[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Preparation of the Monocholine Ester of Succinic Acid and Some Related Derivatives

BY ARTHUR P. PHILLIPS

RECEIVED APRIL 28, 1953

Because of the wide interest in the useful curare-like drug, succinylcholine,[1] and its fate in the body, the related monocholine ester of succinic acid has been synthesized by several routes. A number of derivatives also have been prepared.

Earlier a series of quaternary ammonium salts of bis-dialkylaminoethyl esters of dicarboxylic acids was reported.[2,3] These had been made as curare substitutes and several members of the series were found to have powerful neuromuscular blocking action. The most active member of the series, succinylcholine, has now found widespread application as a versatile curare-like drug. Much of the usefulness of succinylcholine derives from the fact that although it is a very potent neuromuscular blocking agent, it has a short duration of action, presumably because it is destroyed rapidly in the body. This brief period of action and rapid destruction makes it a very desirable product for several reasons: (1) for many purposes for which curare-like drugs are used a short period of relaxation is desired and a rapid recovery interval is much to be hoped for; (2) when a long lasting neuromuscular block is needed this can easily be accomplished with succinylcholine by continuous intravenous administration, when almost any depth and duration of paralysis can be attained, followed by rapid recovery after succinylcholine administration is stopped. Long action can likewise be achieved by concurrent administration of succinylcholine and any one of a number of its potentiators described previously.[4,5]

The short duration of action of succinylcholine was tentatively attributed to its rapid destruction in the body by cholinesterases,[2] based on the noted similarity in structure of this curare-like agent with two molecules of acetylcholine coupled at the α-position of the acetyl group. Some work on the enzymatic hydrolysis of succinylcholine is expected to be published in the near future.[6] Consideration of the possible fate of this drug in the body made it appear of interest to prepare the monocholine ester of succinic acid, so that it could be compared with the bis ester for its physiological activity and for its rate of destruction, presumably hydrolytic, both *in vivo* and *in vitro*.

Three different synthetic routes to the monocholine ester of succinic acid were explored (see Chart I): (1) β-dimethylaminoethanol was treated with succinic anhydride to give the monodimethylaminoethyl ester of succinic acid, which was then alkylated with methyl iodide (or other alkyl halide if desired), (2) choline iodide reacted with succinic anhydride to give the desired product at once and (3) half hydrolysis of succinylcholine iodide was attempted.

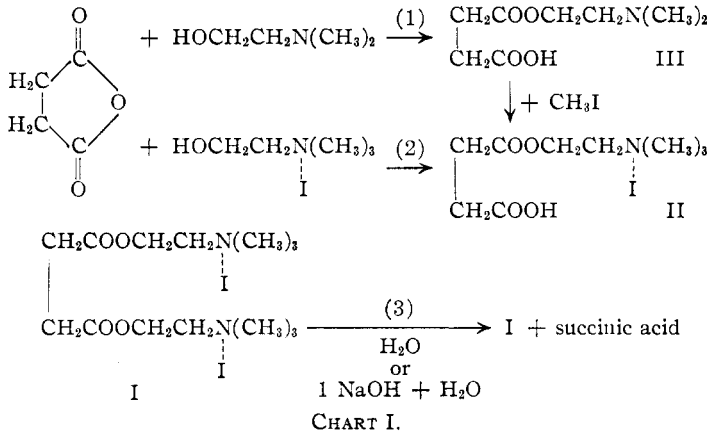

CHART I.

The first two routes each gave the product II easily and in good yield. Several attempts at half hydrolysis of I have so far given no isolable II, the products actually obtained depending on the conditions used. When I was heated in concentrated aqueous solution for several hours at 100° it was recovered unchanged in better than 95% yield. When equimolar amounts of I in water (pH 3.5–4) and sodium hydroxide (pH >11) were heated for five minutes at 100° (pH now 6–7) rapid hydrolysis occurred (evidenced by the rapid drop in pH) but addition of excess acetone gave back 30–40% of the starting compound I unchanged. To a concentrated solution of I in three volumes of water at 100° (pH 3.5–4) a 10% aqueous solution of sodium hydroxide (pH > 11) containing one molar equivalent of alkali was added dropwise over 15–20 minutes. The pH of the reaction mixture rose to 7 upon the first addition of alkali, and remained at 7 thereafter even when more alkali was added. When this reaction was worked up about 35–40% of the starting I was recovered unchanged; about 30–35% of the starting I was recovered as succinic acid, and a corresponding amount of sodium iodide was isolated.

These results suggest the over-all hydrolysis between equimolar amounts of succinylcholine iodide (I) and sodium hydroxide in which one mole of I has reacted with two moles of alkali to give disodium succinate, two moles of choline iodide, while leaving nearly one mole of I unchanged.

If this process is the principal, but not necessarily the exclusive, hydrolysis route it would indicate that the second ester grouping of I is hydrolyzed somewhat more rapidly than the first one. According to a simple analysis of the alkaline hydrolysis of dicarboxylic esters, in which the carboxyl groups

(1) Succinylcholine chloride has been assigned the brand name Anectine by Burroughs Wellcome & Co., Inc., U. S. A.

(2) A. P. Phillips, THIS JOURNAL, **71**, 3264 (1949).

(3) J. C. Castillo and E. J. de Beer, *J. Pharmacol. Exp. Therap.*, **99**, 458 (1950).

(4) A. P. Phillips, THIS JOURNAL, **73**, 5822 (1951).

(5) A. P. Phillips, *ibid.*, **74**, 4320 (1952).

(6) F. Foldes, *et al.*, to be published elsewhere.

are not too widely separated to affect one another, one might expect the negative charge formed by hydrolysis of the first carboxyl to repel attack by a second negative ion, such as OH^-, on the second carboxyl of the half-hydrolyzed material. This should make the second carboxyl more difficult to hydrolyze than the first, and should thus facilitate half hydrolysis to give II. This analysis is analogous to that used to interpret the difference in acidic dissociation constants of the two acidic groups in dibasic acids, such as dicarboxylic acids, again subject to the condition that the two functional groups under consideration be not too widely separated.

Thus the electrostatic charge of the first carboxylate anion would tend to make the loss of the second proton from succinic acid more difficult than the first. Likewise attack by a negative or electron rich particle, such as OH^-, etc., on the half-ester molecule ion should be repelled by the negative charge already present, thus making hydrolysis of the second carboxyl more difficult than the first.

In the few rough attempts to obtain the half-hydrolysis product II from I by aqueous or alkaline hydrolysis, a consideration of the nature and solubilities of the starting substance and the various possible hydrolysis products, II, choline iodide, succinic acid and sodium iodide reveals that the isolation and separation of II might be a difficult problem. If half hydrolysis went exclusively then isolation of II might have been accomplished readily. Thus not the lack of easy isolation of II but rather the recovery of considerable amounts of unchanged I is the interesting discovery here. This unexpected result, involving hydrolysis of the second carboxyl at apparently a faster rate than the first, can be accounted for in two or more possible ways. (1) Perhaps in the hot, concentrated aqueous solutions, chosen to facilitate subsequent isolation of reaction products, the theoretical interpretations outlined above would not hold, and one might get nearly simultaneous hydrolytic cleavage of both the first and second ester groups. This could account for all the alkali being consumed before all the diester had been attacked, leaving some intact I. (2) A more tempting explanation would entail the intramolecular participation of the initially formed carboxylate ion in making easier the hydrolysis of the second ester group as indicated in Chart II. This intramolecular attack should be sterically feasible.

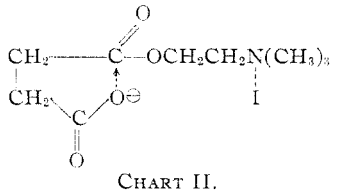

CHART II.

Under certain different conditions it is known that the second ester group is hydrolyzed more rapidly than the first. It has been found in dilute (1%) aqueous solution (of *p*H 3–4) under the same conditions of time and temperature that the half-ester II hydrolyzed about three times as fast as the diester I.[7]

(7) Unpublished results from the Pharmaceutical Development Laboratories of Burroughs Wellcome & Co., Inc., supplied through the courtesy of Drs. E. Beals and M. Trupp.

Further work is planned to elaborate on the mechanism of this and some related hydrolyses.

Pharmacology.—While succinylcholine (I) is a powerful curariform agent of short duration, the monocholine ester of succinic acid (II) is only about $^1/_{30}$ as intense in curare-like activity while having a much longer duration of action than I. This is in agreement with the concept that I is rapidly destroyed in the body by cholinesterases, and thus is of short duration, to give II as the probable principal degradation product. The curare-like activity of II would not show up in the concentrations in which it would appear as a result of the destruction of I. When II is given in high enough concentrations to be effective in producing neuromuscular blocking action, its action lasts longer than that of I, presumably because of less rapid enzymatic breakdown in the body.

Acknowledgment.—The author is indebted to C. H. Ellis, A. L. Wnuck, R. V. Fanelli and E. J. de Beer for the pharmacological results which have been briefly mentioned here. These authors will present a detailed pharmacological report elsewhere. The microanalyses included were supplied by S. W. Blackman.

Experimental

Preparation of the Monocholine Ester of Succinic Acid (II)

Method A. (1) Preparation of Mono-β-dimethylaminoethyl Ester of Succinic Acid (III).—A mixture of 10 g. (0.1 mole) of succinic anhydride, 100 cc. of dry acetone (dried over anhydrous magnesium sulfate) plus 10 g. (0.11 mole) of dimethylaminoethanol was refluxed for three hours on a steam-bath. After filtering off a small amount of a white insoluble precipitate, the acetone filtrates were evaporated to about 30–40 cc. Upon chilling the solution the product separated as white crystals; yield 17 g. (90%). The crystals were purified by several recrystallizations from dry acetone and then melted at 73–74°.

Anal. Calcd. for $C_8H_{15}O_4N$: C, 50.8; H, 8.0. Found: C, 50.5; H, 8.0.

(2) Alkylation of III with Methyl Iodide to Give II.—When 1.9 g. (0.01 mole) of III in 50 cc. of dry acetone was refluxed for 24 hours with 2–3 cc. (excess) of methyl iodide there was obtained 3 g. (90%) of white insoluble crystals. This product was purified by recrystallization from methanol–acetone–ether mixtures, m.p. 157–158°.

Anal. Calcd. for $C_9H_{18}O_4NI$: C, 32.6; H, 5.5. Found: C, 32.8; H, 5.6.

In a similar way III reacted with ethyl iodide and *n*-propyl iodide to yield these higher alkiodides related to II.

The ethiodide analogous to II was obtained in 60–70% yield under the conditions employed for the preparation of II above. After recrystallization from ethanol the white crystals melted at 154–155°.

Anal. Calcd. for $C_{10}H_{20}O_4NI$: C, 34.8; H, 5.8. Found: C, 35.1; H, 5.7.

The *n*-propiodide was obtained similarly in 50–60% yield; after purification by recrystallization from ethanol–ether mixtures it melted at 101–102°.

Anal. Calcd. for $C_{11}H_{22}O_4NI$: C, 36.8; H, 6.2. Found: C, 36.7; H, 6.0.

Method B. Reaction of Choline Iodide with Succinic Anhydride to Give II.—A mixture of 2.3 g. (0.01 mole) of choline iodide (m.p. 269–270°) and 5 g. (0.05 mole, excess) of succinic anhydride was melted and heated for 1–2 hours in a metal-bath at 140°. The reaction mixture was cooled and excess succinic anhydride was washed out of the product with 100 cc. of acetone. After several recrystallizations from methanol–acetone–ether mixtures the pure product, 3.3 g. (100%), melted at 157–158°.

Anal. Calcd. for $C_9H_{18}O_4NI$: C, 32.6; H, 5.5. Found: C, 32.7; H, 5.6.

Method C. Attempted Half Hydrolysis of Succinylcholine (I). (1) **Water.**—A solution of 5.5 g. (0.01 mole) of I in 15 cc. of water was heated for five hours at 100° (initial *p*H 4–5, final *p*H 3.5–4). Upon chilling 4.5 g. (80%) of white crystals separated (unchanged I), m.p. 256–258°. Another 1 g. of I was obtained from the aqueous filtrates upon the addition of excess acetone; m.p. 254–256°. Total recovery of unchanged I was 5.5 g. (100%).

(2) **Aqueous Alkali.**—A solution of 11 g. (0.02 mole) of I in 15 cc. of hot water (80°, *p*H of solution is 4) was mixed quickly with 4.1 cc. of 4.8 *N* aqueous sodium hydroxide solution (= 0.02 mole of NaOH, *p*H < 11). The *p*H of the solution immediately after mixing was 7.5–8. After one or two minutes the *p*H was 7. After ten minutes at 70–80°, 2.5 cc. (4+ g.) of concentrated hydriodic acid solution (sp. g. 1.7) was added to the reaction solution bringing the *p*H to 3–4. Addition of excess acetone (300 cc.) and stirring gave a white crystalline precipitate. When chilled the product was collected by filtration and weighed 4.5 g. (40% of starting I), m.p. 248–252°. After recrystallization from 6 cc. of hot water, 4 g. (35%) of I was recovered melting at 254–256°.

Reworking the aqueous acetone filtrates gave another 0.5–1 g. of I and 1–2 g. of choline iodide.

(3) **Aqueous Alkali.**—To a solution of 5.5 g. (0.01 mole; initial *p*H 4) of I in 15 cc. of water at 100° was added dropwise 5 cc. of 10% aqueous sodium hydroxide (0.01 mole, initial *p*H > 11). Upon the first addition of alkali the *p*H rose at once to 7 and remained at 7 throughout the entire addition of alkali over a 10–15 minute period. When all the alkali had been added the solution was evaporated to dryness *in vacuo* leaving 5.5 g. of white solid insoluble in acetone, and soluble in water. After washing several times with acetone by decantation, the 5.5 g. of white insoluble residue was taken up in 7 cc. of cold water and 1.3 g. (0.01 mole) of hydriodic acid was added to give a *p*H of 2–3. Addition of excess acetone gave 1 g. of white crystals (I) melting at 235–250°. Evaporation of the aqueous acetone filtrates to dryness and addition of more acetone gave another 1 g., m.p. 235–250°. This process was repeated again. The total yield was 2.3–2.5 g. (40–45% of the starting I). After boiling this 2.3–2.5 g. up with hot methanol (in which it was insoluble) there was recovered 2–2.3 g. (35–40%) of the unchanged starting compound I, m.p. 254–256°.

The acetone filtrates from the recovered I were evaporated to dryness and the residue was extracted repeatedly with dry ether. Evaporation of the ether extracts gave 0.35–0.4 g. of tan solid melting at 183–185°. This represents a 30–35% recovery of I as succinic acid.

The ether-insoluble residue weighed about 4 g. When this was extracted several times with acetone, the acetone extracts on evaporation gave 1.5 g. of white crystals melting > 320°. This fraction is mainly sodium iodide.

There remained 2 g. of white solid insoluble in acetone, melting at 121–122° and as yet unidentified; this can be reprecipitated from methanol solution with excess ether.

TUCKAHOE 7, NEW YORK

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Stereochemistry of the 10-Methyl-2-decalols[1]

BY ALLEN S. HUSSEY, HSIANG PENG LIAO AND ROBERT H. BAKER

RECEIVED MAY 2, 1953

cis-10-Methyl-2-*cis*-decalol has been synthesized by stereospecific reactions which leave no doubt of its configuration. An isomer having the same m.p., 66–67°, has been formed by a different route and has been shown by mixed m.p. and m.p. of derivatives to be the epimer, *trans*-10-methyl-2-*cis*-decalol.

The stereochemistry of some of the angularly substituted methyloctahydro- and methyldecahydronaphthalene compounds is of interest because this ring system is found in steroids. We are attempting to establish the configuration of the four geometric isomers of 10-methyl-2-decalol (I) to serve as points of reference for studies of stereochemical aspects of reactions and synthesis procedures pertaining to these compounds. Impure 10-methyl-2-*cis*-decalol has been synthesized previously,[2] but no claims have been made for the configuration of the hydroxyl group. The synthesis and the configuration of two of these isomers, *cis*-10-methyl-2-*cis*-decalol (Ia)[3] and *trans*-10-methyl-2-*cis*-decalol (Ib)[3] are reported here.

The first of these has been synthesized from 2-carbethoxycyclohexanone by a sequence of nine steps, as represented in the equations. The second isomer has been isolated by a chromatographic procedure from a partial reduction of the previously described 10-methyl-2-*cis*-decalone (XVII)[2,4] over platinum oxide. Surprisingly, both isomers melt at 66–67°, but there can be no question of their nonidentity because the m.p. of mixtures may be as low as 48° and the 3,5-dinitrobenzoate derivatives melt at 110–111° and 97–98°, respectively. Both show intense absorptions of almost equal intensities at 2.8, 3.5, 6.9 and 7.3 μ, but there are considerable differences beyond 8.5 μ in the fine structure region.

The assignment of a *cis–cis* configuration to Ia is based upon the following evidence. The keto-ester III was converted to 9-*cis*-decalincarboxylic acid (IV) by Wolff–Kishner reduction; thence by lithium aluminum hydride reduction of IV and then of the *p*-toluenesulfonate VI of the carbinol V to the known 9-methyl-*cis*-decalin (VIIIa).[5] For confirmation, VIIa was isomerized to 9-methyl-*trans*-decalin (VIIb).[5] A *cis* relationship of methyl and hydroxyl in Ia is a consequence of the requirement for a *cis* relationship of carboxyl to hydroxyl in the hydroxyacid IX to permit lactone formation in the precursor VIII.

A *trans–cis* configuration can be assigned to Ib because the parent 10-methyl-2-*cis*-decalone (XVII) from which it is derived by catalytic hydrogenation, has been demonstrated to have a *cis* ring fusion.[4] Therefore, Ib must differ from Ia only in the configuration at C-2.

(1) This research was made possible by a special grant from the Research Corporation and, in part, by funds from the Graduate School of Northwestern University.

(2) V. C. E. Burnop and R. P. Linstead, *J. Chem. Soc.*, 720 (1940); R. B. Woodward, THIS JOURNAL, **62**, 1208 (1940).

(3) The relationship of angular and peripheral substituents is expressed as a prefix of the name; the nature of the ring fusion as a prefix to the root of the name.

(4) E. C. du Feu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.*, 53 (1937).

(5) R. P. Linstead and D. C. Hibbit, *ibid.*, 470 (1936); R. P. Linstead, A. F. Milledge and A. L. Walpole, *ibid.*, 1140 (1937).