(dec.),[1] 149–151° (dec.),[2] 150–151° (dec.),[3] 139–141° (dec.),[4] and 220° (dec.)[5,6] have been reported. The capillary melting point is influenced by the rate of heating[7] and the temperature of the bath. To avoid these effects the melting point apparatus of Dennis and Shelton[8] was used in this work. With this apparatus, the melting point is the lowest temperature of instantaneous melting. The grand average of five melting point values on each of five samples was 240°, with a standard error of approximately ±1°. (Capillary melting points of about 147° (dec.) were obtained by immersion in a bath at 145° with a rate of heating of 3° per minute.) The poor precision is caused by inadequate contact with the surface of the bar and by convection currents which disperse fine particles into the air. With samples of optimum particle size range, the lowest temperature of instantaneous melting obtained by testing at progressively increasing temperatures was the same as the lowest temperature of instantaneous melting obtained by testing at progressively decreasing temperatures.

These conclusions may be reached: (1) The most nearly correct melting point is about 240°. (2) The melting point is not a good criterion of purity. (3) The melting point reported by Seidel and Bittner of 220° (dec.) was probably obtained with aminosalicylic acid, rather than with the hydrochloride, as some have assumed,[9] and must have been taken by some technique involving the observation of instantaneous melting.

(1) Kolbe, U. S. Patent 427,564; German Patent 50,835.
(2) Erlenmeyer, *et al.*, *Helv. Chim. Acta*, 31, 988 (1948).
(3) O'Connor, *Lancet*, 254, 191 (1948).
(4) Whittet, *ibid.*, 254, 268 (1948).
(5) Seidel, *Ber.*, 34, 4351 (1901).
(6) Seidel and Bittner, *Monatsh.*, 23, 415 (1902).
(7) McAnnally and Seymour, *Lancet*, 254, 303 (1948).
(8) Dennis and Shelton, THIS JOURNAL, 52, 3128 (1930).
(9) Sheehan, *ibid.*, 70, 1665 (1948).

CALCO CHEMICAL DIVISION
AMERICAN CYANAMID COMPANY
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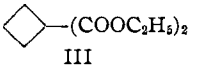
A New Synthesis of Diethyl 1,1-Cyclobutanedicarboxylate

BY HARRY M. WALBORSKY[1]

The standard method for preparation of diethyl 1,1-cyclobutanedicarboxylate (III), the reaction between trimethylene bromide and diethyl malonate, gives a yield of approximately 25%.[2] The major product is tetraethyl 1,1,5,5-pentanetetracarboxylate formed by further reaction of the intermediate II with diethyl malonate. To eliminate this side reaction, II was independently prepared by the addition of hydrogen bromide to diethyl allylmalonate (I)[3] and then cyclized to III by treatment with sodium ethylate. The over-all yield from I is about 50%.

$$CH_2{=}CHCH_2CH(COOC_2H_5) \xrightarrow[\text{Peroxide}]{\text{HBr}} BrCH_2CH_2CH_2CH(COOC_2H_5)_2 \xrightarrow{\text{NaOEt}}$$

I II



III

Experimental

Diethyl γ-Bromopropylmalonate (II).—A solution of 67 g. of I in an equal volume of toluene containing a small amount of dibenzoyl peroxide was saturated at 0° with gaseous hydrogen bromide. After removal of excess hydrogen bromide and toluene, the residue was distilled *in vacuo*. A fraction, 75 g. (79%), boiling over a 6° range was collected, b. p. *ca.* 140° at 5 mm., $n^{28.5}D$ 1.455. A portion of this material was allowed to stand for twelve hours with an excess of trimethylamine in benzene and the resulting quaternary salt was converted[4] to the picrate, m. p. 102.5–103.5° from ethanol.

Anal. Calcd. for $C_{19}H_{28}N_4O_{11}$: C, 46.7; H, 5.8. Found: C, 47.0; H, 5.9.

An authentic sample[5] of II, b. p. 139–141° at 5 mm., $n^{28.5}D$ 1.455, gave the same quaternary picrate, m. p. and mixed m. p. 102.5–103.5°.

Diethyl 1,1-Cyclobutanedicarboxylate (III).—To the refluxing solution of 5.8 g. of sodium dissolved in 600 ml. of absolute ethanol was added slowly with stirring 72 g. of II. After refluxing for two and one-half hours the solvent was removed *in vacuo* and the residue was treated with water; the product was taken up in ether and distilled at 23 mm., b. p. 119–126°, $n^{26}D$ 1.433,[6] yield 38 g. (74%).

This work was performed under a contract between the Office of Naval Research and the California Institute of Technology.

(1) Present address: Chemistry Department, Ohio State University.
(2) Heisig and Stodola, "Organic Syntheses," **23**, 16 (1943).
(3) Linstead and Rydon, *J. Chem. Soc.*, 582 (1933), report the preparation of I in 80% yield from allyl bromide and diethyl malonate.
(4) *Cf.* Howton, THIS JOURNAL, **69**, 2555 (1947), footnote 5.
(5) Willstätter and Ettlinger, *Ann.*, **326**, 99 (1903).
(6) This is the value given in the literature for III, Gladstone cited by Perkin, *J. Chem. Soc.*, **51**, 4 (1887).

GATES AND CRELLIN LABORATORIES OF CHEMISTRY
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PASADENA 4, CALIFORNIA RECEIVED JANUARY 31, 1949

The Synthesis of Some 4-Alkoxy-7-chloroquinaldic Acid Derivatives

BY ALEXANDER R. SURREY

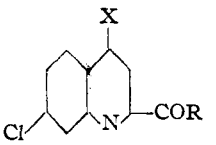
Although the 2-alkoxycinchoninic acid derivatives[1] are known to possess strong local anesthetic activity, the corresponding quinoline derivatives in which substituents in the 2- and 4-positions are interchanged have not been reported in the literature. Inasmuch as a suitable starting material, ethyl 7-chloro-4-hydroxyquinaldate, was available in this Laboratory, it seemed desirable to prepare the 4-alkoxy derivatives in order to compare their physiological activity with the corresponding 2-alkoxy compounds.

Accordingly, 7-chloro-4-hydroxyquinaldic acid and its ethyl ester were treated with phosphorous oxychloride to give the corresponding 4-chloro compounds, I and II (Table I), respectively.

(1) Miescher, *Helv. Chim. Acta*, **15**, 163 (1932).

TABLE I

QUINALDIC ACID DERIVATIVES,



No.	X	R	M. p., °C.[a]	Formula	Analyses, % Calcd.	Found
I	Cl	OH	182–183	$C_{10}H_5Cl_2NO_2$	N, 5.79	5.76
II	Cl	OC_2H_5	77.5–78.5	$C_{12}H_9Cl_2NO_2$	N, 5.19	5.11
III	Cl	NH_2	288–290	$C_{10}H_6Cl_2N_2O$	N, 11.62	11.83
IV	OC_2H_5	NH_2	201–202	$C_{12}H_{11}ClN_2O_2$	C, 57.49	57.44
					H, 4.42	4.21
V	Cl	$N(C_2H_5)_2$	107–108	$C_{14}H_{14}Cl_2N_2O$	Cl, 23.86	23.80
VI	Cl	[b]	69–70[c]	$C_{16}H_{18}Cl_2N_2O_2$	Cl, 20.78	20.60
VII	Cl	[d]	82–83[e]	$C_{16}H_{18}Cl_2N_3O$	N, 12.35	12.52
VIII	OC_2H_5	[d]	65–66[f]	$C_{18}H_{24}ClN_3O_2$	N, 12.01	12.29
IX	OC_3H_7-*n*	[d]	66–67	$C_{19}H_{26}ClN_3O_2$	N, 11.55	11.31
X	OC_4H_9-*n*	[d]	68–69	$C_{20}H_{28}ClN_3O_2$	N, 11.12	10.80

[a] All melting points are uncorrected. [b] R = $OCH_2CH_2N(C_2H_5)_2$. [c] Hydrochloride from dilute hydrochloric acid, m. p. 233–234°; calcd. N, 7.42; found: N, 7.35. [d] R = $NHCH_2CH_2N(C_2H_5)_2$. [e] Hydrochloride from isopropyl alcohol, m. p. 230–231°; calcd. N, 11.16: Cl^-, 9.41; found: N, 11.20; Cl^-, 9.36. [f] Hydrochloride from alcohol–acetone–ether mixture, m. p. 178–179° d.; calcd. N, 10.88; Cl^-, 9.18; found: N, 11.30; Cl^-, 8.86.

Treatment of either 4,7-dichloroquinaldic acid (I) or its ethyl ester (II) with sodium ethylate failed to give the desired 4-ethoxy derivatives. Similar results were obtained starting with the basic ester, diethylaminoethyl 4,7-dichloroquinaldate (VI). The sodium salt of the free acid, which apparently formed in each instance, was too insoluble to react. However, the basic amide, N-diethylaminoethyl 4,7-dichloroquinaldamide (VII), prepared from the dichloro ester (II) by heating with N,N-diethylethylenediamine, did react with the appropriate sodium alkoxide to give the 4-alkoxyquinaldamides, VIII, IX and X.

Preliminary investigation indicated that N-diethylaminoethyl 7-chloro-4-ethoxyquinaldamide (VIII) had little if any local anesthetic activity at a concentration of 1% when tested on the external canthus of rabbits. Compounds IX and X, the 4-propoxy and 4-butoxyquinaldamides, are too insoluble in the desired *p*H range to be of any practical value as local anesthetics.

Experimental

Preparation of 4,7-Dichloroquinaldic Acid (I) and Ethyl Ester (II).—The appropriate 7-chloro-4-hydroxyquinoline derivative (5 g.) was refluxed for one hour with 30 ml. of phosphorous oxychloride. After cooling, the solution was poured into ice-water and the product was filtered off, washed with water, dried and recrystallized from toluene for I and ethanol for II. The yields were approximately 70%.

Preparation of 4,7-Dichloroquinaldamide (III).—Ammonia was bubbled into a stirred solution of 20 g. of ethyl 4,7-dichloroquinaldate in 200 ml. of absolute ethanol. The crude amide which separated in practically quantitative yield, was recrystallized from butanol.

Preparation of 7-Chloro-4-ethoxyquinaldamide (IV).—Twelve grams of the amide (III) was added to an excess of sodium ethylate in absolute ethanol and refluxed with stirring for two hours. The solid which remained undissolved was filtered off and recrystallized from acetic acid to give 5.5 g. of starting amide. Two grams of material was obtained from the filtrate melting at 190–192°. The product was recrystallized from acetic acid and then from ethanol.

Preparation of 4,7-Dichloro-N-diethylquinaldamide (V) and 4,7-Dichloro-N-(2-diethylaminoethyl)-quinaldate (VI).—The dichloro acid (I) in five volumes of xylene was refluxed with two volumes of thionyl chloride for two hours and the solvent removed *in vacuo*. The residue was suspended in dry benzene and refluxed for one hour with diethylamine (for V) or diethylaminoethanol (for VI) and poured into water. The solution was made alkaline with sodium carbonate solution and extracted with ether. Removal of the ether in the case of V gave the crude diethylamide. For the basic ester (VI) the ether was dried and the hydrochloride prepared. After purification it was converted to the base which was then recrystallized from Skellysolve A.

Preparation of 4,7-Dichloro-N-(2-diethylaminoethyl)-quinaldamide (VII).—A mixture of 56.8 g. of the dichloro ester (II), 35 g. of N,N-diethylethylenediamine and 350 ml. of ligroin (b.p. 100–140°) was refluxed for four hours and the solvent removed by distillation. The residue was dissolved in hot ligroin (b.p. 60–68°), filtered with charcoal, and the filtrate cooled to give 60 g. of crude amide (VII), m.p., 73–76°. The product was purified *via* its hydrochloride and then recrystallized from ligroin (b.p. 28–38°).

Preparation of Compounds VIII, IX and X.—The basic amide, VII (0.04 mole) was added to a solution of sodium (0.05 mole) in 100 ml. of the appropriate alcohol. After refluxing for one-half hour, the solvent was distilled and the residue taken up in water and ether extracted. The ether was dried and removed to yield the crude 4-alkoxyquinolines. The purified products from ligroin (b.p. 28–38°) were obtained in approximately 30% yields.

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The Use of Counter-Current Distribution for the Characterization of Streptomyces Antibiotics[1]

BY E. AUGUSTUS SWART

The search for new antibiotics produced by various species and strains of actinomycetes has often led to the isolation of substances previously

(1) Supported by a grant from the Commonwealth Fund.