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NEW HETEROCYCLIC SYSTEMS—I

5,6-DIHYDRO-7*H*, 12*H*-DIBENZ[*c,f*]AZOCINE

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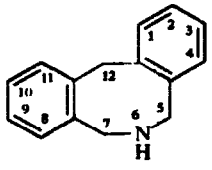
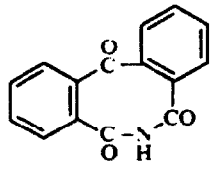
Abstract—The synthesis of 5,6-dihydro-7*H*,12*H*-dibenz[*c,f*]azocine (I), a new tricyclic system, has been realized. I was clearly identified by the usual analytical data, spectral properties and threefold mode of formation. PMR shows that the dibenzazocine ring system does not rotate freely at room temperature.

THE present series describes the synthesis of new heterocyclic systems potentially useful as starting materials for derivatives of pharmaceutical interest.[1] Due to the pharmacological properties of derivatives of phenothiazine, 6,7-dihydro-5*H*-dibenz[*c.e*]azepine, 10,11-dihydro-5*H*-dibenz[*b,f*]azepine, and 5,10,11,12-tetrahydrobidenz[*b.g*]azocine, we initially searched for related new heterocyclic systems. We describe here the synthesis of 5,6-dihydro-7*H*,12*H*-dibenz[*c,f*]azocine (I), a tricyclic system which had not been previously reported except for 5,6-dihydro-7*H*,12*H*-dibenz[*c,f*]azocine-5,7,12-trione (II), obtained in 1959 by Baker *et al.*[2] The general structure of I was listed in 1962 in U.S. Patent No. 3,038,896,[3] but neither its preparation nor that of its derivatives was reported or claimed.



I

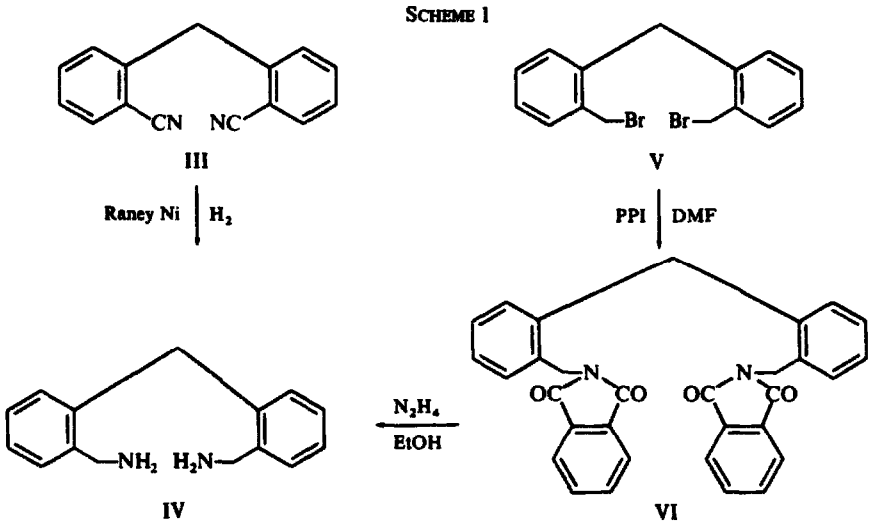


II

I was initially synthesized by closure of 2,2'-bis-aminomethyldiphenylmethane (IV), which was prepared both by catalytic hydrogenation of 2,2'-bis-cyanodiphenylmethane (III), and by making 2,2'-bis-bromomethyldiphenylmethane (V)[4] react in DMF with potassium phthalimide (PPI) and subsequently reacting the diphthalimide derivative VI with N_2H_4 (Scheme 1). An 8 hr. heating at 300° of an equimolecular mixture of IV and its dihydrochloride afforded I in scarcely 35% yield. The overall yield of I was very nearly 34% from III and 23% from V.

While seeking alternate routes which would give higher yields of I, V was made to react with compounds suitable for obtaining dibenzazocines carrying groups on nitrogen which could then be easily eliminated. In the first route (Scheme 2) reaction of V with sodium cyanamide gave 5,6-dihydro-7*H*,12*H*-cyanodibenz[*c,f*]azocine (VII), which was subsequently decyanated by sodamide to afford I in an overall yield of only 27·5%. In the second route (Scheme 3) I was successfully obtained in the overall

SCHEME 1



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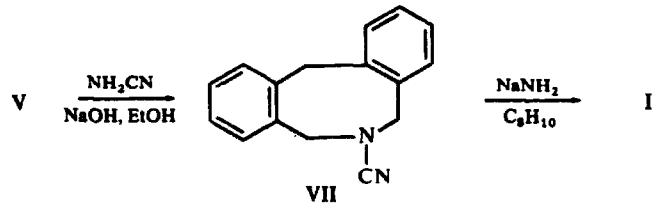
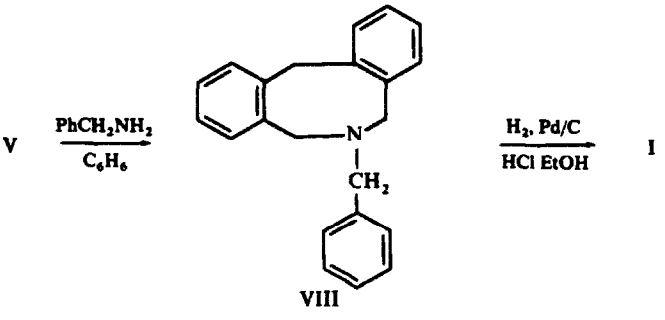


SCHEME 3



yield of 52% by reaction of V with benzylamine followed by catalytic debenzylation of 5,6-dihydro-7*H*,12*H*-6-benzyldibenz[*c,f*]azocine (VIII) hydrochloride.

Besides the threefold mode of formation, the identity of I was clearly established by the usual analytical data and spectral properties (Experimental).

The PMR spectra of I, VII, and VIII in $CDCl_3$ solution at various temperatures (Fig. 1) exhibit a typical temperature dependent coalescence sequence of all the three methylene groups of the heterocyclic ring attributable to the fact that dibenzazocine is not a freely rotating ring system. At a temperature of $-30°$ for I and VII and $-10°$

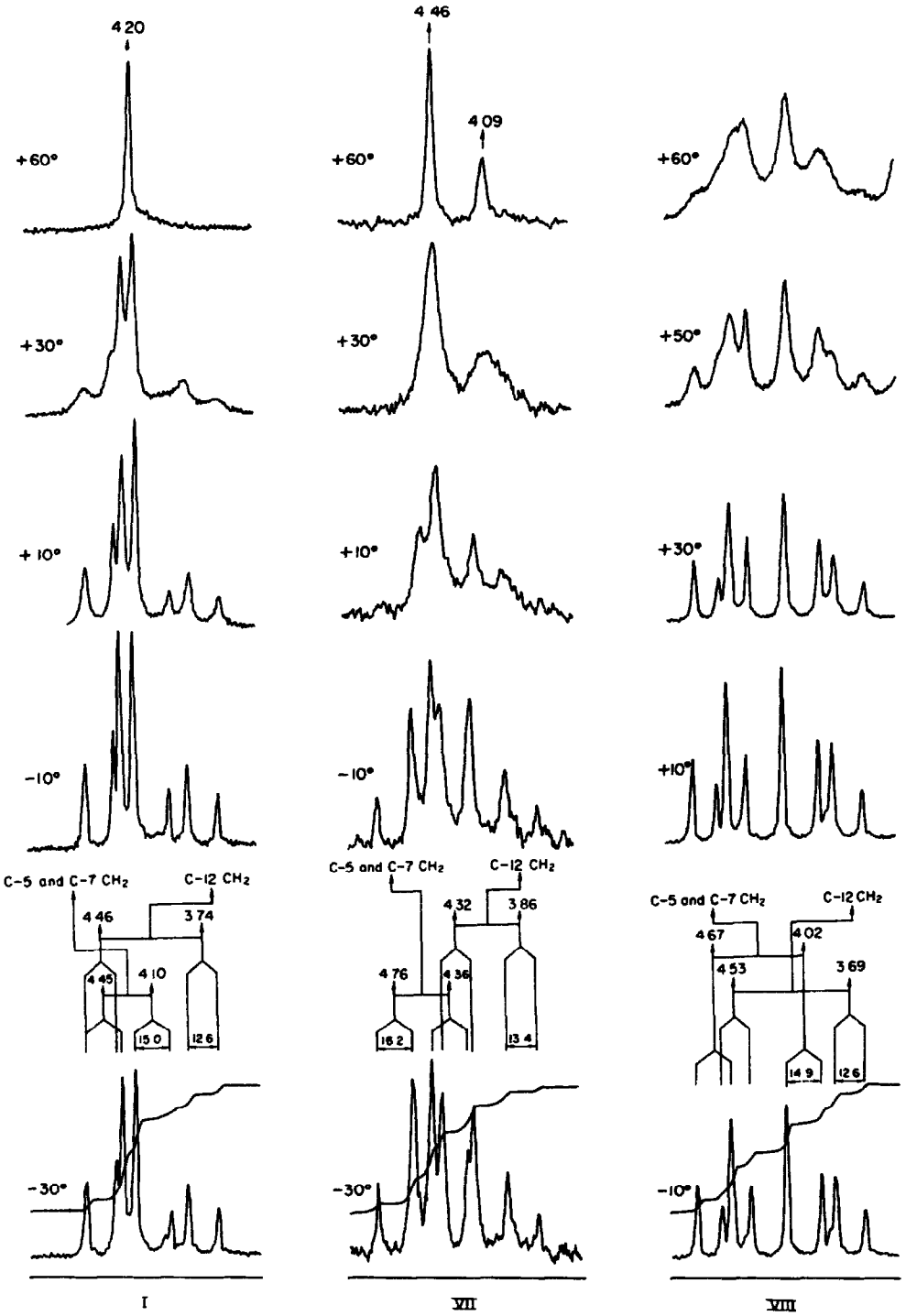


FIG 1. PMR coalescence spectra of I, VII, and VIII in $CDCl_3$ solution. J values given in cycles per second; chemical shifts given in parts per million (δ)

for VIII, a complete rigidity of the system is obtained. In these spectra, the methylene pattern of the azocine ring is composed of two quartets. One of them corresponds to the C-5 and C-7 chemically equivalent methylene groups, which give rise to two equal AB systems with two unequal protons in each. The C-12 methylene group gives rise to another AB system, which is however chemically different from the other two. Increasing temperature to +60° causes a nearly complete coalescence of the signals of all the methylene groups of the azocine ring in I and VII. This temperature is unable to give in VIII an even partial coalescence of these signals, thus indicating that in this compound the azocine ring has a degree of rigidity greater than in I and VII.

EXPERIMENTAL

M.ps were taken on a Büchi capillary m.p. apparatus and are corrected. The UV spectrum of I was determined in abs EtOH using a Beckman DB spectrophotometer. IR spectra were recorded as nujol mulls (unless otherwise stated) using a Perkin–Elmer 337 grating spectrometer. PMR spectra were run in $CDCl_3$ soln on a Varian A-60 A spectrometer, operating at 60·00 Mc/s in a radio-frequency range of 0·02–0·06 milligauss; the reference zero was internal TMS and the chemical shifts were expressed in ppm down-field from this point (δ-scale); temps were maintained with the V-6057 controller and were calibrated with the standard samples of MeOH and ethylene glycol supplied by Varian. Microanalyses were carried out by Dr. G. Sekules.

2,2'-Bis-carbamyldiphenylmethane (IX)

2,2'-Bis-carboxydiphenylmethane[4] (30 g; 0·117 mole) and $SOCl_2$ (300 ml; 4·17 mole) were warmed 1 hr at 60°. The soln was evaporated to dryness and the residue was extracted with C_6H_6. Evaporation of the solvent gave 30 g (87%) of the acid chloride, which was then gradually poured into 28% NH_4OH (160 ml) with external cooling. The mixture was stirred 30 min at room temp and the solid was filtered and washed with H_2O, to give 25·6 g (98·5%) of IX, m.p. 238–239°. (Found: C, 70·74; H, 5·59; N, 10·93. $C_{15}H_{14}N_2O_2$ requires: C, 70·85; H, 5·55; N, 11·02%.)

2,2'-Bis-cyanodiphenylmethane (III)

Compound IX (30·9 g; 0.1215 mole) and $SOCl_2$ (150 ml; 2·08 mole) were warmed 18 hr at 65–75°. The reaction mixture was evaporated to dryness and the residue was crystallized from 95% EtOH, to give 20 g (75%) of III, m.p. 147–148°. (Found: C, 82·38; H, 4·70; N, 12·77. $C_{15}H_{10}N_2$ requires: C, 82·54; H, 4·62; N, 12·84%.)

2,2'-Bis-aminomethyldiphenylmethane (IV)

(a) *From 2,2'-bis-cyanodiphenylmethane* (III). A soln of 10·9 g (0·05 mole) of III in abs EtOH (300 ml) was saturated with NH_3 and hydrogenated over Raney Ni at 120° and 120 atm initial H press. The catalyst was then filtered off and the soln was evaporated to dryness to give 11 g (97%) of crude IV as a thick oil. Vacuum distillation furnished an analytical sample, b.p. 142–145° (0·15 mm). (Found: C, 79·72; H, 7·95; N, 12·28. $C_{15}H_{18}N_2$ requires: C, 79·60; H, 8·02; N, 12·38%); IR (liquid film): 3371 and 3288 cm^{-1} (NH_2), 740 cm^{-1} (*ortho* substituted benzenes); PMR: 1·24 δ (NH_2, s, 4 H), 3·80 δ (CH_2-N, s, 4 H), 4·12 δ (Ar-CH_2-Ar, s, 2 H), 6·8–7·5 δ (aromatics, complex, 8 H.)

By adding excess conc HCl to a soln of the free base IV (5 g, 0·022 mole) in boiling EtOH (50 ml), 6·5 g (98%) of the *dihydrochloride* separated on standing as colourless needles, m.p. 279–280°. (Found: C, 60·17; H, 6·80; N, 9·33; Cl, 23·52. $C_{15}H_{20}N_2Cl_2$ requires: C, 60·22; H, 6·74; N, 9.37; Cl, 23·68%.)

(b) *From 2,2'-bis-bromomethyldiphenylmethane* (V). 40 g (0·113 mole) of V[4] and 42·68 g (0·23 mole) of PPI were warmed 3 hr at 160° in DMF (120 ml). The reaction mixture was poured into H_2O (1·8 l.) and the solid was filtered, washed with H_2O, and dried. Recrystallization from C_6H_6 gave 46·4 g (84%) of the *diphthalimido derivative* VI, m.p. 216–217°. (Found: C, 76·40; H, 4·71; N, 5·70. $C_{31}H_{22}N_2O_4$ requires: C, 76·53; H, 4·56; N, 5·76%.)

36·8 g (0·074 mole) of VI and 13·9 g (0·222 mole) of 80% $N_2H_4 \cdot H_2O$ were refluxed 7 hr in 95% EtOH (720 ml). The reaction mixture was evaporated to dryness and the residue was refluxed 10 min with 18% HCl (1·5 l.). The suspension was filtered and the solid was taken up with H_2O (250 ml). The solid which remained was filtered off and the filtrate was saturated with HCl. The ppt which formed was filtered and dried, to give 17·1 g (77%) of IV *dihydrochloride*, m.p. and m.m.p. 279–280°. The yield was 64·7%, based on V.

5,6-Dihydro-7H,12H-6-cyanodibenz[c.f]azocine (VII)

Compound V[4] (20 g; 0·0565 mole) NH_2CN (2·38 g; 0·0565 mole) and NaOH (4·52 g; 0·113 mole) were refluxed 12 hr with stirring in 70% EtOH (100 ml). The reaction mixture was evaporated to dryness and the residue was taken up with H_2O, filtered and dissolved in acetone. After filtration, removal of acetone furnished a solid which was crystallized from acetonitrile to give 7·27 g (55%) of pure VII as colourless crystals, m.p. 239–240°. (Found: C, 81·94; H, 6·07; N, 11·90; mol. wt. 232 by cryoscopy. $C_{16}H_{14}N_2$ requires: C, 82·02; H, 6·02; N, 11·96%; mol. wt. 234); IR: 2200 cm^{-1} (CN), 740 and 720 cm^{-1} (*ortho* substituted benzenes); PMR: 6·9–7·6 δ (aromatics, complex, 8 H.)

5,6-Dihydro-7H,12H-6-benzyldibenz[c.f]azocine (VIII)

A soln of 97 g (0·906 mole) of benzylamine in anhyd C_6H_6 (200 ml) was added dropwise at room temp into a soln of 100 g (0·282 mole) of V[4] in anhyd C_6H_6 (500 ml). The mixture was refluxed 3 hr with stirring, cooled to room temp and filtered to remove benzylamine hydrobromide. After washing with H_2O, the soln was dried over Na_2SO_4 and then evaporated to dryness to give 66 g (78%) of crude VIII, m.p. 108–111°. Recrystallization from 95% EtOH furnished an analytical sample as colourless crystals, m.p. 113–114°. (Found: C, 88·95; H, 7·04; N, 4·55; mol. wt. 298 by cryoscopy. $C_{22}H_{21}N$ requires: C, 88·25; H, 7·07; N, 4·68%; mol. wt. 299); IR: 753 cm^{-1} (*ortho* substituted benzenes), 723 and 699 cm^{-1} (mono-substituted benzene); PMR: 3·22 δ (benzyl-CH_2, s, 2 H), 6·7–7·5 δ (aromatics, complex, 13 H).

By bubbling HCl into a soln of the free base VIII (44·9 g, 0·15 mole) in C_6H_6 (500 ml), 48·9 g (97%) of the *hydrochloride* separated as a white solid. Recrystallization from 95% EtOH afforded an analytical sample as colourless crystals, m.p. 257–258°. (Found: C, 78·04; H, 6·44; N, 4·42; Cl, 10·41. $C_{22}H_{22}NCl$ requires: C, 78·67; H, 6·60; N, 4·17; Cl, 10·56%.)

5,6-Dihydro-7H,12H-dibenz[c.f]azocine (I)

(a) *By closure of the diamine* IV. 1·6 g (0·07 mole) of IV and 2·12 g (0·007 mole) of its dihydrochloride were warmed 8 hr at 300° in a sealed tube in H_2O (80 ml). The mixture was taken up in dil HCl and the soln, after filtering, was made alkaline with 10% NaOH aq. The ppt which formed was filtered and crystallized from 40% EtOH to give 1·03 g (35%) of I as colourless and tasteless needles, m.p. 124·5–125°. (Found: C, 86·11; H, 7·24; N, 6·71; mol. wt. 209 by cryoscopy. $C_{15}H_{15}N$ requires: C, 86·08; H, 7·22; H, 6·69%; mol. wt. 209). Sublimes at 120° at 760 mm and at 110° at 15 mm. Insoluble in H_2O, freely sol in acids and in the common organic solvents. Quite stable in air, in sunlight and on heating; UV (ε): 211 mμ (12, 220), 224 mμ (8,690), 261 mμ (702); IR: 3216 cm^{-1} (NH), 747 cm^{-1} (*ortho* substituted benzenes); PMR: 1·40 δ (NH, s, 1 H), 6·9–7·6 δ (aromatics, complex, 8 H).

The *hydrochloride* was prepared by adding ethanolic HCl to a soln of the free base in boiling abs EtOH, m.p. 332–334°. (Found: C, 73·55; H, 6·61; N, 5·65; Cl, 14·35. $C_{15}H_{16}$ NCl requires: C, 73·30; H, 6·56; N, 5·70; Cl, 14·43%.)

The *picrate* was prepared by adding an aq soln of picric acid to an aq soln of I hydrochloride. The ppt which formed was filtered and crystallized from 95% EtOH to give orange-yellow crystals, m.p. 223·5–224·5°. (Found: C, 58·65; H, 4·14; N, 12·65. $C_{21}H_{18}N_4O_7$ requires: C, 57·53; H, 4·14; N, 12·78%.)

The *tosyl derivative* was prepared by refluxing 30 min a soln of I and *p*-toluenesulphonyl chloride in dry pyridine. Recrystallized from 95% EtOH, it melted at 184–185°. (Found: C, 73·01; H, 5·93; N, 3·78; S, 8·94. $C_{22}H_{21}NO_2S$ requires: C, 72·69; H, 5·82; N, 3·85; S, 8·82%.)

(b) *By decyanation of* VII. A mixture of VII (1·8 g, 0·0077 mole) and $NaNH_2$ (1·2 g, 0·0307 mole) was refluxed 7 hr in xylene (20 ml). The mixture was cooled and cautiously decomposed with H_2O. The organic layer was diluted with C_6H_6, extracted with dil HCl, and the acidic soln was made alkaline with 10% NaOH aq and extracted with ether. After evaporation of the solvent, the residue was crystallized from 40% EtOH to give 0·8 g (50%) of I, m.p. and m.m.p. 124·5–125°.

(c) *By catalytic debenzylation of* VIII. A soln of 8·95 g (0·026 mole) of VIII hydrochloride in abs EtOH (1·2 l.) was hydrogenated over 5 g of 5% Pd/C at room temp and press. The catalyst was then filtered off, and the soln was concentrated to small volume to give 4·3 g (67%) of crude I hydrochloride. Recrystallization from abs EtOH furnished an analytical sample as colourless crystals, m.p. and m.m.p. 332–334°.

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