180. *The Reaction between Amines and Unsaturated Compounds containing Halogen attached to one of the Ethylenic Carbon Atoms. Part II. The Preparation and Constitution of some New Diamines.*

By John C. Roberts.

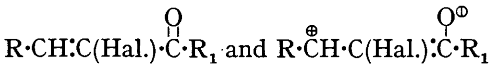
Reactions similar to that between ethyl α-chlorocrotonate and dimethylamine (Part I, J., 1936, 1169), which involves addition at the point of unsaturation and replacement of the halogen by the dimethylamino-group, have been investigated. The most successful results have been obtained with dimethylamine and piperidine.

Piperidine and dimethylamine, in alcoholic solution, react readily with ethyl α-chlorocrotonate or ethyl α-bromocinnamate to yield substituted diamino-esters; *e.g.*, $\mathrm{CHMe{:}CCl{\cdot}CO_2Et + 3NHMe_2 = NMe_2{\cdot}CHMe{\cdot}CH(NMe_2){\cdot}CO_2Et + NHMe_2,HCl}$. With 3 mols. of the base the reaction proceeds almost to completion, without application of heat, within 20 hours—sometimes within a very much shorter time. Side reactions do not occur to any appreciable extent and good yields are obtained. Ammonia and methylamine give much less definite results.

In all the reactions the rate of production of ionisable halogen was followed approximately, and as far as conditions would permit, by acidification and titration of aliquot portions of the mixture. The bases were used in approximately equimolecular concentrations. Dimethylamine and, to a less extent, piperidine produced ionisable halogen most readily. Methylamine and ammonia displaced a considerable amount (70—80%) of the halogen, but diamino-esters were not isolated; more complicated reactions apparently took place.

The αβ-structure is assigned to the new diamines, although the investigations of Dufraisse and Moureu (*Bull. Soc. chim.*, 1927, **41**, 457, 850) on the reactions between amines and α-halogenated αβ-unsaturated ketones do not exclude the αα-structure, and the hydrolysis of *ethyl bis(dimethylamino)*-β-*phenylpropionate* by dilute sulphuric acid yields a substance which appears to be a mixture of phenylglycidic and phenylpyruvic acids, the former indicating an αβ-structure and the latter an αα-structure. Phenylglycidic acid, however, is partly converted into phenylpyruvic acid by heating with mineral acids (Erlenmeyer, *Ber.*, 1900, **33**, 3001: cf. also the change of phenylethylene oxide into phenylacetaldehyde; Zinke, *Ber.*, 1878, **11**, 1402). There is therefore no evidence against phenylglycidic or phenylglyceric acid being the first product of hydrolysis.

Theoretical considerations favour the αβ-structure for the diamines. Halogen attached to an ethylenic carbon atom is firmly held. This would indicate that addition of the amine to the unsaturated compound takes place before elimination of halogen occurs. The unsaturated halogenated compounds referred to above all contain a conjugated unsaturated system, are capable of mesomeric change, and can therefore exist as resonance hybrids of the two forms



$$\mathrm{R{\cdot}CH{:}C(Hal.){\cdot}\overset{O}{\overset{\|}{C}}{\cdot}R_1} \text{ and } \mathrm{R{\cdot}\overset{\oplus}{C}H{\cdot}C(Hal.){:}\overset{O^{\ominus}}{\overset{|}{C}}{\cdot}R_1}$$

(R = Me or Ph; R_1 = OEt or Ph)

Amines are well-recognised nucleophilic reagents (cf. Chattaway, J., 1936, 355), indicating that attachment of the amino-group will take place on the β-carbon atom.

Experimental.

Reaction between Ethyl α-Chlorocrotonate and Piperidine.—1·08 G. of the ester (J., 1936, 1170; this vol., p. 779) were mixed with 2·15 c.c. of piperidine (3 mols.) in 4·7 c.c. of absolute alcohol; some heat was evolved. After ½ hour, 0·6 c.c. of the mixture was added to 10 c.c. of dilute nitric acid; titration with 0·1N-silver nitrate indicated that about 63% of the chlorine had been removed from the ester. After 45 minutes, long needle-shaped crystals separated, preventing the further abstraction of aliquot portions.

Ethyl αβ-*Dipiperidinobutyrate.*—A mixture of 6·17 g. of ethyl α-chlorocrotonate, 12·3 c.c.

of piperidine (3 mols.), and 28·3 c.c. of absolute alcohol was after 2 hours neutralised with concentrated hydrochloric acid (about 4 c.c.), and alcohol (18 c.c.) distilled off on the water-bath. The residual crystals were cooled in ice and treated with 40 c.c. of ice-cold water. The cloudy reddish-brown solution was acidified with concentrated hydrochloric acid (4 c.c.), shaken with ether (15 + 15 c.c.), and basified with ice-cold 33% sodium hydroxide solution. The yellow oil obtained was extracted with ether (20 + 15 + 10 c.c.), washed with water (10 + 10 c.c.), and dried (sodium sulphate), the solvent evaporated, and the residue distilled in a vacuum, yielding 7·4 g. of *ethyl* αβ-*dipiperidinobutyrate* as a pale yellow, very viscous oil of pronounced basic and rather unpleasant odour, b. p. 181—183°/14 mm., practically insoluble in water (Found: C, 68·1; H, 10·5; N, 9·7. $C_{16}H_{30}O_2N_2$ requires C, 68·1; H, 10·6; N, 9·9%).

Reaction between Ethyl α-Bromocinnamate and Dimethylamine.—2·28 G. of the ester were mixed with 3·84 g. of a 33% solution of dimethylamine (3 mols.) in absolute alcohol. After 10 minutes considerable heat was evolved and the mixture was cooled in running water. After 1½ hours, an excess of dilute nitric acid (30 c.c.) was added, and the volume made up to 100 c.c.; titration of 10 c.c. with 0·1N-silver nitrate indicated that about 95% of the bromine had been removed from the ester.

Ethyl αβ-Bis(dimethylamino)-β-phenylpropionate.—9·5 G. of ethyl α-bromocinnamate were mixed with 15·2 g. of a solution of the base (3 mols.), with subsequent cooling as described above. After 15 minutes crystals of dimethylamine hydrobromide separated and after 1½ hours the product was isolated in the way described above in the case of ethyl αβ-dipiperidinobutyrate. *Ethyl αβ-bis(dimethylamino)-β-phenylpropionate* (6 g.) was obtained as a colourless viscous oil of rather unpleasant odour, b. p. 154—155°/8 mm., practically insoluble in water (Found: C, 68·0; H, 8·9; N, 10·5. $C_{15}H_{24}O_2N_2$ requires C, 68·2; H, 9·1; N, 10·6%); after several months' keeping in a stoppered bottle it formed prisms, m. p. 37—38°. The *platinichloride* crystallised in deep orange-coloured pyramids, m. p. 185° (decomp.) (Found: Pt, 28·5. $C_{15}H_{24}O_2N_2,H_2PtCl_6$ requires Pt, 29·0%). The picrate separated from acetone in small, yellow, irregular prisms, m. p. 148—149°; from alcoholic solutions two distinct crystalline compounds separated, which were not investigated. The *dihydrochloride* was prepared by means of ethereal hydrogen chloride. The white crystalline precipitate obtained, when dissolved in absolute alcohol and reprecipitated by ether, separated as a glue. This was placed in a vacuum over concentrated sulphuric acid, powdered, and again dried in the same manner (Found: Cl, 20·3. $C_{15}H_{24}O_2N_2,2HCl$ requires Cl, 21·1%). Hydrogen chloride was lost on drying in a vacuum. Other methods of drying were unsuccessful.

Reaction between Ethyl α-Bromocinnamate and Piperidine.—1·94 G. of the ester were mixed with 2·3 c.c. of piperidine (3 mols.) dissolved in 5·0 c.c. of absolute alcohol. By titration of aliquot portions it was found that about 46% of the bromine had been replaced after 1 hour and about 69% after 2 hours; crystals then separated.

Ethyl αβ-Dipiperidino-β-phenylpropionate.—6·4 G. of ethyl α-bromocinnamate were treated with 7·4 c.c. of piperidine (3 mols.) dissolved in 17 c.c. of absolute alcohol; the temperature rose to 31° after 1 hour. After 12 hours, the almost solid, crystalline mass was shaken with 20 c.c. of water and 6 c.c. of 33% sodium hydroxide solution and the cream-coloured precipitate which separated was washed successively with water, 45% alcohol (30 c.c.), and water, dried (yield, 8·4 g.), recrystallised from a small quantity of boiling alcohol (95%) in a continuous extraction apparatus, and dried in a vacuum over concentrated sulphuric acid. *Ethyl αβ-dipiperidino-β-phenylpropionate* was obtained as a pale cream-coloured powder—very small, colourless crystals when seen under the microscope—m. p. 74—75°, practically insoluble in water and rather sparingly soluble in alcohol (Found: C, 73·5; H, 9·1; N, 8·2. $C_{21}H_{32}O_2N_2$ requires C, 73·2; H, 9·3; N, 8·1%). A dihydrochloride, which readily lost hydrogen chloride, and a picrate (yellow prisms, m. p. 122—123°, from alcohol) were prepared, but a pure platinichloride could not be obtained; on attempted recrystallisation from water a strong odour of benzaldehyde was observed.

Degradation of Ethyl αβ-Bis(dimethylamino)-β-phenylpropionate.—(i) *With alkali.* 0·246 G. of the ester was refluxed for 6 hours with 6 g. of potassium hydroxide in 30 c.c. of water. Air bubbling through the boiling solution and for 2 hours during cooling was drawn through the condenser into two absorption flasks containing 25 c.c. and 10 c.c. of 0·1N-sulphuric acid. The alkaline gases evolved neutralised 7·1 c.c., corresponding to about a 76% liberation of one of the dimethylamino-groups as dimethylamine. By concentration of the neutralised acid, decomposition by boiling with excess of sodium hydroxide solution, and passage of the gas evolved through an alcoholic solution of picrolonic acid, a light yellow, crystalline precipitate was obtained. After recrystallisation from alcohol this was identified as dimethylamine picrolonate

—it lost its crystalline shape and colour at 222° and decomposed vigorously at 232°, behaving identically with an authentic sample. After another 3 hours' refluxing, with fresh standard acid in the absorption flasks, a theoretical titre was obtained. The residue in the reaction flask had a strong odour of benzaldehyde.

(ii) ***With dilute sulphuric acid.*** (a) 0·95 G. of the ester was refluxed for 20 minutes with 10 c.c. of 15% sulphuric acid; after a few minutes, oily drops were observed in the condensate. 10 C.c. of water were added, and 10 c.c. distilled. The distillate gave with 100 c.c. of a solution of 2 : 4-dinitrophenylhydrazine (0·33% in 2N-hydrochloric acid) a precipitate which, recrystallised from benzene–alcohol and examined under the microscope, was seen to consist of two crystalline substances. On cooling, the liquid in the distillation flask gave a crystalline precipitate. This was extracted with ether, the ether evaporated, and the product recrystallised from 5% alcohol; it melted over a range of 20°. An attempt to purify it by precipitation with acid from warm sodium carbonate solution was not successful, an emulsion being produced which had an odour resembling that of hyacinths. Phenylglyceric or phenylglycidic acid was therefore suspected.

(b) In another similar experiment, the ethereal extract was washed with water, the ether evaporated, and the residue recrystallised from warm ether–benzene. The product was dried at 100° for 20 minutes and then over calcium chloride in a desiccator. Lustrous leaflets (0·23 g.) were obtained which under the microscope appeared as long prisms. The m. p. was indefinite and varied according to the rate of heating; a meniscus formed at 143° on very slow heating (Found: C, 65·8; H, 5·0. Calc. for phenylglycidic or phenylpyruvic acid, $C_9H_8O_3$: C, 65·9; H, 4·9%). An ethereal solution of the product gave the characteristic colour reaction for phenylpyruvic acid with dilute aqueous ferric chloride. When the product was warmed with sodium carbonate solution, an odour of phenylacetaldehyde was evolved. It was therefore concluded that the product was a mixture of phenylpyruvic and phenylglycidic acids.

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