4. The investigation of the phenol derivatives of aromatic sulfides is being continued in this Laboratory.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

THE MECHANISM OF THE CLEAVAGE OF DIETHYL α,α'-DIBROMO-ADIPATE BY SECONDARY AMINES. A NEW SYNTHESIS OF CYCLOBUTANE DERIVATIVES[1]

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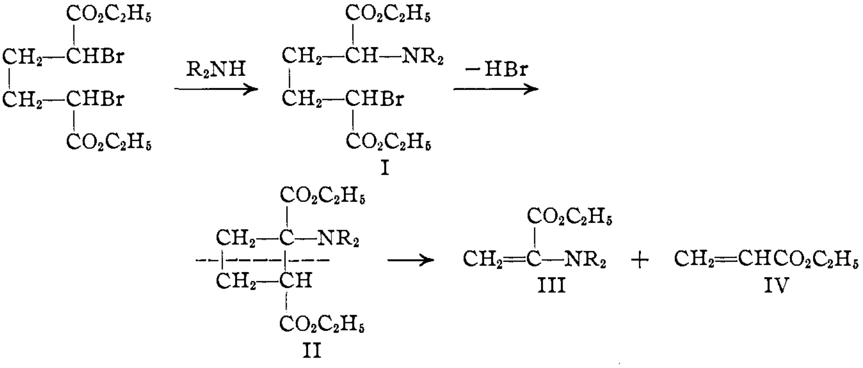
According to evidence presented in previous papers by Fuson[2] and Fuson and Bradley,[3] the cleavage of diethyl α,α'-dibromo-adipate by secondary amines discovered by von Braun, Leistner and Münch[4] probably takes place in the following manner



The first step in the reaction is assumed to be the normal replacement of one of the bromine atoms by a dialkylamino group. The cyclobutane intermediate (II) is then produced by the elimination of a molecule of hydrobromic acid. This aminocyclobutane derivative, being unstable under the conditions of the experiment, undergoes dissociation into ethyl acrylate (IV) and ethyl α-dialkylamino-acrylate (III).

The cleavage products actually isolated are ethyl pyruvate and ethyl β-dialkylaminopropionate and are satisfactorily accounted for by the assumption that the α-dialkylamino-acrylic ester is hydrolyzed to the pyruvic ester and that ethyl acrylate unites with the dialkylamine to give the β-dialkylaminopropionic ester.

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[1] Presented before the Midwest Regional Meeting of the American Chemical Society at Minneapolis, June 9, 1928.

[2] Fuson, THIS JOURNAL, **50**, 1444 (1928).

[3] Fuson and Bradley, *ibid.*, **51**, 599 (1929).

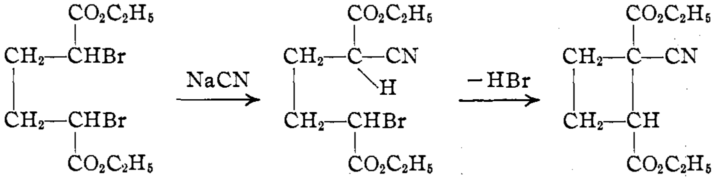
[4] Von Braun, Leistner and Münch, *Ber.*, **59B**, 1950 (1926). See also von Braun, Jostes and Wagner, *ibid.*, **61B**, 1423 (1928).

In an attempt to demonstrate the intermediate existence of II, the authors undertook to prepare it from the corresponding cyclobutanedicarboxylic acid. Although this has as yet not been accomplished, an improved method of synthesis of cyclobutane acids has been worked out which apparently bears out the cleavage mechanism in question. The present article deals with a preparation of the *trans*-1,2-cyclobutanedicarboxylic acid, which not only represents a new type of synthesis but which as intimated above sheds considerable light upon the mechanism of the cleavage of the adipic ester molecule by secondary amines.

It will be noticed that the second step in the mechanism outlined above involves the closure of the cyclobutane ring by the elimination of hydrobromic acid between the two α-carbon atoms. Moreover, since the yield of cleavage products is frequently very high, it is implied by the mechanism in question that the ring closure proceeds smoothly and in good yield. This assumption is at variance with experience inasmuch as closures of the cyclobutane ring by such means have been found to take place with difficulty and generally in small yield.

The authors have made the assumption that the great ease with which the ring closes in this case is due to the presence of the dialkylamino group, which probably activates the hydrogen atom attached to the carbon atom holding the amino group. It is evident that, if the mechanism is the correct one and if the activation of the hydrogen atom is responsible for the ease of the ring closure, it ought to be possible to carry out the synthesis of cyclobutane derivatives in which the dialkylamino group is replaced by some group known to have an activating effect on the hydrogen atoms on the adjacent carbon atom.

Accordingly, to test these speculations, *meso*-diethyl α,α'-dibromoadipate was treated with sodium cyanide. The expected reactions were as follows



V

The cyclobutane derivative formed in this case (V) should differ from that formed when secondary amines are used (II) only in having a cyano group in place of the dialkylamino group. It was to be expected that V would be more stable than II on this account, and the experiment was undertaken with the hope that V might not undergo the cleavage and so could be isolated and studied.

Experiment has verified these predictions. When refluxed with sodium cyanide, diethyl α,α′-dibromo-adipate gives a 70 to 80% yield of a diethyl 1-cyanocyclobutane-1,2-dicarboxylate which has been shown to have the structure represented by V.

The proof of the structure of V was carried out in the following manner. When this compound was hydrolyzed and the resulting mixture of acids was heated above its melting point, carbon dioxide was eliminated and a mixture of acids was obtained which melted at 98–115°. This mixture, which was assumed to contain the *cis*- and *trans*-cyclobutane-1,2-dicarboxylic acids, was treated with concentrated hydrochloric acid—a method used by Perkin[5] to transform the *cis* acid into the *trans* isomer. The product after several recrystallizations from concentrated hydrochloric acid melted at 129–130°.[6] By means of a mixed melting-point determination, this acid was shown to be identical with the *trans*-1,2-cyclobutanedicarboxylic acid obtained by Perkin.[5]

The effect of *amino* groups on the stability of cyclobutane derivatives is being investigated.

Experimental Part

Diethyl 1-Cyanocyclobutane-1,2-dicarboxylate.—This ester was obtained when an absolute alcohol solution of *meso*-diethyl-α,α′-dibromo-adipate (m. p. 67°) was refluxed with an excess of sodium or potassium cyanide on the steam-bath. The cyanide used was of commercial grade which had been finely powdered. Preliminary experiments indicated that sodium cyanide gave somewhat better yields than did potassium cyanide and, accordingly, in subsequent work only the sodium cyanide was used. It was found that the progress of the reaction could be followed by testing the solution from time to time for halogen. When the ester no longer showed a positive test for bromine the reaction was complete. A number of runs were made in which the amount of materials used and the time of treatment were varied. The results are shown in the following table.

Table I

Results of Runs

Run	Refluxing, hours	Abs. ethanol, cc.	NaCN, g.	Bromo-ester, g.	Yield of cyano ester, g.	Yield, %
1	96	15	8	20	8.5	68
2	48	15	8	20	8.6	69
3	48	15	8	20	6.2	50
4	24	25	16	40	19.9	80
5	28	25	16	40	20.0	80
6	30	50	40	100	50.0	80
7	30	25	20	50	22.0	73

There was apparently always a little decomposition, because at the end of the reaction the mixture was dark in color. The dark brown alcohol solution was filtered from the mixture of alkali bromide and unchanged cyanide. The alcohol was removed by distillation at atmospheric pressure and the residual oil was then distilled under

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[5] Perkin, *J. Chem. Soc.*, **65**, 585 (1894).

[6] Perkin gives 131° as the melting point of the *trans* acid.

diminished pressure. It passed over at 160–169° (17 mm.). Redistillation gave a product boiling at 152–154° (9 mm.); d^{20}, 1.1103; n_D^{20}, 1.4519.

Anal. Calcd. for $C_{11}H_{15}O_4N$: N, 6.2. Found: N, 6.0%.

Hydrolysis of Diethyl 1-Cyanocyclobutane-1,2-dicarboxylate.—The ester was hydrolyzed by hot concentrated barium hydroxide solution (20%) according to Perkin's method.[7] The reaction took place rapidly with the evolution of ammonia. The yield of barium salt is about 85 to 95% of the theoretical.

Preparation of Trans-cyclobutane-1,2-dicarboxylic Acid.—The barium salt of the cyclobutane-1,1',2-tricarboxylic acid was treated with slightly less than the theoretical amount of sulfuric acid according to the directions of Perkin. The crude acid, which crystallized from the concentrated water solution after one or two weeks in a vacuum desiccator, was heated above its melting point in an oil-bath whose temperature was maintained at 150° for three to four hours. The brown mass which solidified on cooling was recrystallized from a mixture of benzene and ethyl acetate. The product was nearly colorless.

The crude acid which melts at 98–115° was apparently a mixture of *trans* and *cis* forms. It was treated with concentrated hydrochloric acid at 190° according to Perkin's method in order to convert it into the pure *trans* acid. The acid obtained melted at 129–130° and was shown to be identical with the *trans* acid obtained by the synthesis of Perkin.

Summary

When diethyl-α,α'-dibromo-adipate is treated with sodium cyanide, it is converted into diethyl 1-cyanocyclobutane-1,2-dicarboxylate, which on being hydrolyzed loses carbon dioxide to yield a mixture of acids. On treatment with concentrated hydrochloric acid, this mixture is converted into *trans*-cyclobutane-1,2-dicarboxylic acid. The identity of the latter has been established by comparison with a specimen of this acid prepared by the method of Perkin.

This synthesis is interpreted as evidence in favor of the cyclobutane mechanism proposed for the cleavage of diethyl α,α'-dibromo-adipate by secondary amines.

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[7] Perkin, *J. Chem. Soc.*, **65**, 580 (1894).