[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, VANDERBILT UNIVERSITY SCHOOL OF MEDICINE]

The Preparation of *t*-Butylmalonic Acid and Some of its Derivatives

BY MILTON T. BUSH

Some time ago Abderhalden and Rossner[1] apparently obtained a small amount of ethyl *t*-butylmalonate from sodioethylmalonate and *t*-butyl bromide. Recently Dox and Bywater,[2] in a report on tertiary alkyl barbituric acids, described this same preparation and reported a yield of 6% of the substituted ester. They converted this to a barbituric acid having m. p. 231°. Their effort to obtain ethyl *t*-butylethylmalonate by a similar method, from ethyl ethylmalonate, was apparently less successful, since the corresponding barbituric acid was obtained, if at all, in an admittedly grossly impure state.

Since there should be, theoretically, many pharmacologically interesting derivatives of C-*t*-butylbarbituric acid, it seemed desirable to investigate other methods of obtaining *t*-butylmalonic acid. Morton and Fallwell[3] have shown that carbonation of the product of the interaction of phenylsodium and sodium caproate gives a 15–20% yield of *n*-butylmalonic acid. I have found that a similar procedure produces better than a 45% yield of *t*-butylmalonic acid from sodium *t*-butylacetate.

Several derivatives of the malonic acid have been prepared, including the monosubstituted (pharmacologically inactive) barbituric acid. With larger amounts of starting material it is hoped that there can be obtained a number of 5,5-disubstituted barbituric acid derivatives which should have interesting hypnotic properties.

Experimental

t-Butylmalonic Acid.—The procedure of Morton and Fallwell[3] was modified somewhat. The sodium (21 g.) was powdered under toluene, which was then siphoned off and the metal washed with several portions of benzene. Forty-five ml. of benzene and 9.0 g. of *t*-butylacetic acid[4] dissolved in 10 ml. of petroleum ether were added. To make good stirring possible, more petroleum ether (43–65°) was added from time to time (total 95 ml.) during an hour. The addition of *n*-amyl chloride (30 g.) was likewise accompanied by the addition of petroleum ether (80 ml.) during one and one-half hours, and the stirring was continued for another hour. The petroleum ether was distilled off until the inside temperature reached 64°. An addition of 50 ml. of benzene was made and 25 cc. more distillate collected. The reaction mixture was then refluxed with stirring at 70–75° during four hours, allowed to cool and treated with carbon dioxide. During this reaction 40 ml. of petroleum ether–benzene was added to the reaction mixture to facilitate stirring. Carbonation was complete in forty minutes at 44–63°. The mixture was first treated with alcohol to decompose excess sodium, and finally with water, and by the isolation procedure of Morton and Fallwell[3] there was obtained 7.19 g. of crude malonic acid. By dissolving in water, decolorizing the warm solution with norit, extracting with ether, and finally crystallizing from ether–benzene, the acid was obtained as colorless, massive prisms; very soluble in water and in ether, slightly soluble in benzene. The yield of pure product was 45%, based on the *t*-butylacetic acid. It had m. p. 155–157° (corr.) with gas evolution.

Neutralization equivalent. Calcd.: 80.0. Found: 80.9.

The relationship of this malonic acid to the original *t*-butylacetic acid was ascertained as follows. The malonic acid (160 mg.) was decarboxylated by heating at 170–180° for fifteen minutes, the product treated with thionyl chloride, and finally converted to the amide with concentrated aqueous ammonia. The mixture was extracted with ethyl acetate, this solution evaporated to dryness, and the product crystallized from anhydrous ethyl acetate–petroleum ether. The purified amide (62 mg., 54% yield) melted at 131–132.5° (corr.), and the mixed m. p. with the amide prepared from *t*-butylacetic acid was the same.

By the procedure of Abderhalden and Rossner,[1] 140 mg. of the malonic acid was converted to the bromomalonic acid. Recrystallization from ether–benzene gave 66 mg. of white crystals having m. p. 180–183° (corr.) with evolution of gas. (Abderhalden and Rossner obtained a substance decomposing at 183°.) The decantate from this was evaporated, and the crude bromomalonic acid remaining (133 mg.) was decarboxylated, converted to the acid chloride and finally to α-bromo-*t*-butylacetamide. After five recrystallizations from ethyl acetate–petroleum ether, there remained 32 mg. (30% yield) of material having m. p. 136.5–138° (corr.). The mixed m. p. with an authentic specimen[4] was the same.

***t*-Butylmalon-N,N'-diethylamide.**—The malonic acid was allowed to react overnight with thionyl chloride, the excess reagent evaporated at 70° and the crude *t*-butylmalonyl chloride (132 mg.) treated with 1 ml. of Eastman 33% aqueous ethylamine. The amide was obtained by extraction with ethyl acetate and purified by three recrystallizations from acetone: yield 44 mg. (31%) having m. p. 151.3–151.7° (corr.).

Anal. Calcd. for $C_{11}H_{22}O_2N_2$: N, 13.07. Found: N, 12.86.

***t*-Butylbarbituric Acid.**—The malonic acid (320 mg.) was converted to the acid chloride, thence to the ethyl

(1) Abderhalden and Rossner, *Z. physiol. Chem.*, **163**, 177 (1927).
(2) Dox and Bywater, THIS JOURNAL, **58**, 731 (1936).
(3) Morton, Fallwell, Jr., and Palmer, *ibid.*, **60**, 1428 (1938).
(4) Supplied by the Mallinckrodt Chemical Works. The preparation of this substance and many of its derivatives is described by Homeyer, Whitmore and Wallingford, THIS JOURNAL, **55**, 4209 (1933).

ester. After removal of hydrogen chloride and excess alcohol, the crude ester was heated with 70 mg. of urea and 3.6 ml. of sodium ethylate solution (1.73 *N*) at 80° for twenty-two hours. The product was isolated by ether extraction of the acidified water solution, and after recrystallization from 5 to 6 ml. of water (the hot solution was decolorized with 10 mg. of purified norit), there was obtained 139 mg. (38% yield) of dry, white crystals. The melting point was 235.5–236.8° (corr.) (Dox and Bywater[2] give m. p. 230–231°). In a 23-g. mouse, an intravenous dose of 800 mg. per kg. (as sodium salt in 1.3 cc.) produced no observable effect for at least an hour after the injection. As expected, this confirmed the finding of Dox and Bywater.[2]

Anal. Calcd. for $C_8H_{12}O_3N_2$: N, 15.21. Found: N, 15.03.

Summary

Pure *t*-butylmalonic acid has been obtained in moderately good yield from *t*-butylacetic acid. That the *t*-butyl group is present in the malonic acid has been shown by conversion of the latter to known derivatives of *t*-butylacetic acid. Two derivatives of *t*-butylmalonic acid have been characterized.

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Piperidinium Analogs of Choline and its Homologs. Onium Compounds. XX[1]

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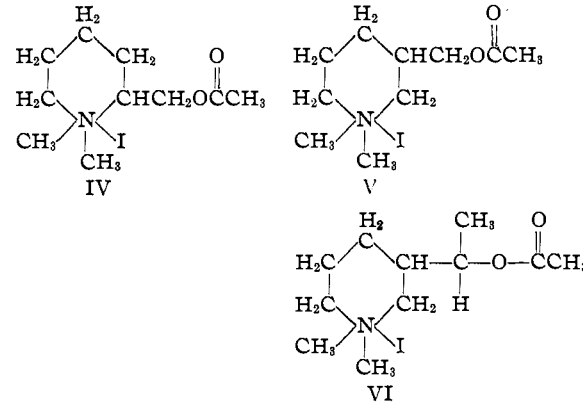
The pronounced parasympathetic activity of arecoline and several derivatives of nicotinic and nipecotic acids[3–5] has suggested the preparation of heterocyclic derivatives analogous to acetylcholine and its homologs for investigation of their effects on the autonomic nervous system. In previous publications, the synthesis[6,7] and pharmacological effects[3,8] of a number of quaternary heterocyclic ethers and esters have been described. Compounds of this type, unsubstituted on the cyclic carbon atoms, have acted on the autonomic nervous system, producing an acetylcholine effect, a nicotine effect or both.

In continuation of this investigation, the preparation of ethers and esters of the choline type, substituted on the cyclic carbon atoms was begun.[7] In this paper, the preparation and brief description of the physiological properties of piperidinium salts of the choline ester type are given. These compounds contain the methylated quaternary nitrogen present in choline; the carbon chain of the latter compound is contained partly in the heterocyclic ring and partly in carbinol groups substituted in the ring.

Ethyl picolinate[9] and ethyl nicotinate[10] were reduced, using sodium and alcohol, to α-piperidylcarbinol (I) and β-piperidylcarbinol (II), respectively, by the method previously applied by Sandborn and Marvel[11] to the synthesis of the β-carbinol. The α-carbinol, a new compound, was obtained in 29% yield. Sodium and alcohol reduction, rather than the high pressure catalytic reduction methods developed by Adkins and co-workers, was used because the latter have reported alkylation of the ring nitrogen atom, undesirable in this case.[12] β-Piperidylmethylcarbinol (III) was prepared by the catalytic reduction of β-acetylpyridine according to the method of

CHART I



(1) This paper is being published, following the death of Professor Renshaw, by his collaborators. Paper XIX, THIS JOURNAL, **60**, 1765 (1938).

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(3) Hunt and Renshaw, *J. Pharmacol.*, **35**, 75 (1929).

(4) Loewy and Wolffenstein, *Therap. Gegenwart.*, **61**, 287 (1920).

(5) Haramaki, *Biochem. Z.*, **130**, 267 (1922).

(6) Renshaw and Shand, THIS JOURNAL, **54**, 1474 (1932).

(7) Renshaw and Conn, *ibid.*, **59**, 297 (1937).

(8) Hunt and Renshaw, *J. Pharmacol.*, **37**, 177 (1929).

(9) Camps, *Arch. Pharm.*, **240**, 346 (1903).

(10) LaForge, THIS JOURNAL, **50**, 2479 (1928).

(11) Sandborn and Marvel, *ibid.*, **50** 565 (1928).

(12) Folkers and Adkins, *ibid.*, **54**, 1145 (1932).