XXXIV.—*Formation of Heterocyclic Compounds.*
Part I. 1-Phenylpyrrolidine-2 : 5-dicarboxylic Acid
from Adipic Acid.

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CONSIDERABLE quantities of muconic acid being required for an investigation in connexion with this substance, the action of diethylaniline on ethyl $\alpha\delta$ -dibromoadipate was tried, in the hope that two molecules of hydrogen bromide would be eliminated from the latter substance with production of the ester of the desired acid. It was soon seen, however, that the action of diethylaniline in this case was not the normal one, as a considerable quantity of ethyl bromide was liberated during the reaction. Since ethyl bromide was also obtained by the action of diethylaniline on methyl $\alpha\delta$ -dibromoadipate, it was clear that the ethyl group arose from the diethylaniline and not from the ester. This led to the study of the action of monoethylaniline on ethyl $\alpha\delta$ -dibromoadipate, and the results obtained form the subject of this communication.

The action of diethylaniline on ethyl $\alpha\delta$ -dibromoadipate is being studied fully, and the results obtained will be communicated in due course.

Ethyl $\alpha\delta$ -dibromoadipate has been prepared previously by Willstätter and Lessing (*Ber.*, 1902, **35**, 2065), who also obtained a liquid by-product which they regarded as a liquid form of the solid ester, but which they could not obtain in the pure state. The pure liquid ethyl $\alpha\delta$ -dibromoadipate has now been obtained, and is undoubtedly stereoisomeric with the solid form, since, on keeping the former, it is partly, but not entirely, converted into the latter.

When ethyl $\alpha\delta$ -dibromoadipate is heated with an excess of monoethylaniline, a 62.5 per cent. yield of *ethyl 1-phenylpyrrolidine-2:5-dicarboxylate* (I) is obtained, together with a small quantity of *ethyl diethylanilinoadipate* (II) :

Hydrogen bromide is also eliminated, and combines with the excess of monoethylaniline to form the crystalline hydrobromide of this base.

The formation of the above pyrrolidine ester might result from a direct condensation of one molecule of monoethylaniline with one molecule of the ethyl dibromoadipate.

This is not the case, however, as no ethyl bromide could be detected at any stage of the reaction ; moreover, the whole of the bromine is eliminated as hydrogen bromide, as was proved by the fact that the weight of monoethylaniline hydrobromide actually obtained accounted for 93 per cent. of the total bromine, whereas if the reaction had taken place according to the above equation, only half of the bromine would have been recovered in this form.

In view of this fact, and that ethyl $\alpha\delta$ -diethylanilinoadipate was isolated from the products of the reaction, it is very highly probable that this latter substance is first formed, and that it loses diethylaniline with production of the pyrrolidine ester :

This ready formation of a ring compound from an open chain of six carbon atoms is no doubt due to the close proximity of the end carbon atoms, and also to the stability of five-membered ring compounds in general.

A reaction similar to the one described above enabled Willstätter and Lessing (*loc. cit.*) to prepare 1-methylpyrrolidine-2:5-dicarboxylic acid, but it appears that the formation of heterocyclic compounds from open-chain compounds and more particularly dicarboxylic acids has not been studied systematically, and this investigation is now being carried out.

EXPERIMENTAL.

The adipic acid used in this investigation was obtained by the oxidation of *cyclohexanol* with concentrated nitric acid (Bouveault, *Bull. Soc. chim.*, 1908, [iv], 3, 437); this method is much more rapid than that depending on the oxidation of *cyclohexanone* with potassium permanganate, and the yield of adipic acid is 62 per cent. of that theoretically obtainable.

Fifty grams of adipic acid were converted into the dibromo-acid chloride by means of phosphorus pentachloride and bromine as described in a previous communication (Trans., 1908, 93, 718). The resulting dibromo-acid chloride was gradually added to twice its volume of absolute alcohol, and the solution allowed to remain overnight, at the end of which time 35 grams of ethyl $\alpha\delta$ -dibromoadipate had separated out. This, after recrystallisation from light petroleum, melted at 67° , a melting point which agrees with that found for this substance by Willstätter and Lessing (*loc. cit.*, p. 2067):

0.1772 gave 0.1864 AgBr. Br = 44.75.

$C_{10}H_{16}O_4Br_2$ requires Br = 44.44 per cent.

The alcoholic mother liquor was diluted with a large volume of water, extracted with ether, the ethereal solution washed, dried, evaporated, and the residue distilled under 33 mm. pressure, when the following fractions were obtained:

130—190°	5 grams	210—220°	25 grams
190—210°	40 „		

The last two fractions were redistilled together, when 57.4 grams of pure ester, boiling at $204\text{--}206^\circ$, were obtained. A portion collected at 204° was analysed:

0.2264 gave 0.2342 AgBr. Br = 44.02.

$C_{10}H_{16}O_4Br_2$ requires Br = 44.44 per cent.

The liquid form of ethyl $\alpha\delta$ -dibromoadipate is a viscid, oily liquid, which, on keeping, is partly, but not wholly, converted into the solid form melting at 67° . The total yield of pure ester, both solid and

liquid, from 50 grams of adipic acid amounted to 92.4 grams, which corresponds with 75.2 per cent. of the theoretical.

Methyl $\alpha\delta$ -dibromoadipate was prepared in exactly the same way as the ethyl ester, methyl alcohol being used instead of ethyl alcohol. It is readily soluble in benzene, chloroform, acetone, ether, moderately so in alcohol, and sparingly so in light petroleum, from which it crystallises in long needles melting at 75—76°:

0.1844 gave 0.2108 AgBr. Br = 48.6.

$C_8H_{12}O_4Br_2$ requires Br = 48.2 per cent.

Action of Monoethylaniline on Ethyl $\alpha\delta$ -Dibromoadipate.

Fifty grams of ethyl $\alpha\delta$ -dibromoadipate and 70 grams of monoethylaniline were heated together in a flask attached to a reflux condenser and immersed in boiling water for thirteen and a-half hours; on cooling, a large quantity of a crystalline solid separated; a large quantity of ether was then added to the contents of the flask, which were then filtered, and the solid well washed with ether. The solid weighed 50 grams, and consisted of the hydrobromide of monoethylaniline, as was proved by crystallising it from a mixture of alcohol and ether, when it melted at 166°.

Bischoff (*Ber.*, 1897, **30**, 3178) gives 165—166° as the melting point of the pure substance.

The ethereal filtrate was evaporated, and the residue again heated in boiling water for twenty-eight and a-half hours. The product was then dissolved in dilute hydrochloric acid, the solution extracted with ether, the ethereal solution well washed with water, dried, evaporated, and the residue distilled under 35 mm. pressure:

224—240°	27 grams	260—286°	6.6 grams
240—260	3 „		

The first fraction was redistilled under 30 mm. pressure, when 24 grams, distilling at 226—230°, were obtained. A portion boiling at 227—228° was analysed:

0.1560 gave 0.3762 CO_2 and 0.1052 H_2O . C = 65.77; H = 7.50.

0.1622 „ 6.5 c.c. N_2 (moist) at 15° and 770 mm. N = 4.76.

$C_{16}H_{21}O_4N$ requires C = 65.98; H = 7.22; N = 4.81 per cent.

A molecular-weight determination by the freezing-point method gave the following results:

0.6776 in 19.1388 naphthalene gave Δt - 0.87°; whence M.W. = 281.

$C_{16}H_{21}O_4N$ requires M.W. = 291.

Ethyl 1-phenylpyrrolidine-2:5-dicarboxylate,

is a pale yellow, oily liquid boiling at 227—228°/30 mm. It is insoluble in water, but dissolves readily in all the ordinary organic solvents and in concentrated aqueous hydrochloric acid. Its solution in chloroform readily absorbs bromine, with evolution of hydrogen bromide.

Methyl 1-phenylpyrrolidine-2:5-dicarboxylate,

was obtained by heating together methyl $\alpha\delta$ -dibromoadipate (30 grams) and monoethylaniline (50 grams), and working up the product exactly as described for the preparation of the corresponding ethyl ester. The residue left after evaporation of the ethereal solution deposited a large amount of crystalline solid. This was separated and crystallised from light petroleum, when the methyl ester was obtained in stellar aggregates of needles which melted at 88°.

It is insoluble in water, alcohol or light petroleum in the cold, and readily dissolves in ether, chloroform, acetone or benzene, and in hot alcohol:

0.1682 gave 7.5 c.c. N_2 (moist) at 10° and 756 mm. $\text{N} = 5.31$.

$\text{C}_{14}\text{H}_{17}\text{O}_4\text{N}$ requires $\text{N} = 5.32$ per cent.

1-Phenylpyrrolidine-2:5-dicarboxylic Acid,

—Nine grams of ethyl 1-pyrrolidine-2:5-dicarboxylate were dissolved in a solution of 8.5 grams of potassium hydroxide in 80 c.c. of alcohol and 2 c.c. of water, contained in a flask attached to a reflux condenser, and the resulting solution boiled for nine hours. When cold, the solution was extracted once with ether in order to remove any unchanged ester, and then acidified with dilute sulphuric acid, when the acid was precipitated in a crystalline state, and, when dry, weighed 6.5 grams. It was recrystallised from a mixture of acetone and light petroleum and analysed:

0.1574 gave 0.3516 CO_2 and 0.0798 H_2O . $\text{C} = 60.92$; $\text{H} = 5.63$.

0.1674 „ 8.7 c.c. N_2 (moist) at 14° and 775 mm. $\text{N} = 6.23$.

$\text{C}_{12}\text{H}_{13}\text{O}_4\text{N}$ requires $\text{C} = 61.27$; $\text{H} = 5.53$; $\text{N} = 5.96$ per cent.

1-Phenylpyrrolidine-2:5-dicarboxylic acid crystallises from a mixture of acetone and light petroleum in well-defined, oblong plates, and decomposes with evolution of gas at 252°. It dissolves readily in cold alcohol or hot acetone, is insoluble in benzene, light petroleum or chloroform, sparingly soluble in cold ether or water, and moderately so in boiling water or concentrated hydrochloric acid. It decolorises an acid or alkaline solution of potassium permanganate, and its aqueous

solution gives a flocculent precipitate with an aqueous solution of bromine.

The vapour produced by heating the acid alone, or preferably with soda-lime, imparts a red colour to a pine shaving which has been previously moistened with hydrochloric acid.

The molecular weight was determined by dissolving the acid in alcohol and titrating with *N*/10 sodium hydroxide, using phenolphthalein as indicator :

0.2122 required 17.7 c.c. *N*/10 NaOH. M.W. = 239.6.

A dibasic acid, $C_{12}H_{18}O_4N$, requires M.W. = 235.

The *silver* salt was obtained as a white precipitate by adding an ice-cold solution of the ammonium salt of the acid to an ice-cold solution of silver nitrate, the operation being carried out in the dark. If the precipitation is carried out in warm solutions the salt immediately decomposes and black, metallic silver is precipitated :

0.2540 gave 0.1214 Ag. Ag = 47.80.

$C_{12}H_{11}O_4NAg_2$ requires Ag = 48.10 per cent.

The *barium* salt was prepared by carefully neutralising the acid with an aqueous solution of barium hydroxide. The solution was filtered and, after concentration to a small bulk, alcohol was added, when, on cooling, the barium salt separated in stout needles, which were collected and dried in the air for several days. The salt is readily soluble in water, and is insoluble in absolute alcohol :

0.2062 gave 0.0930 $BaSO_4$. Ba = 26.52.

0.7506 lost 0.2042 at 135° . H_2O = 27.20.

$C_{12}H_{11}O_4NBa, 8H_2O$ requires Ba = 26.65 ; H_2O = 28.0 per cent.

The *monoanilide*, $C_6H_5 \cdot N \begin{cases} CH(CO_2H) - CH_2 \\ CH(CO \cdot NHPh) \cdot CH_2 \end{cases}$, was prepared by

boiling the acid with an excess of recently-distilled aniline for six and a-half hours. The resulting product was treated with dilute hydrochloric acid, extracted with ether, the ethereal solution washed, dried, evaporated, and the residue crystallised from a mixture of chloroform and benzene, when the substance was obtained in small needles which decompose at 184° . It readily dissolves in an aqueous solution of potassium hydroxide, alcohol or acetone, and is but slightly soluble in benzene, light petroleum, chloroform or cold water. Its solution in hot water has a well marked acid reaction :

0.1006 gave 7.7 c.c. N_2 (moist) at 17° and 749 mm. N = 8.76.

$C_{18}H_{18}O_3N_2$ requires N = 9.03 per cent.

Ethyl $\alpha\delta$ -Diethylanilinoadipate,

$CO_2Et \cdot CH(NEtPh) \cdot CH_2 \cdot CH_2 \cdot CH(NEtPh) \cdot CO_2Et$.

—The fraction boiling at $260-286^\circ$ (see p. 276) was kept for several

weeks, at the end of which time it had partly solidified. It was then well pressed on porous plate, and the solid thus obtained crystallised from dilute alcohol:

0.1588 gave 0.4110 CO_2 and 0.1190 H_2O . $\text{C} = 70.59$; $\text{H} = 8.32$.

0.1766 „ 9.7 c.c. N_2 (moist) at 12.5° and 758 mm. $\text{N} = 6.49$.

$\text{C}_{26}\text{H}_{36}\text{O}_4\text{N}_2$ requires $\text{C} = 70.90$; $\text{H} = 8.18$; $\text{N} = 6.36$ per cent.

Ethyl α -diethylanilino adipate crystallises from alcohol in stout prisms melting at $88-90^\circ$. It is insoluble in water or light petroleum, but dissolves readily in ether, benzene, chloroform, acetone or dilute hydrochloric acid.

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