284. *Synthesis of* 1-*Aryl*-4 : 5-*dihydroglyoxalines.*

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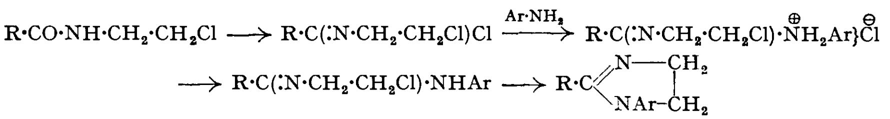
An *N*-2-chloroethylcarboxyamide, when converted into the corresponding imido-chloride in the presence of an arylamine, affords an *N'*-substituted *N*-2-chloroethylamidinium chloride, which is cyclized to a 1-aryl-4 : 5-dihydroglyoxaline on treatment with alkali.

2-SUBSTITUTED 1-alkyl-4 : 5-dihydroglyoxalines are known to exhibit a wide range of biological activity (see, *e.g.*, Kyrides, Zienty, Steahly, and Morrill, *J. Org. Chem.*, 1947, **12**, 577), whereas little appears to be known of the activities of 2-substituted 1-aryl-4 : 5-dihydroglyoxalines. Clayton (*Ber.*, 1895, **28**, 1665) has described the preparation of a few 2 : 5-disubstituted 1-aryl-4 : 5-dihydroglyoxalines from *N*-allylcarboxyamides and amine hydrochlorides. Possible extensions of the more elegant methods for the production of 2-substituted 4 : 5-dihydroglyoxalines (Oxley and Short, *J.*, 1947, 497; Chitwood and Reid, *J. Amer. Chem. Soc.*, 1935, **57**, 2424; Scholtz, *Ind. Eng. Chem.*, 1945, **37**, 120; Kyrides *et al.*, *loc. cit.*) appeared inapplicable to 2-substituted 1-aryl-4 : 5-dihydroglyoxalines because of the inaccessibility of the necessary intermediates.

We find that the method of preparing an *NN'*-disubstituted amidine from an *N*-substituted carboxyamide, *via* an imido-chloride can be adapted to the production of 2-substituted 1-*aryl*-4 : 5-*dihydroglyoxalines* in good yield from *N*-2-chloroethylcarboxyamides :



N-2-Chloroethylcarboxyamides are easily prepared by a rearrangement of imino-2-chloroethyl ethers, which are readily accessible (Gabriel and Neumann, *Ber.*, 1892, **25**, 2383; Wislicenus and Körber, *Ber.*, 1902, **35**, 164) and thereby one avoids the unsatisfactory acylation of the vesicant, 2-chloroethylamine. *N*-2-Chloroethylbenzamide, treated with phosphorus pentachloride, afforded N-2-*chloroethylbenzimidochloride* in 70% yield. Imido-chlorides, $R'{\cdot}CH_2{\cdot}C(\colon NR'')Cl$, are very unstable and readily change into chlorovinylamidinium chlorides (Heymons, *Ber.*, 1932, **65**, 320). By conducting the conversion of an *N*-2-chloroethylcarboxyamide,

$$R'{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2Cl,$$

into the imido-chloride in the presence of an arylamine, a change of this type does not occur, and the expected *NN'*-disubstituted amidinium chloride is obtained. In this way, N-2-*chloroethyl*-N'-*phenyl*- and N'-p-*tolyl*-*phenylacetamidinium chloride* were prepared in 87% and 97% yields respectively. The corresponding free *NN'*-disubstituted amidines could not be isolated because of the extreme facility with which cyclization occurred. Indeed, attempts to convert these amidinium chlorides into their picrates resulted in the formation of the corresponding *dihydroglyoxaline picrates*. *N*-2-Chloroethylbenzimidochloride and aniline afforded a product which could not be crystallised but similarly yielded 1 : 2-*diphenyl*-4 : 5-*dihydroglyoxaline picrate* (91%). Treatment of *N*-2-chloroethyl-*N'*-phenyl- and -*N'*-*p*-tolyl-phenylacetamidinium chloride with alkali yielded respectively 1-phenyl-2-benzyl-4 : 5-dihydroglyoxaline (95%), characterised as its picrate and *Reineckate*, and 1-p-*tolyl*-2-*benzyl*-4 : 5-*dihydroglyoxaline* (97%), characterised as its picrate. The complete series of changes is readily effected; the *N*-2-chloro-

ethylcarboxyamide is converted into the corresponding imido-chloride in the presence of an arylamine, and the 1-aryl-4 : 5-dihydroglyoxaline is obtained from the resulting amidinium chloride by treatment with alkali. The scope of the process is illustrated by the examples described in the experimental section.

Because the rearrangement of an imino 2-chloroethyl ether to a 2-chloroethylcarboxyamide involves an oxazoline as an intermediate (Wislicenus and Körber, *loc. cit.*), and in order to avoid, if possible, the use of aqueous alkali hydroxides in this reaction, experiments were carried out on the use of ammonia under anhydrous conditions. *Phenylacetimino 2-chloroethyl ether hydrochloride* with ethereal ammonia yielded *N*-2-chloroethylphenylacetamide (52%) and 2-benzyloxazoline (41%); with ethanolic ammonia, phenylacetamidine (78%) was obtained. Benzimino 2-chloroethyl ether hydrochloride with ethanolic ammonia afforded 2-phenyloxazoline (72%) and benzamidine (10%).

Experimental.

Phenylacetimino 2-Chloroethyl Ether Hydrochloride.—A mixture of ethylene chlorohydrin (28 g.), dried by refluxing with benzene under a phase separator and fractionation, with benzyl cyanide (35 g., 0·85 mol.) was saturated at 0° with anhydrous hydrogen chloride and kept at 0° overnight. The powdered *hydrochloride* (69 g.; 98%) was washed with anhydrous ether; m. p. 160° (decomp.) (Found: N, 6·05, 6·1. $C_{10}H_{13}ONCl_2$ requires N, 6·0%). In anhydrous ether, the yield decreased to 66 g. (94%).

N-2-*Chloroethylphenylacetamide.*—(*a*) The base liberated at 0° by potassium hydroxide from the foregoing hydrochloride (46·8 g.) was collected in ether, dried, and, after recovery from the ether, heated at 130° for 1 hour. The crude product (30 g., m. p. 66°), obtained by extraction with benzene, crystallised from light petroleum (b. p. 60—80°); m. p. 80° (29·5 g.; 75%) (Found: N, 7·1; Cl, 17·8. Calc. for $C_{10}H_{12}ONCl$: N, 7·1; Cl, 18·0%). When isomerisation was effected at 100° for 30 minutes, the yield was 7·55 g. (19%).

(*b*) The product obtained on interaction of phenylacetyl chloride (11·6 g.), 2-chloroethylamine hydrochloride (15·5 g.; 1·02 mols.) (Ward, *J. Amer. Chem. Soc.*, 1935, **57**, 914), and 5N-sodium hydroxide (42 c.c.) under Schotten–Baumann conditions was crystallised from light petroleum (b. p. 60—80°); yield 5·5 g. (28%); m. p. and mixed m. p. 80°. Phillips and Baltzly (*J. Amer. Chem. Soc.*, 1947, **69**, 200) describe a compound, m. p. 82—83°, which they thought to be impure *N*-2-chloroethylphenylacetamide.

N-2-*Chloroethylbenzamide.*—(*a*) The base, obtained from benzimino 2-chloroethyl ether hydrochloride (Gabriel and Neumann, *loc. cit.*) as described for *N*-2-chloroethylphenylacetamide, was heated at 100° for 30 minutes. The crude *N*-2-chloroethylbenzamide was crystallised from benzene–light petroleum (b. p. 80—100°); yield 26 g. (86%); m. p. 105°. Gabriel and Neumann (*loc. cit.*) record m. p. 102—103° for this substance.

(*b*) The product which separated when benzoyl chloride (7 g.) was gradually added, with vigorous shaking, to a solution of 2-chloroethylamine hydrochloride (5·8 g.; 1 mol.) in 5N-sodium hydroxide (20 c.c.; 1 mol.) was crystallised from benzene–light petroleum; yield 8 g. (87%); m. p. 105°, undepressed on admixture with material prepared from benzimino 2-chloroethyl ether hydrochloride.

N-2-*Chloroethylbenzimidochloride.*—A mixture of 2-chloroethylbenzamide (9·2 g.) and phosphorus pentachloride (11·5 g.; 1·1 mols.), heated together at 110° for 3 hours and fractionated in a vacuum, afforded N-2-*chloroethylbenzimidochloride* (7·1 g.; 70%), b. p. 120—122°/1 mm. (Found: N, 6·9. $C_9H_9NCl_2$ requires N, 6·9%).

N′-*Phenyl*-N-2-*chloroethylphenylacetamidinium Chloride.*—Finely powdered phosphorus pentachloride (5·75 g.) was dissolved in dry benzene (30 c.c.), *N*-2-chloroethylphenylacetamide (4·9 g.; 0·9 mol.) in dry benzene (20 c.c.) was added, the mixture was heated under reflux for 10 minutes, aniline (2·35 g.; 0·91 mol.) was added gradually, and the mixture was heated under reflux for 3 hours. The residue, left on evaporation under reduced pressure, afforded N′-*phenyl*-N-2-*chloroethylphenylacetamidinium chloride* on crystallisation from aqueous alcohol; m. p. 193—194°; yield 6·7 g.; 87% (Found: C, 62·0; H, 5·9; Cl′, 11·3. $C_{16}H_{17}N_2Cl,HCl$ requires C, 62·1; H, 5·9; Cl′, 11·5%).

N′-p-*Tolyl*-N-2-*chloroethylphenylacetamidinium Chloride.*—The method used was as described for the preceding preparation, *p*-toluidine (2·7 g.; 0·91 mol.) being used instead of aniline. N′-p-*Tolyl*-N-2-*chloroethylphenylacetamidinium chloride* crystallised from water; m. p. 196—197°; yield 7·8 g. (97%) (Found: N, 8·75. $C_{17}H_{20}N_2Cl_2$ requires N, 8·7%).

1-*Phenyl*-2-*benzyl*-4 : 5-*dihydroglyoxaline.*—(*a*) N′-Phenyl-*N*-2-chloroethylphenylacetamidinium chloride (6·2 g.) was dissolved in warm water, and the solution made alkaline to Titan-yellow with 5N-sodium hydroxide and extracted with chloroform. The basic gum (4·7 g.), obtained on evaporation, afforded 1-*phenyl*-2-*benzyl*-4 : 5-*dihydroglyoxaline picrate* on neutralisation to brilliant-yellow with alcoholic picric acid; needles from aqueous alcohol, m. p. 188°; yield 8·8 g. (95%) (Found: C, 57·0; H, 4·1; N, 15·15. $C_{22}H_{19}O_6N_5$ requires C, 56·8; H, 4·1; N, 15·05%).

(*b*) A warm aqueous solution of N′-phenyl-*N*-2-chloroethylphenylacetamidinium chloride (3·1 g.), with excess of neutral saturated aqueous sodium picrate, afforded the same compound (4·2 g.; 90%), m. p. and mixed m. p. after recrystallisation, 188°. The *Reineckate* crystallised from aqueous acetone; m. p. 158—159° (decomp.) (Found: SCN, 41·8. $C_{16}H_{16}N_2,H[Cr(SCN)_4(NH_3)_2]$ requires SCN, 41·8%).

1-p-*Tolyl*-2-*benzyl*-4 : 5-*dihydroglyoxaline.*—(*a*) The method described for the phenyl analogue was used; 12 g. of N′-*p*-tolyl-*N*-2-chloroethylphenylacetamidinium chloride yielded 9·1 g. of basic gum which, with picric acid, afforded 1-p-*tolyl*-2-*benzyl*-4 : 5-*dihydroglyoxaline picrate* (17·3 g.; 97%); needles from aqueous ethanol, m. p. 170° (Found: N, 14·4. $C_{23}H_{21}O_7N_5$ requires N, 14·6%).

(*b*) The same compound was obtained by interaction of the substituted amidinium chloride and neutral sodium picrate solution; m. p. and mixed m. p. 170°.

1 : 2-*Diphenyl*-4 : 5-*dihydroglyoxaline.*—(*a*) *N*-2-Chloroethylbenzimidochloride (3·4 g.) and aniline

(1·55 g.; 1 mol.) were mixed in dry benzene (10 c.c.) and heated under reflux for 90 minutes. The gum which separated could not be obtained crystalline; an aqueous solution, after being decolorised with charcoal and treated with saturated aqueous picric acid, afforded 1 : 2-*diphenyl*-4 : 5-*dihydroglyoxaline picrate* (6·8 g.; 91%); prisms from ethanol, m. p. 174—175° (Found : N, 15·6. $C_{21}H_{17}O_7N_5$ requires N, 15·6%).

(*b*) Phosphorus pentachloride (11·5 g.) was dissolved in dry benzene (50 c.c.), *N*-2-chloroethylbenzamide (9·2 g.; 0·9 mol.) was added and dissolved, and then aniline (4·65 g.; 0·9 mol.), dissolved in benzene (20 c.c.), was added slowly. The mixture was heated under reflux, protected by a calcium chloride tube, for 3 hours, and the solvent and phosphorus oxychloride were evaporated off in a vacuum. A solution of the residue in hot water (250 c.c.) was treated with charcoal; the *base*, liberated by ammonia, collected in chloroform, and recovered by evaporation, crystallised slowly from benzene–light petroleum (b. p. 80—100°); yield 10·2 g. (92%), m. p. 74—75° (Found : N, 12·5. $C_{15}H_{14}N_2$ requires N, 12·6%). The *toluene*-p-*sulphonate* crystallised when an equivalent of toluene-*p*-sulphonic acid was added to a solution of the base in *iso*propanol; m. p. 205—207° (Found : N, 7·0. $C_{22}H_{22}O_3N_2S$ requires N, 7·1%). The picrate was obtained by interaction of a solution of the base in an equivalent of N-hydrochloric acid and sodium picrate solution; m. p. and mixed m. p. with material prepared as described above, 174—175°.

2-*Phenyl*-1-p-*tolyl*-4 : 5-*dihydroglyoxaline*.—The method (*b*) described for the 1 : 2-diphenyl analogue was employed, *p*-toluidine (5·4 g.; 0·91 mol.) being used instead of aniline; the base (11·7 g.) was converted into the *toluene*-p-*sulphonate*; colourless prisms from *iso*propanol, m. p. 165°; yield 18·8 g. (91%) (Found : N, 7·0. $C_{23}H_{24}O_3N_2S$ requires N, 6·85%). The *picrate* crystallised from aqueous ethanol; m. p. 162—163° (Found : N, 15·2. $C_{22}H_{19}O_7N_5$ requires N, 15·05%).

2-*Phenyl*-1-p-*chlorophenyl*-4 : 5-*dihydroglyoxaline*.—*p*-Chloroaniline (6·4 g.; 0·9 mol.) was used in place of aniline in the same method (*b*); the base (12·1 g.) afforded the *toluene*-p-*sulphonate*, which crystallised from *iso*propanol; m. p. 163—164°; yield 19·2 g. (90%) (Found : N, 6·5. $C_{22}H_{21}O_3N_2ClS$ requires N, 6·5%). The *picrate*, yellow needles from aqueous ethanol, had m. p. 190° (Found : N, 14·5. $C_{21}H_{16}O_7N_5Cl$ requires N, 14·4%).

2-*Phenyl*-1-p-*nitrophenyl*-4 : 5-*dihydroglyoxaline*.—The volume of benzene employed in a procedure analogous to that (*b*) described for the 1 : 2-diphenyl analogue was increased to 200 c.c. owing to the lower solubility of *p*-nitroaniline (6·9 g.; 0·97 mol.). The *dihydroglyoxaline* crystallised from *iso*propanol in yellow leaflets, m. p. 177·5°; yield, 8·9 g. (67%) (Found : C, 67·2; H, 5·1; N, 16·1. $C_{15}H_{13}O_2N_3$ requires C, 67·4; H, 4·9; N, 15·7%). The *picrate* crystallised from chloroform, m. p. 173—174° (Found : N, 17·2. $C_{21}H_{16}O_8N_8$ requires N, 16·95%).

2-*Phenyl*-1-2′-*naphthyl*-4 : 5-*dihydroglyoxaline*.—2-Naphthylamine (7·15 g.; 0·9 mol.) was employed in the usual method. The *base* (12·3 g.; 90%) crystallised from benzene, m. p. 131° (Found : C, 83·2; H, 6·0; N, 10·1. $C_{19}H_{16}N_2$ requires C, 83·8; H, 5·9; N, 10·3%). The *toluene*-p-*sulphonate* crystallised from *iso*propanol; m. p. 106° (Found : N, 6·0. $C_{26}H_{24}O_3N_2S$ requires N, 6·3%). The *picrate* was obtained as needles from aqueous ethanol; m. p. 230° (Found : N, 14·1. $C_{25}H_{19}O_7N_5$ requires N, 14·0%).

Ammonolysis of Phenylacetimino-2-*Chloroethyl Ether*.—(*a*) A suspension of finely powdered phenylacetimino 2-chloroethyl ether hydrochloride (18 g.) in anhydrous ether (250 c.c.) was treated with a stream of dry ammonia for 48 hours. After removal of ammonium chloride, the ether was evaporated; towards the end of the evaporation, an exothermic reaction occurred and the temperature of the residue rose from 40° to 120°. The product was separated into basic (5·3 g.) and neutral (8·1 g.) fractions by extraction with aqueous lactic acid. The neutral fraction crystallised from light petroleum (b. p. 80—100°) (7·9 g.; 52%), m. p. 79—80°, not depressed on admixture with *N*-2-chloroethylphenylacetamide (Found : N, 7·2. Calc. for $C_{10}H_{12}ONCl$: N, 7·1%). The solution of the lactate of the basic fraction, when treated with excess of sodium picrate, afforded 2-benzyloxazoline picrate (12·1 g.; 41%); m. p. 144°. Elfeldt (*Ber.*, 1891, **24**, 3218) records m. p. 130—131° for this compound (Found : N, 14·2. Calc. for $C_{16}H_{14}O_8N_4$: N, 14·35%).

(*b*) A solution of phenylacetimino 2-chloroethyl ether hydrochloride (4·7 g.) in anhydrous ethanol (50 c.c.) containing dry ammonia (4·5 g.) was kept for 6 hours. The solvent was removed under reduced pressure, the residue basified with 5N-sodium hydroxide (5 c.c.), and the base collected in chloroform. The dry chloroform solution, divided into equal parts, afforded (i) with alcoholic picric acid, phenylacetamidinium picrate, m. p. 227—228°, not depressed on admixture with an authentic specimen (2·85 g.; 78%) (Found : N, 19·4. Calc. for $C_{14}H_{13}O_7N_5$: N, 19·3%), and (ii) with benzenesulphonic acid, phenylacetamidinium benzenesulphonate, m. p. and mixed m. p. 185—186° (Oxley and Short, *J.*, 1946, 147).

Ammonolysis of Benzimino 2-*Chloroethyl Ether*.—A solution of benzimino 2-chloroethyl ether hydrochloride (4·4 g.) in anhydrous ethanol (50 c.c.) containing dry ammonia (4·5 g.) was kept for 6 hours. Removal of the solvent and extraction with ether followed by fractionation afforded 2-phenyloxazoline, b. p. 245° (decomp.) (2·1 g.; 72%); picrate, m. p. 180—180·5°, not depressed on admixture with the picrate prepared according to Gabriel and Heymann (*Ber.*, 1890, **23**, 2493) (Found : N, 15·0. Calc. for $C_{15}H_{12}O_8N_4$: N, 14·9%). The ether-insoluble residue, after being basified with 5N-sodium hydroxide and collected in chloroform, yielded, with alcoholic picric acid, benzamidinium picrate, m. p. 238—238·5°, not depressed on admixture with authentic benzamidinium picrate (0·7 g.; 10%).

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