

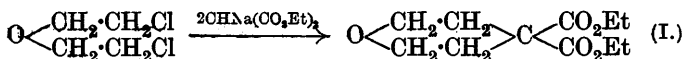
CCCXXXIII.—*Syntheses with $\beta\beta'$ -Dichlorodiethyl Ether.*
Part I. Derivatives of Tetrahydropyran.

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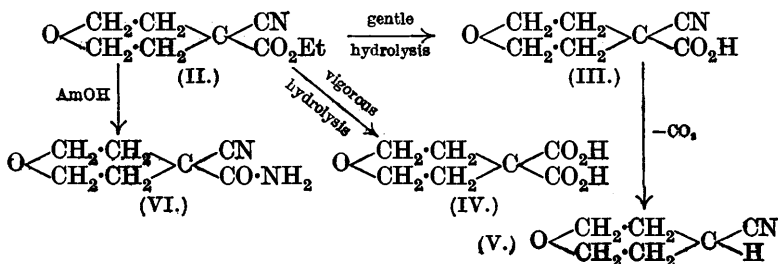
THE present series of investigations has for its object the production from the readily available $\beta\beta'$ -dichlorodiethyl ether of various types of heterocyclic compounds containing an oxygen atom and another atom other than carbon as members of the ring system. It was first necessary to supplement previous work so as to obtain information regarding the reactivity of this compound and its suitability for the object in view.

$\beta\beta'$ -Di-iododiethyl ether, hitherto only obtained in an impure state by Sand (*Ber.*, 1901, 34, 1385, 2908), has now been prepared by the action of excess of sodium iodide in acetone solution on $\beta\beta'$ -dichlorodiethyl ether. If superheating be avoided, it can be distilled under diminished pressure without decomposition (contrast Sand, *loc. cit.*), and the compound has the stability of ordinary alkyl iodides.

Ethyl tetrahydropyran-4 : 4-dicarboxylate (I) has been prepared by von Braun and Köhler (*Ber.*, 1917, 50, 1657) from the di-iodo-ether and ethyl malonate and by Kamm and Waldo (*J. Amer. Chem. Soc.*, 1921, 43, 2223), who used the dichloro-ether. We also used the dichloro-ether for the preparation of the ester (I), and converted this into tetrahydropyran-4-carboxylic acid (also prepared by von Braun and Köhler), from which the *chloride*, *amide*, *anilide* and the *methyl* and *ethyl* esters were readily obtained by standard reactions.



$\beta\beta'$ -Dichlorodiethyl ether condensed fairly readily with ethyl sodiocyanoacetate, yielding the expected *ethyl 4-cyanotetrahydropyran-4-carboxylate* (II); this on gentle hydrolysis in the cold was converted into the corresponding *acid* (III), vigorous hydrolysis yielding the dicarboxylic acid (IV).



The decarboxylation of 4-cyanotetrahydropyran-4-carboxylic acid took place smoothly and readily, the *nitrile* of tetrahydropyran-4-carboxylic acid (V) being produced. The cyano-ester (II) readily furnished the corresponding *cyano-carboxyamide* (VI) on treatment with a concentrated solution of ammonia.

Ethyl sodioacetoacetate condensed only to a slight extent with the dichloro-ether, but readily with the di-iodo-ether. The boiling points of the condensation product and of the di-iodo-ether are so close that complete separation from small quantities of unchanged material could not be effected. The nature of the condensation product was, however, clear, since, on hydrolysis, tetrahydropyran-4-carboxylic acid, acetic acid, and a trace of a ketonic substance were produced.

The high solubility in water of these tetrahydropyran derivatives is a characteristic property.

The following preparations were unsuccessfully attempted: (a) Pyrazolone derivatives from the condensation product of ethyl acetoacetate and the di-iodo-ether. (b) The arsenical compound (VII); this was unsuccessful because the dichloro-ether did not react with sodium arsenite. (c) The arsenical compound (VIII) by means of the Grignard reaction; this failed because the dichloro-ether showed no tendency to form a magnesium compound and the di-iodo-compound did not yield an isolable product.



The use of $\beta\beta'$ -dichlorodiethyl ether and of the corresponding di-iodo-compound for the preparation of heterocyclic compounds in which oxygen and a congener of oxygen are the heterocyclic atoms has, however, been successful. A description of 1:4-selenoxan and some of its derivatives will shortly be submitted for publication.

EXPERIMENTAL.

The $\beta\beta'$ -dichlorodiethyl ether used in these experiments was distilled first under atmospheric and then under reduced pressure (b. p. $66^\circ/12$ mm., $70^\circ/15$ mm., and $176^\circ/744$ mm.; m. p. -24.5°).

For the successful preparation of $\beta\beta'$ -*di-iododiethyl ether* a large excess of sodium iodide is necessary. A mixture of $\beta\beta'$ -dichlorodiethyl ether (28.6 g.; 1 mol.), sodium iodide (120 g.; 4 mols.), and acetone (500 c.c.) was boiled for three periods of 8 hours, being kept over-night between the periods. Sodium chloride was separated by filtration whenever the quantity was so large as to cause excessive bumping. The acetone was distilled off, water added to the residue, and the oil which separated extracted with

ether. The extract was washed with water, dried with calcium chloride, and evaporated, and the residue distilled under diminished pressure, an oil-bath being used to minimise the tendency to superheating which caused decomposition of the substance. The first few drops of the di-iodo-compound to distil (after a small quantity of unchanged dichloro-compound had passed over), which were always contaminated with a little free iodine, were rejected. The di-iodo-compound (52 g.) was obtained as a colourless heavy liquid, b. p. 123.5—124°/10 mm., having an odour typical of alkyl iodides (Found: I, 78.6. $C_4H_8OI_2$ requires I, 77.9%). It darkened slowly on keeping.

Tetrahydropyran-4-carboxylic Acid.—Ethyl tetrahydropyran-4:4-dicarboxylate (compare von Braun and Köhler, *loc. cit.*; Kamm and Waldo, *loc. cit.*) was readily prepared by boiling a mixture of $\beta\beta'$ -dichlorodiethyl ether (107.2 g.), ethyl malonate (240 g.), and sodium (34.5 g.) in alcohol (500 c.c.) for 5 hours, keeping the product for 12 hours, and working it up in the usual manner; yield, 70 g. of refractionated material, b. p. 134—135°/12 mm. The use of the di-iodo-ether for this reaction, while possibly resulting in a better yield, produces a substance contaminated with unchanged di-iodo-ether (compare von Braun and Köhler, *loc. cit.*) (Found: C, 57.4; H, 7.8. Calc.: C, 57.4; H, 7.8%). The ester (75 g.) was boiled with a solution of potassium hydroxide (55 g.) in alcohol (980 c.c.) for 2 hours, a little water added, the alcohol boiled off, and more water added; the solution was then acidified with dilute sulphuric acid, and extracted nine times with ether, since the acid is not very soluble in ether and is appreciably soluble in water. The acid (81% yield) solidified immediately after evaporation of the ether and was contaminated with only a little oil. On being heated at ordinary pressure at 175—185°, it lost carbon dioxide and gave tetrahydropyran-4-carboxylic acid (94.5% yield), which distilled completely at 146—147°/15 mm. and solidified immediately on cooling.

The *chloride* (21 g.) of tetrahydropyran-4-carboxylic acid, prepared by heating a mixture of the acid (20 g.) and thionyl chloride (30 c.c.) on a water-bath for 30 minutes, followed by distillation under reduced pressure, was a colourless liquid, b. p. 85—86°/16 mm., which did not solidify at -15° (Found: Cl, 24.35. $C_6H_9O_2Cl$ requires Cl, 23.9%). *Methyl tetrahydropyran-4-carboxylate* (7.4 g.), prepared from the chloride (12.7 g.) and methyl alcohol (a very vigorous reaction taking place on mixing), was a colourless liquid, b. p. 80.5—81°/16 mm., having a pleasant odour (Found: C, 58.5; H, 8.5. $C_7H_{12}O_3$ requires C, 58.3; H, 8.3%). The *ethyl ester*, prepared in an analogous manner, had similar properties; b. p.

82.5°/12 mm. (Found : C, 60.7; H, 8.8. $C_8H_{14}O_3$ requires C, 60.8; H, 8.8%).

Tetrahydropyran-4-carboxamide, which is very soluble in water and hot alcohol, was prepared by mixing the acid chloride (4.2 g.) and ammonia solution (d , 0.880; 10 c.c.), a vigorous reaction taking place. The colourless solid precipitated on cooling was filtered off, warmed with a little concentrated ammonia solution to remove ammonium chloride, and recrystallised from the minimum quantity of alcohol, giving colourless plates, m. p. 179° (Found : N, 10.7. $C_6H_{11}O_2N$ requires N, 10.9%). The same substance was obtained by shaking the above methyl ester (7 g.) and ammonia solution (d , 0.880; 20 c.c.) for 5 hours, evaporating the homogeneous liquid to small bulk, and recrystallising from alcohol the solid which separated. The ethyl ester did not yield the amide when treated in an analogous manner.

The *anilide* of tetrahydropyran-4-carboxylic acid, prepared from the acid chloride (3.8 g.) in dry ether (50 c.c.) and aniline (5 g.), was recrystallised from aqueous alcohol and obtained in small colourless plates, almost insoluble in ether; m. p. 163° (Found : N, 6.8. $C_{12}H_{15}O_2N$ requires N, 6.8%).

Ethyl 4-Cyanotetrahydropyran-4-carboxylate (II).— $\beta\beta'$ -Dichlorodiethyl ether (97 g.) was added to an alcoholic solution of ethyl sodiocyanoacetate, prepared from sodium (31.5 g.), alcohol (446 c.c.), and ethyl cyanoacetate (155 g.), and the mixture was heated on the water-bath for 3 hours and then kept for 12 hours. Water was added, the precipitated oil extracted with ether, and the extract washed with sodium carbonate solution to remove colouring matter, then with water, dried with calcium chloride, and evaporated. The residue was fractionated under reduced pressure; all material distilling below 100°/16 mm. was neglected, and that boiling between 105° and 132°/16 mm. was collected and refractionated, a yield of 43 g. (33%) of the *cyano-ester*, b. p. 122—125°/16 mm. (mainly at 125°/16 mm.), being obtained (Found : N, 8.0. $C_9H_{13}O_3N$ requires N, 7.6%).

4-Cyanotetrahydropyran-4-carboxylic Acid (III).—The preceding ester (32 g.; 1 mol.) was mixed with a cold solution of potassium hydroxide (10.8 g.; 1.1 mols.) in aqueous methyl alcohol (9 c.c. of water; 192 c.c. of methyl alcohol) and kept for 15 hours. Carbon dioxide was passed through the clear solution, which was then concentrated on the water-bath. When solid matter began to separate, water was added until a clear solution was obtained, and the cold liquid was acidified. The precipitated *acid* was filtered off, and the filtrate extracted three times with ether. The ethereal solution, washed with water, dried with calcium chloride, and

evaporated, yielded a further quantity of the acid. The acid was recrystallised from the minimum quantity of water (decolorising charcoal) and 16.4 g. were obtained in stout colourless prisms, m. p. 160—162° (Found: N, 9.3. $C_7H_9O_3N$ requires N, 9.0%). The acid is highly soluble in hot water and appreciably soluble in cold.

On hydrolysis of ethyl 4-cyanotetrahydropyran-4-carboxylate (4.1 g.; 1 mol.) with aqueous-alcoholic potassium hydroxide (50% KOH, 3 mols., 7.5 g.; alcohol, 30 c.c.) by boiling for 4 hours and working up the product as described for tetrahydropyran-4:4-dicarboxylic acid, an acid identical with the latter was obtained.

4-Cyanotetrahydropyran-4-carboxamide was obtained by shaking the ethyl ester (7.1 g.) with ammonia solution (d , 0.880; 20 c.c.) for 1½ hours, a homogeneous solution resulting. A little water was added, and the solution concentrated on the water-bath. The amide readily separated on cooling and was recrystallised from the minimum quantity of alcohol, being obtained in colourless rhomb-shaped plates, m. p. 158° after slight softening. It is somewhat sparingly soluble in cold water (Found: N, 18.1. $C_7H_{10}O_2N_2$ requires N, 18.2%).

4-Cyanotetrahydropyran (V).—4-Cyanotetrahydropyran-4-carboxylic acid (16.4 g.) was heated under reflux in an oil-bath at 180—200° until the evolution of carbon dioxide (1 hour) had ceased: the product was allowed to cool slowly in the oil-bath. On distillation under diminished pressure a colourless liquid passed over at 82—83°/10 mm. and a colourless crystalline residue remained. The latter was again heated at 200—210° for 30 minutes, and the product distilled under reduced pressure, a further 1.1 g. passing over at 82—83°/10 mm. The combined distillates (66% yield) were redistilled and had b. p. 82—83°/10 mm. (Found: N, 12.6. C_6H_9ON requires N, 12.6%). The nitrile is a colourless liquid which does not solidify at -15° and is very soluble in water.

An attempt to reduce the nitrile to the corresponding amine by means of sodium in amyl alcohol was unsuccessful, although a very small quantity of a basic substance was obtained.

Condensation of $\beta\beta'$ -Dichloro(Di-iodo)diethyl Ether with Ethyl Sodiaoacetate.—The dichloro-ether when condensed under the conditions used for the di-iodo-ether gave only a small quantity of high-boiling material.

A mixture of $\beta\beta'$ -di-iododiethyl ether (97.8 g.; 1 mol.) and an alcoholic solution of ethyl sodiaoacetate prepared from sodium (15.2 g.; 2.2 atoms), alcohol (300 c.c.), and ethyl acetoacetate (85.8 g.; 2.2 mols.) was boiled under reflux for 3 hours, kept for 16 hours, and again boiled for 7 hours. After cooling, water was

added, the liquid extracted with ether, and the extract washed with water, dried with calcium chloride, and evaporated. The residue was distilled under diminished pressure. A small quantity of liquid distilled below $126^{\circ}/11$ mm. The fraction boiling between 126° and $130^{\circ}/11-9$ mm. was collected; the residue had no constant boiling point. The fraction collected contained a trace of halogen; on redistillation, 31.9 g. of a colourless liquid having a pleasant odour and still containing a trace of halogen were obtained, b. p. $122.5-123.5^{\circ}/9$ mm. The boiling point and the products of hydrolysis showed conclusively that it mainly consisted of the normal cyclic condensation product.

The ester just described (38.4 g.; 1 mol.) was boiled for $2\frac{1}{2}$ hours with alcoholic potassium hydroxide (43 g. KOH, 4 mols.; 530 c.c. alcohol); after cooling, water was added and the liquid extracted twice with ether. The extract, worked up in the usual way, gave only a small quantity of a colourless liquid, b. p. $140-200^{\circ}$. This gave a semicarbazone, but the quantity obtained was too small for analysis. The aqueous liquid remaining after the ether extraction was concentrated, filtered, acidified with dilute sulphuric acid, and extracted three times with ether. The extract, washed with water and dried with calcium chloride, gave tetrahydropyran-4-carboxylic acid (identified by direct comparison) and acetic acid.

No results were obtained in attempts to carry out the Friedel-Crafts reaction on the dichloro-ether and benzene, and to prepare $\beta\beta'$ -dicyanodiethyl ether by boiling the dichloro-ether with an aqueous-alcoholic solution of potassium cyanide.

Attempt to condense $\beta\beta'$ -Dichlorodiethyl Ether with Sodium Arsenite.
—A mixture of the dichloro-ether (28.6 g.; 1 mol.), sodium hydroxide solution (10*N*, 132 c.c.; 6.6 mols.), and arsenious oxide (43.6 g.; 1.1 mols.) was boiled gently and stirred (mercury seal) under reflux. At the end of 8 hours, 1 c.c. of the aqueous solution was diluted to a known volume, and an aliquot portion titrated with standard iodine solution: there was no change in the arsenite content of the liquid.

We are greatly indebted to Imperial Chemical Industries Limited, British Dyestuffs Corporation, Dalton Works, Huddersfield, for the considerable quantity of $\beta\beta'$ -dichlorodiethyl ether which is being used in these investigations.

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[Received, October 13th, 1930.]