*Cyclic Amidines. Part IV.** 5 : 6 : 11 : 12-*Tetrahydro*-5 : 11-endo-*methylenephenhomazine and Tröger's Base.*

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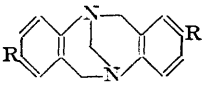
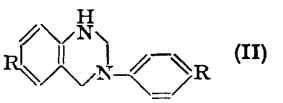
[Reprint Order No. 5938.]

5 : 11-Dichlorophenhomazine and its 2 : 8-dimethyl homologue are reduced with lithium aluminium hydride to the corresponding 5 : 6 : 11 : 12-tetrahydrophenhomazines, which with formaldehyde afford 5 : 6 : 11 : 12-tetrahydro-5 : 11-*endo*methylene- and 5 : 6 : 11 : 12-tetrahydro-2 : 8-dimethyl-5 : 11-*endo*methylene-phenhomazine (Tröger's base) respectively.

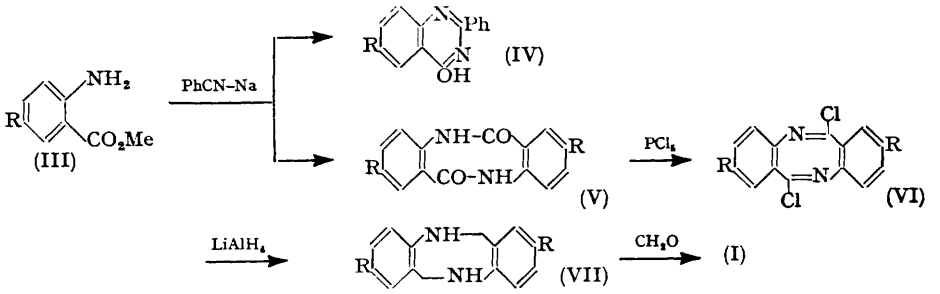
The ring system 5 : 11-*endo*methylene-5 : 6 : 11 : 12-tetrahydrophenhomazine {5 : 11-6*H* : 12*H*)-methanodibenzo[*b*, *f*][1 : 5]diazocine; Ring Index no. 2651} (I; R = H) has hitherto been known in the form of its 2 : 8-dimethyl derivative, Tröger's base (I; R = Me) (Tröger, *J. pr. Chem.*, 1887, **36**, 227; Spielman, *J. Amer. Chem. Soc.*, 1935, **57**, 583), and a few other derivatives (Miller and Wagner, *ibid.*, 1941, **63**, 832; Smith and Schubert, *ibid.*, 1948, **70**, 2656). In confirmation of the structure proposed, Spielman (*loc. cit.*) prepared the base by treatment of 1 : 2 : 3 : 4-tetrahydro-6-methyl-3-*p*-tolylquinazoline (II; R = Me) with formaldehyde. The success of this preparation appears to depend on the

* Part III, *J.*, 1955, 510.

reactivity of the 2′-position, since the quinazolines (II; R = OMe or OEt) afford the corresponding analogues of Tröger's base (I; R = OMe or OEt), whereas the eight-membered ring is not formed from the halogenated quinazolines (II; R = Cl or Br) (Miller and Wagner, *loc. cit.*). Wagner (*J. Amer. Chem. Soc.*, 1935, **57**, 1296) speculated on the

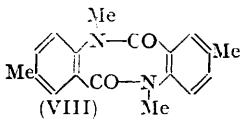
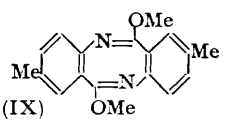
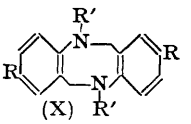
(I)   (II)

possibility of a more direct synthesis by the condensation of formaldehyde and 5 : 6 : 11 : 12-tetrahydro-2 : 8-dimethylphenhomazine (VII; R = Me), but this compound was not then available. We have now investigated the synthesis of 5 : 6 : 11 : 12-tetrahydrophenhomazines and their conversion into their 5 : 11-*endo*methylene derivatives.



Methyl 5-methylanthranilate (III; R = Me) reacts exothermally with benzonitrile in the presence of " powdered " sodium to furnish (cf. Part I, *J.*, 1954, 3429), in addition to 4-hydroxy-6-methyl-2-phenylquinazoline (IV; R = Me), 2 : 8-dimethyldianthranilide (V; R = Me) which affords its *NN*′-dimethyl derivative (VIII) with methyl sulphate. 6 : 12-Dichloro-2 : 8-dimethylphenhomazine (VI; R = Me) results when the foregoing dianthranilide is brought into reaction with phosphorus pentachloride; experiments with dianthranilide itself (V; R = H) indicated that an analogous reaction cannot be effected with thionyl chloride or phosphorus oxychloride. Interaction of the dichloro-compound (VI; R = Me) and sodium methoxide gives the dimethoxyphenhomazine (IX).

Schroeter (*Ber.*, 1919, **52**, 2224) has reported his inability to reduce 6 : 12-dichlorophenhomazine (VI; R = H). We find that most of the compound is recovered unchanged after treatment of it with Raney alloy and alkali. Attempts to reduce dianthranilide with hydriodic acid without fission of the ring system were also unsuccessful. However,

 (VIII)  (IX)  (X)

dichlorophenhomazines (VI; R = H or Me) furnish 5 : 6 : 11 : 12-tetrahydrophenhomazines (VII; R = H or Me) when lithium aluminium hydride is employed as reducing agent. These tetrahydrophenhomazines react readily with formaldehyde to yield their 5 : 11-*endo*methylene derivatives (I; R = H or Me). The 2 : 8-dimethyl derivative (I; R = Me) is identical with Tröger's base.

In agreement with Spielman's observations (*loc. cit.*), we find that, on acylation or treatment with nitrous acid, 5 : 6 : 11 : 12-tetrahydro-2 : 8-dimethyl-5 : 11-*endo*methylenephenhomazine loses the *endo*methylene group to afford derivatives of tetrahydrophenhomazine (X; R = Me, R′ = Ac, Bz, or NO) identical with authentic specimens prepared directly from the tetrahydrophenhomazine (X; R = Me, R′ = H). The 5 : 11-dibenzoyl (X; R = H, R′ = Bz) and the 5 : 11-dinitroso-derivative (X; R = H, R′ = NO) may be obtained in a similar manner both directly from the secondary amine (X; R = R′ = H) and, with loss of the *endo*methylene group, from the tertiary amine (I; R = H). The

dinitrosamine (X; R = H, R′ = NO) could not be induced to undergo the Fischer–Hepp rearrangement.

Experimental

Spectroscopic measurements were made in absolute ethanol.

5 : 6 : 11 : 12-*Tetrahydrophenhomazine.*—There was a mildly exothermic reaction when lithium aluminium hydride (0·5 g.) in ether (80 ml.) was added to a suspension of 6 : 12-dichlorophenhomazine (Schroeter, *loc. cit.*) (2·5 g.) in ether (50 ml.). After 4 hours' refluxing, excess of reductant was decomposed by ethyl acetate (5 ml.), water (50 ml.) was added, and the mixture was made alkaline with sodium hydroxide (7 g.). The ether-soluble fraction (2·05 g.) afforded 5 : 6 : 11 : 12-*tetrahydrophenhomazine* (1·45 g., 76%) as colourless needles, m. p. 138·5—139·5°, after two recrystallisation from light petroleum (b. p. 100—120°) (charcoal) [Found: C, 80·2; H, 6·8; N, 13·4%; *M* (Rast), 215. $C_{14}H_{14}N_2$ requires C, 79·95; H, 6·7; N, 13·3%; *M*, 210]. Light absorption: $\lambda_{max.}$ 206, 242, 290 mμ (ε 40,000, 13,400, 2900). The *dihydrochloride*, obtained as small prisms by the addition of concentrated hydrochloric acid to a solution of the base in ethanol, was very sparingly soluble and could not be recrystallised; it darkened above 260° and did not melt below 400° (Found: C, 59·1; H, 5·55; N, 9·6. $C_{14}H_{16}N_2Cl_2$ requires C, 59·35; H, 5·7; N, 9·9%). Interaction of the base in ethanol with picric acid gave the *dipicrate* as clusters of minute needles, m. p. 161—163° (Found: C, 47·0; H, 2·8; N, 16·6. $C_{26}H_{20}O_{14}N_8$ requires C, 46·7; H, 3·0; N, 16·75%).

The *diacetyl* derivative, prepared by boiling the base with acetic anhydride, crystallised from aqueous acetic acid as small prisms, m. p. 335—337° (Found: C, 73·5; H, 5·95; N, 9·75. $C_{18}H_{18}O_2N_2$ requires C, 73·45; H, 6·15; N, 9·5%).

Benzoylation under Schotten–Baumann conditions afforded 5 : 11-*dibenzoyl*-5 : 6 : 11 : 12-*tetrahydrophenhomazine* which crystallised from *n*-butanol as platelets, m. p. 306·5—307·5° (Found: C, 80·3; H, 5·55; N, 6·85. $C_{28}H_{22}O_2N_2$ requires C, 80·35; H, 5·3; N, 6·7%).

5 : 6 : 11 : 12-*Tetrahydro*-5 : 11-*dinitrosophenhomazine* separated immediately on the addition of sodium nitrite to a solution of the base in dilute hydrochloric acid, and it crystallised from benzene as small prisms, m. p. 233—234° (Found: C, 62·9; H, 4·6; N, 20·2. $C_{14}H_{12}O_2N_4$ requires C, 62·65; H, 4·5; N, 20·9%). This compound gave a positive Liebermann nitroso-reaction.

5 : 6 : 11 : 12-*Tetrahydro*-5 : 11-endo*methylenephenhomazine.*—To a cold mixture of concentrated hydrochloric acid (5 ml.), 40% formaldehyde solution (2 ml.), and ethanol (10 ml.) was added finely powdered 5 : 6 : 11 : 12-tetrahydrophenhomazine (0·5 g.). The solid (0·45 g.) which was slowly deposited was collected next day, dissolved in hot water, and treated with excess of ammonia; the precipitate (0·35 g.; m. p. 138—139°) on crystallisation from light petroleum (b. p. 100—120°) furnished the 5 : 11-endo*methylene* derivative as prisms, m. p. 138—139°; a mixed m. p. with 5 : 6 : 11 : 12-tetrahydrophenhomazine was 108—115°. A further quantity (0·1 g., m. p. 138—139°) was recovered from the filtrate from the reaction mixture (total yield 85%) [Found: C, 80·95; H, 6·4; N, 12·3%; *M* (Rast), 274. $C_{15}H_{14}N_2$ requires C, 81·0; H, 6·35; N, 12·6%; *M*, 222]. Light absorption: $\lambda_{max.}$ 203, 240, 280 mμ (ε 33,700, 6300, 1600). Its *hydrochloride* crystallised from dilute hydrochloric acid as small prisms which shrank at about 250° and darkened without melting up to 360°; when inserted into the heating bath at 300°, the compound effervesced and resolidified (Found: C, 69·2; H, 5·65. $C_{15}H_{15}N_2Cl$ requires C, 69·6; H, 5·85%). The *picrate* was obtained as small prisms, m. p. 190—191° (decomp.), from *n*-butanol (Found: C, 56·1; H, 3·6. $C_{21}H_{17}O_7N_5$ requires C, 55·85; H, 3·8%).

The product of treatment of the foregoing base with nitrous acid had, after crystallisation from benzene, m. p. 233—234° alone or in admixture with 5 : 6 : 11 : 12-tetrahydro-5 : 11-dinitrosophenhomazine. The compound obtained on benzoylation as described for 5 : 11-dibenzoyl-5 : 6 : 11 : 12-tetrahydrophenhomazine was identical with this compound as shown by m. p. and mixed m. p.

2 : 8-*Dimethyldianthranilide.*—There was an exothermic reaction when methyl 5-methylanthranilate (38·8 g.), prepared by the Fischer–Speier esterification of 5-methylanthranilic acid, and benzonitrile (48·4 g.) were added to "powdered" sodium (10·8 g.) in dry benzene (125 ml.). When the spontaneous boiling had subsided, the mixture was refluxed for 5 hr. Ethanol (10 ml.) and water (150 ml.) were added. The insoluble material was collected, washed with dilute hydrochloric acid and with water, and fractionally crystallised from ethanol. 2 : 8-*Dimethyldianthranilide* (11·6 g., 37%) occurred as small rods, m. p. 298—299° (Found: C, 72·4; H, 5·5; N, 10·8. $C_{16}H_{14}O_2N_2$ requires C, 72·15; H, 5·3; N, 10·5%). Light absorption: $\lambda_{max.}$ 210 mμ (ε 35,600). This compound was but sparingly soluble in aqueous sodium hydroxide.

The second product, *4-hydroxy-6-methyl-2-phenylquinazoline* (5·7 g.), separated as pale yellow needles, m. p. 265—266° (Found: C, 76·5; H, 4·9; N, 12·1. $C_{15}H_{12}ON_2$ requires C, 76·25; H, 5·1; N, 11·85%). Light absorption: $\lambda_{max.}$ 209, 237, 294 mμ (ε 28,700, 27,700, 16,000). Light absorption of 4-hydroxy-2-phenylquinazoline: $\lambda_{max.}$ 206, 237, 291 mμ (ε 25,100, 26,500, 14,300). A further quantity (3·1 g.) of the quinazoline was recovered by faintly acidifying the aqueous layer obtained in working up.

2 : 8 : N : N′-*Tetramethyldianthranilide*, prepared by treatment of the foregoing dianthranilide (0·4 g.) with methyl sulphate (0·5 ml.) and 2N-sodium hydroxide (10 ml.), crystallised from benzene–light petroleum (b. p. 80—100°) as needles, m. p. 254—255° (Found: C, 73·7; H, 6·1. $C_{18}H_{18}O_2N_2$ requires C, 73·45; H, 6·15%). Light absorption: $\lambda_{max.}$ 213 mμ (ε 31,100)

6 : 12-*Dichloro*-2 : 8-*dimethylphenhomazine*.—Finely powdered 2 : 8-dimethyldianthranilide (7·45 g.) and phosphorus pentachloride (12·5 g.) were boiled together in chloroform (50 ml.) for 4 hr. After filtration, the solid (4·85 g.) which separated on concentration of the filtrate was crystallised from light petroleum (b. p. 100—120°) and afforded 6 : 12-*dichloro*-2 : 8-*dimethylphenhomazine* (4·05 g., 48%) as prisms, m. p. 209—210° (Found: C, 63·7; H, 3·65; N, 9·3. $C_{16}H_{12}N_2Cl_2$ requires C, 63·35; H, 4·0; N, 9·25%).

6 : 12-*Dimethoxy*-2 : 8-*dimethylphenhomazine* was formed in 90% yield by boiling the foregoing dichloro-compound in methanolic sodium methoxide for 23 hr., and it crystallised from light petroleum (b. p. 100—120°) as prisms, m. p. 155—156° (Found: C, 73·4; H, 5·9; N, 9·4. $C_{18}H_{18}O_2N_2$ requires C, 73·45; H, 6·15; N, 9·5%). Light absorption: $\lambda_{max.}$ 204, 258 mμ (ε 47,100, 6600). Light absorption of 6 : 12-dimethoxyphenhomazine: $\lambda_{max.}$ 203, 253 mμ (ε 46,100, 5900) and of 6 : 12-diethoxyphenhomazine: $\lambda_{max.}$ 203, 252 mμ (ε 45,500, 6100); the values for these two compounds recorded in Part I (*loc. cit.*) are incorrect.

5 : 6 : 11 : 12-*Tetrahydro*-2 : 8-*dimethylphenhomazine*.—After 6 : 12-dichloro-2 : 8-dimethylphenhomazine (2·7 g.) and lithium aluminium hydride (0·5 g.) had been brought into reaction for 2¼ hr. as described for 5 : 6 : 11 : 12-tetrahydrophenhomazine, the ether-soluble material (1·85 g.) was separated by treatment with aqueous lactic acid into a neutral fraction (0·6 g.), which was unchanged starting material, and a basic fraction (0·8 g., m. p. 197—201°). The latter on crystallisation from light petroleum (b. p 100—120°) afforded 5 : 6 : 11 : 12-*tetrahydro*-2 : 8-*dimethylphenhomazine* as colourless leaflets, m. p. 205—206°, depressed to below 190° by the original dichloro-compound (Found: C, 80·6; H, 7·65; N, 11·7. $C_{16}H_{18}N_2$ requires C, 80·6; H, 7·6; N, 11·75%). Light absorption: $\lambda_{max.}$ 207, 242, 295 mμ (ε 46,900, 16,200, 3200). Prolongation of the period of reduction to 8½ hr. gave the desired product in 74% yield. Its *dipicrate* separated as small prisms, m. p. 162—164°, when the base and picric acid reacted in ethanol (Found: C, 48·1; H, 3·4. $C_{28}H_{24}O_{14}N_8$ requires C, 48·3; H, 3·45%).

Acetylation of the base with boiling acetic anhydride afforded 5 : 11-diacetyl-5 : 6 : 11 : 12-tetrahydro-2 : 8-dimethylphenhomazine which separated as small prisms, m. p. 297—298°, from aqueous acetic acid (Found: N, 8·85. Calc. for $C_{20}H_{22}O_2N_2$: N, 8·7%). This compound did not depress the m. p. of the product of acetylation of Tröger's base, m. p. 297—298°, obtained by the method of Spielman who records (*loc. cit.*) m. p. 286—288°.

The dibenzoyl derivative, prepared under Schotten–Baumann conditions, occurred as platelets, m. p. 301—302°, from xylene (Found: C, 80·6; H, 5·9. Calc. for $C_{30}H_{26}O_2N_2$: C, 80·7; H, 5·85%). By this method, the same compound, m. p. and mixed m. p. 301—302°, was obtained from Tröger's base in 56% yield; by Spielman's method the yield was only 10%. Spielman records m. p. 290—291° for this compound.

On being treated with nitrous acid, this base afforded the 5 : 11-dinitroso-derivative, m. p. 247—248°, undepressed on admixture with the compound obtained by Spielman's method from Tröger's base (Found: C, 65·0; H, 5·7. Calc. for $C_{16}H_{16}O_2N_4$: C, 64·85; H, 5·45%). Spielman records m. p. 246—247° (254—255° corr.) for this compound.

5 : 6 : 11 : 12-*Tetrahydro*-2 : 8-*dimethyl*-5 : 11-endo*methylenephenhomazine*, prepared from the corresponding tetrahydrophenhomazine and formaldehyde in 95% yield, was obtained as colourless needles, m. p. 136—137°, undepressed on admixture with Tröger's base prepared in 30% yield by Goecke's method (*Z. Elektrochem.*, 1903, **9**, 470). Light absorption: $\lambda_{max.}$ 205, 235, 285 mμ (ε 35,700, 8300, 2000); in hexane, $\lambda_{max.}$ 246, 290 mμ (ε 8200, 2200). Wepster (*Rec. Trav. chim.*, 1953, **72**, 661) records for Tröger's base in *iso*octane: $\lambda_{max.}$ 247·5, 291 mμ (ε 8490, 2230).

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[*Received, December 3rd*, 1954.]