42. *Some Amidines and Dihydroglyoxalines of the* 1 : 1-*Diphenylethane and* 1 : 1-*Diphenylpropane Series.*

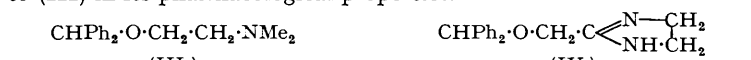
By J. O. Jílek and M. Protiva.

In view of the well-known similarity of the pharmacological properties between ethyldialkylamines and 2-methyldihydroglyoxaline derivatives 2-(2 : 2-*diphenylethyl*)-4 : 5-*dihydroglyoxaline* (VI) has been prepared as a glyoxaline analogue of "Aspasan" (V). Three similar amidines (VIII) and two lower homologues (IX and X) have also been prepared, one of them (VIII; R = H) exerting a relatively strong antihistaminic action.

Djerassi and Scholz (*J. Amer. Chem. Soc.*, 1947, **69**, 1688) noticed the analogy between the known antihistaminic agents "Antergan" (I) and "Antistin" (II). (II) differs from (I) only in that the 2-methyldihydroglyoxaline group replaces the dimethylaminoethyl moiety.

(I.) (II.)

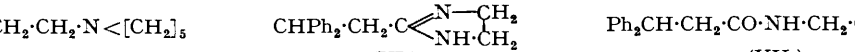
Making use of this analogy, these authors prepared a series of aryloxyacetamidines and 2-aryloxymethyldihydroglyoxalines and found them to show antihistaminic activity similar to that of the corresponding aryloxyethyldialkylamines. On the basis of the same assumptions the dihydroglyoxaline analogue (IV) of "Benadryl" (III) was recently prepared almost simultaneously in different laboratories (Protiva and Urban, *Coll. Trav. chim. Tchécosl.*, 1948, **13**, 340; Cavallini and Mazzucchi, *Farmaco*, 1947, **2**, 273; Dahlbom and Sjögren, *Acta Chem. Scand.*, 1947, **1**, 777; Djerassi and Scholz, *J. Org. Chem.*, 1948, **13**, 830) and was found to be quite similar to (III) in its pharmacological properties.



(III.) (IV.)

Considering these results, it seemed desirable to prepare amidine and dihydroglyoxaline analogues of 3 : 3-diphenylpropylamine derivatives, another pharmacologically interesting

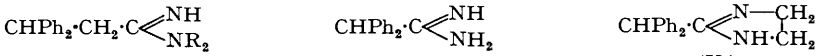
group characterised by " Aspasan " (V), showing antispasmodic and antihistaminic activity (Bockmühl and Ehrhart, *Annalen*, 1948, **561**, 52). Attention was paid first to the preparation



(V.) (VI.) (VII.)

of 2-(2 : 2-*diphenylethyl*)-4 : 5-*dihydroglyoxaline* (VI), the analogue of " Aspasan " (V). This compound was obtained from ββ-diphenylpropionitrile either through *ethyl* ββ-*diphenylpropionimidate hydrochloride* by the method of Klarer and Urech (*Helv. Chim. Acta*, 1944, **27**, 1762), or by fusion with 2-aminoethylammonium toluene-*p*-sulphonate (Oxley and Short, *J.*, 1947, 497). The first method yielded an impure hydrochloride, which by the action of ammonia gave the base (VI), m. p. 101°. From the base a crystalline *hydrochloride* (m. p. 88—90°) and *picrate* were prepared. By the second method, a crystalline *toluene*-p-*sulphonate* was obtained, which could be converted into the base and hydrochloride, identical with the products obtained by other route. The base, toluene-*p*-sulphonate, and picrate gave good analytical results; the hydrochloride in contrast, even when thoroughly dried *in vacuo*, gave results which indicated that it was a monohydrate. Since, however, it might have been ββ-diphenylpropiono-2-aminoethylamide hydrochloride (VII), which could be formed by opening the glyoxaline ring of (VI), the *base* (VII) was prepared from ethyl ββ-diphenylpropionate by the action of excess of ethylenediamine at 210—220° (Hill and Aspinall, *J. Amer. Chem. Soc.*, 1939, **61**, 822). The hydrochloride of (VII) melts at 214—215° and differs from that having m. p. 88—90°. The base (VII) is a solid of m. p. 118°.

Three new ββ-diphenylpropionamidines (VIII; $NR_2 = NH_2$, NMe_2 and $N<[CH_2]_5$) of a similar type were prepared by the action of an excess of ammonia or of the appropriate amine on ethyl ββ-diphenylpropionimidate hydrochloride. For comparison *diphenylacetamidine* (IX) and 2-benzhydryl-4 : 5-dihydroglyoxaline (X) were also prepared by standard methods.



(VIII.) (IX.) (X.)

The soluble derivatives of compounds (VI), (VIII), (IX), and (X) were tested for antihistamine activity. Only the hydrochloride of (VIII; R = H) was found to be approximately equal in activity to " Aspasan " (0·1 unit of " Benadryl " activity). Further testing for antispasmodic, analgesic, and pressor activity is in progress.

Experimental.

M.p.s are corrected. Analytical samples were dried at 0·2 mm. (P_2O_5) for 10 hours at suitable temperatures. Semimicro-analyses were by Miss Bruchalová, Ing. Mňouček, Dr. Králíčková, and Ing. Rýpar.

ββ-Diphenylpropionitrile.—This was prepared from α-cyano-ββ-diphenylpropionic acid by the method of Kohler and Reimer (*Amer. Chem. J.*, 1905, **33**, 338) and purified by distillation *in vacuo* (Freeman, Ringk, and Spoerri, *J. Amer. Chem. Soc.*, 1947, **69**, 858) and by crystallisation from ethyl alcohol–light petroleum. Yield 72%. B. p. 175—178°/2 mm. M. p. 88·5°.

Ethyl ββ-Diphenylpropionimidate Hydrochloride.—A solution of the above nitrile (11·7 g.) in a mixture of chloroform (60 c.c.) and absolute ethyl alcohol (7·5 c.c.) was saturated with dry hydrogen chloride at 0° and set aside for 10 days in a closed flask at 20°. After removal of the solvents at 30° *in vacuo* a crystalline residue remained, representing the crude product of m. p. 128°, in quantitative yield.

2-(2 : 2-*Diphenylethyl*)-4 : 5-*dihydroglyoxaline* (VI).—(*a*) The above imidate hydrochloride (8·8 g.), absolute ethylenediamine (1·9 g.), and absolute ethyl alcohol (50 c.c.) were refluxed for 7 hours in a slow stream of dry air in a bath at 100—115°. After cooling, the solution was filtered from ethylenediamine dihydrochloride [0·1 g.; m. p. 335—338° (decomp.)] which separated. The filtrate was concentrated under reduced pressure, the oily residue dissolved in water (70 c.c.), and the solution filtered and treated with concentrated aqueous ammonia (7 c.c.). The *base* (4·4 g.) was filtered off and recrystallised from 50% ethyl alcohol. It had m. p. 84—86°, or, after drying (P_2O_5 *in vacuo*), m. p. 101° (Found: C, 81·2; H, 7·5. $C_{17}H_{18}N_2$ requires C, 81·6; H, 7·2%). In another similar experiment the crude oily hydrochloride was dissolved in acetone (10 c.c.) and the solution treated with absolute ether (10 c.c.). The oil which separated crystallised (7·5 g.). Crystallisation from acetone raised the m. p. of the *hydrate* to 88—90° (Found: N, 9·2; Cl, 11·8. $C_{17}H_{19}N_2Cl,H_2O$ requires N, 9·2; Cl, 11·6%). The *picrate* crystallised from ethyl alcohol and melted at 168—170° (Found: C, 57·8; H, 4·9. $C_{23}H_{21}O_7N_5$ requires C, 57·6; H, 4·4%).

(*b*) A mixture of *ββ*-diphenylpropionitrile (35·0 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (39·2 g.) (m. p. 122—124°; Oxley and Short, *loc. cit.*) was heated for 3 hours at 200°. After cooling, the solidified mass was recrystallised from aqueous ethyl alcohol. The yield of *toluene*-p-*sulphonate*, m. p. 170—174°, was 92·5% (Found: C, 68·5; H, 6·5; N, 6·7. $C_{24}H_{26}O_3N_2S$ requires C, 68·2; H, 6·2; N, 6·6%). A suspension of this salt (15·0 g.) in hot water was treated with 20% sodium hydroxide

(30 c.c.) and extracted with chloroform. After evaporation of the solvent the residue crystallised (7·8 g.). After recrystallisation from acetone, the m. p. was 102° (Found : N, 11·3%). This base (2·0 g.) in acetone (2 c.c.) was treated with 23% alcoholic hydrogen chloride solution (1·2 c.c.). Recrystallisation of the crude product from acetone gave the hydrated hydrochloride, m. p. 88—90° (Found : C, 66·9; H, 7·0; N, 9·1%), whence the base, m. p. 100·5°, could be regenerated.

Ethyl ββ-Diphenylpropionate.—This was prepared from the nitrile by application of Spiegel's method (*Ber.*, 1918, **51**, 296). Diphenylpropionitrile (8·0 g.), absolute ethyl alcohol (7 c.c.), and concentrated sulphuric acid (2·0 c.c.) were refluxed for 3 hours at 120—130° (bath). Ethyl alcohol was distilled off *in vacuo* and the residue mixed with water (100 c.c.). The oil which separated was extracted with ether, and the solution was dried and evaporated. The residue distilled from a Hickman flask at 138—141°/0·25 mm. (yield, 5·5 g.). Wislicenus and Eble (*Ber.*, 1917, **50**, 253) gave b. p. 190—193°/12 mm.

ββ-Diphenylpropiono-2-aminoethylamide (VII).—The above ester (5·5 g.) and absolute ethylenediamine (6·0 c.c.) were heated in a sealed tube for 18 hours at 210—230°. After cooling, the excess of diamine was distilled off and the residual oil transformed (in ethyl alcohol solution) into the *hydrochloride*. Crystallisation from ethyl alcohol gave 2·0 g. of the product, m. p. 214—215° (Found : N, 9·5; Cl, 11·7. $C_{17}H_{21}ON_2Cl$ requires N, 9·2; Cl, 11·6%). From aqueous solution of this the *base* was obtained by treatment with 40% aqueous sodium hydroxide. Recrystallisation from benzene gave white prisms, m. p. 118° (Found : N, 10·6. $C_{17}H_{20}ON_2$ requires N, 10·4%).

ββ-Diphenylpropionamidine (VIII; R = H).—To a suspension of the crude imidate hydrochloride (prepared from 4·5 g. of nitrile) in absolute ethyl alcohol (10 c.c.), 8% absolute ethyl-alcoholic ammonia (100 c.c.) was added and the mixture was shaken in a closed flask for 3 hours at 20°. After 12 hours, shaking was repeated for a further 2 hours. Ammonium chloride, which separated, was filtered off and the filtrate evaporated *in vacuo* at 30—35° (bath). The residue was dissolved in chloroform (30 c.c.), the solution washed with water, 10% sodium hydroxide solution, and water, and the chloroform was distilled off. The oily residue (5·2 g.) is the crude base (VIII; R = H). The *picrate*, after recrystallisation from absolute ethyl alcohol, melted at 209—209·5° (Found : C, 55·8; H, 4·0; N, 15·5. $C_{21}H_{19}O_7N_5$ requires C, 55·6; H, 4·2; N, 15·5%).

NN-*Dimethyl-ββ-diphenylpropionamidine* (VIII; R = Me).—The crude imidate hydrochloride (4·5 g.) was dissolved in ethyl alcohol (20 c.c.), 18% ethyl-alcoholic dimethylamine solution (4·5 c.c.) was added and the mixture was set aside for 24 hours at room temperature. After evaporation of alcohol the residue was recrystallised from ethyl alcohol–ether. 3·2 G. of *hydrochloride*, m. p. 249°, were obtained (Found : C, 70·5; H, 7·3; N, 9·5. $C_{17}H_{21}N_2Cl$ requires C, 70·7; H, 7·3; N, 9·7%).

NN-*Pentamethylene-ββ-diphenylpropionamidine* (VIII; $NR_2 = N<[CH_2]_5$).—To the solution of crude imidate hydrochloride (6·2 g.) in absolute ethyl alcohol (30 c.c.) piperidine (2·0 g.) was added and the mixture set aside for 12 hours at room temperature. It was then evaporated *in vacuo* to dryness and gave, as above, 4·2 g. of *hydrochloride*, m. p. 250° (Found : C, 73·1; H, 7·6. $C_{20}H_{25}N_2Cl$ requires C, 73·0; H, 7·7%).

Ethyl Diphenylacetimidate Hydrochloride.—A solution of diphenylacetonitrile (6·6 g.), m. p. 74°, prepared by dehydration of diphenylacetamide (Neure, *Annalen*, 1889, **250**, 142), in a mixture of chloroform (30 c.c.) and absolute ethyl alcohol (5·0 c.c.) was saturated with hydrogen chloride at 0° and set aside for 14 days at room temperature in a closed flask. After evaporation of the solvents a crude product suitable for the preparation of the amidine was obtained.

Diphenylacetamidine (IX).—(*a*) A suspension of the above imidate hydrochloride in absolute ethyl alcohol (20 c.c.) was mixed with 8% ethyl-alcoholic ammonia (18·5 c.c.), and the mixture shaken for 2 hours at 20°. After 12 hours, shaking was repeated for an hour. Ammonium chloride was filtered off and the filtrate evaporated under reduced pressure. The remaining oil was dissolved in chloroform (50 c.c.), the solution washed with 5N-sodium hydroxide and water, and the chloroform evaporated. The residue is the crude amidine, m. p. 95—97° (7·1 g.). It gave a *picrate* which after recrystallisation from ethyl alcohol melted at 224—225° (decomp.) (Found : C, 54·8; H, 3·6. $C_{20}H_{17}O_7N_5$ requires C, 54·7; H, 3·9%). The hydrochloride could not be obtained crystalline.

(*b*) A mixture of diphenylacetonitrile (2·5 g.) and dried ammonium thiocyanate (4·0 g.) was heated for 5 hours at 180°. After cooling, the product was treated with hot water (10 c.c.), and the solution filtered. The filtrate was made alkaline with 5N-sodium hydroxide (10 c.c.) and extracted with chloroform. After evaporation of the solvent the residue gave a picrate (0·4 g.), m. p. 224—225°, identical with the above product.

2-*Benzhydryl-4 : 5-dihydroglyoxaline* (X).—A mixture of diphenylacetonitrile (9·6 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (11·6 g.) was heated for 3 hours at 200—210°, during which ammonia was evolved. The cooled mass was extracted with hot water (500 ml.), the mixture made alkaline with 5N-sodium hydroxide (50 c.c.) and extracted with chloroform (200 c.c.). After drying of the solution the chloroform was evaporated off. The residue (61%) is the base, which after recrystallisation from acetone melts at 133—135° (Aspinall, *J. Amer. Chem. Soc.*, 1939, **61**, 3195, gives 137°). From the base were prepared the picrate, crystallising from ethyl alcohol and melting at 184·5° (Aspinall, *loc. cit.*, gives 185°) (Found : C, 56·6; H, 4·4; N, 15·6. Calc. for $C_{22}H_{19}O_7N_5$: C, 56·8; H, 4·1; N, 15·1%), and hydrochloride, crystallising from ethyl alcohol–ether and melting at 180—182° (Ciba, Austrian P. 150,307; *Zentr.*, 1937, II, 3039, gives 192—193°) (Found : N, 10·0; Cl, 12·5. Calc. for $C_{16}H_{17}N_2Cl$: N, 10·3; Cl, 13·0%).

The authors are indebted to Mr. J. Křeček and Mrs. J. Křečková for testing the above compounds for antihistaminic activity.

Research and Control Institute of Spofa,
United Pharmaceutical Works,
Praha XI, Husinecka 11.

[*Received, September 19th*, 1949.]