallized phenylhydrazone melted at 264–265°.

7-Aminofluorenone-2-carboxylic Acid.—To a suspension of 10 g. (0.04 mole) of 7-nitrofluorenone-2-carboxylic acid in 600 cc. of ethyl alcohol was added 80 cc. of concentrated ammonium hydroxide. The suspension was heated to its boiling point and hydrogen sulfide gas was passed into it for one hour during which time the solid material dissolved and the solution took on a dark red color. The solution was boiled an additional half hour to remove excess hydrogen sulfide and ammonia. After cooling the solution it was filtered and the filtrate poured into 800 cc. of water. Acidification of the aqueous solution with 1:5 hydrochloric acid gave a dark red solid. The crude product was dissolved in 400 cc. of hot 2% potassium hydroxide and 0.5 g. of Darco. After filtration the hot filtrate was acidified by dropwise addition of 20 cc. of hydrochloric acid (1:5), the product separating as a precipitate. The resulting dark red powder did not melt below 360°. The yield was 7.5 g. (85%).

Anal. Calcd. for $C_{14}H_9O_3N$: C, 70.29; H, 3.77; N, 5.85. Found: C, 69.89; H, 4.00; N, 5.73.

7-Nitro-2-acetylfluorenone.—The alkali insoluble material from the oxidation described above was recrystallized twice from glacial acetic acid and once from xylene. The product formed as fine lemon-yellow needles, melting sharply at 234°.

Anal. Calcd. for $C_{15}H_9O_4N$: N, 5.24. Found: N, 5.08.

7-Nitrofluorenone-2-carbonyl Chloride.—Fifteen grams (0.056 mole) of crude 7-nitrofluorenone-2-carboxylic acid was refluxed with 400 g. of redistilled thionyl chloride for twelve hours, provision being made to trap the escaping sulfur dioxide and hydrochloric acid. The excess thionyl chloride was removed by distillation and the residue recrystallized from toluene or chlorobenzene. The yield of acid chloride was 15.0 g. (99 + % theoretical). The bright yellow crystalline compound melted at 246–248°.

Anal. Calcd. for $C_{14}H_6O_3NCl$: N, 4.87; Cl, 12.34. Found: N, 5.16; Cl, 12.42.

β-Diethylaminoethyl-7-nitrofluorenone-2-carboxylate Hydrochloride.—This preparation is typical of the method used for the preparation of the esters used in this work. To a solution of 6.5 g. (0.023 mole) of 7-nitrofluorenone-2-carbonyl chloride in 350 cc. of dry chlorobenzene in reflux was added dropwise over a period of one half hour a solution of 3.2 cc. (2.8 g., 0.025 mole) of β-diethylaminoethanol in 25 cc. of chlorobenzene. The hydrochloride of the alkylamine ester separated as a yellow crystalline solid which was collected and washed twice with 30-cc. portions of ether. The yield of the crude product was 8.5 g. (92.4 %). A portion, recrystallized from methyl alcohol, melted with decomposition at 230–232°.

The free base, prepared by dropwise addition of sufficient ammonium hydroxide to neutralize the hydrochloride, separated as bright yellow crystals which, recrystallized from a methyl alcohol–water mixture, melted at 134–136°.

Anal. Calcd. for $C_{20}H_{20}O_5N_2$: N, 7.61. Found: N, 7.67.

The nitric acid salt was prepared as a finely crystalline, water insoluble, yellow material by adding 5 cc. of dilute nitric acid (6 *N*) to a solution of 0.1 g. of the ester hydrochloride in 250 cc. of hot water. The product melted sharply at 214–215°.

Anal. Calcd. for $C_{20}H_{21}O_8N_3$: N, 9.75. Found: N, 10.03.

β-Diethylaminoethyl-7-aminofluorenone-2-carboxylate.—Six grams (0.015 mole) of β-diethylaminoethyl-7-nitrofluorenone-2-carboxylate was dissolved in 400 cc. of hot ethyl alcohol and 8 cc. of ammonium hydroxide. Hydrogen sulfide was bubbled into the hot solution over a period of one half hour, the solution changing to a dark red color. A solution of 50 cc. of 12 *N* hydrochloric acid in 400 cc. of water was added to the warm reaction mixture. The hot acid solution was filtered twice to remove free sulfur and then made alkaline with 6 *N* ammonium hydroxide and allowed to stand overnight. The bright red, finely divided precipitate which separated was recrystallized from an alcohol–water solution yielded 2.5 g. (50% theoretical) of the amine as red needles which melted at 215–216°.

Anal. Calcd. for $C_{20}H_{22}O_3N_2$: N, 8.28. Found: N, 8.02.

Summary

1. A series of alkylamino esters of 7-nitrofluorenone-2-carboxylic acid and 7-aminofluorenone-2-carboxylic acid have been prepared for evaluation as topical anesthetics or for possible antispasmodic action.

2. The preparation of pure 7-nitrofluorenone-2-carboxylic acid and the proof of its structure has resolved the question of its correct melting point.

CINCINNATI 21, OHIO RECEIVED MARCH 17, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Lower Iodides of Boron

BY WALTER C. SCHUMB, E. LEE GAMBLE AND MARIO D. BANUS

Although numerous points of resemblance may be observed in the chemistry of boron and silicon compounds, up to the present time a striking exception in the behavior of boron has been the lack of halides other than the well-known series of trihalides, BX_3. Except for the compound B_2Cl_4, first reported by Stock,[1] who succeeded in isolating a drop of the unstable liquid, no binary halides with B–B bonds appear to have been prepared. From the known instability of Stock's B_2Cl_4, it seemed reasonable to believe that synthetic methods operating at elevated temperatures would probably fail to yield such compounds as B_2Br_4 or B_2I_4 unless some means of "freezing-out" the desired products could be resorted to, whereby their decomposition might be held in check.

Preliminary experiments in which it was planned to prepare a lower iodide of boron, such as B_2I_4, by reduction of boron triiodide under conditions favoring the prevention of decomposition of the desired product, included the use of the "hot–cold" tube devised by St. Claire Deville[2]

---

[1] Stock, Brandt and Fischer, *Ber.*, 58B, 653 (1925).

[2] St. Claire Deville, "Leçons sur la Dissociation, Leçons de Chemie," Soc. Chim. de Paris, 1864–1865.