SYNTHESIS OF SOME DERIVATIVES OF 1-PHENYL-2,3,4,5-TETRAHYDRO-1*H*-3-BENZAZEPINE AND 11-PHENYL-5,6-DIHYDRO-11*H*-*s*-TRIAZOLO[3,4-*b*]-3-BENZAZEPINE

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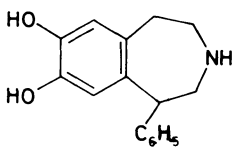
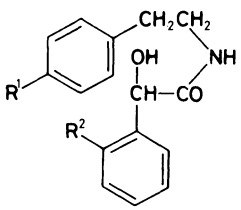
Hydroxylated derivatives of 1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, e.g. *I*, are being investigated in the last ten years as dopaminomimetic or antidopaminergic agents[1]. Methods of synthesis of 3-benzazepine derivatives were reviewed by Kametani and Fukumoto[2].

The following preparative work was carried out as synthetic model experiments in the field. The mandelic acid amide *II* (refs[3-5]) was cyclized with polyphosphoric acid according to ref.[5] (for the method, cf. also ref.[6]) to *VIa* which was transformed by heating with phosphorus pentasulfide in pyridine to the thiolactam *VIb* (band of N—C=S in the IR spectrum at 1 567 cm^{-1}).

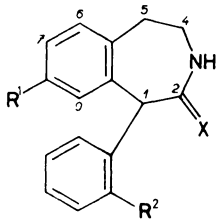
The following reaction with acethydrazide[7] in boiling 2-(ethoxy)ethanol or butanol (for the method, cf.[8]) afforded the annelated triazole derivative *X* of elemental composition $C_{18}H_{17}N_3$ (analysis and mass spectrum) which was characterized by the UV and IR spectra. The mandelic acid amide *III* (ref.[9]) was similarly cyclized to *VIIa* (ref.[9]) which was further transformed via *VIIb* to the triazolo compound *XI* (elemental composition $C_{18}H_{16}ClN_3$ on the basis of analysis and mass spectrum). 2-Chloromandelic acid[10] was reacted with 2-phenylethylamine and 2-(4-chlorophenyl)-ethylamine[11] by heating with boiling xylene; the crystalline amides *IV* and *V* were obtained and characterized by IR and ^{1}H NMR spectra. They were cyclized with polyphosphoric acid to the lactams *VIIIa* and *IXa* which were transformed to the thiolactams *VIIIb* and *IXb*. These lactams and thiolactams were, likewise, characterized by IR and ^{1}H NMR spectra. The preparation of 2-(4-chlorophenyl)ethylamine, which was described by reduction of (4-chlorophenyl)acetonitrile[12] with lithium aluminium hydride in ether[11] (yield of 58% in our hands), was improved by using aluminium hydride (from lithium aluminium hydride and aluminium chloride); the yield was almost quantitative. The hydrochloride, prepared from our product, melted at 216–217°C which is distinctly higher than the literature[11] value (208–209°C).



I

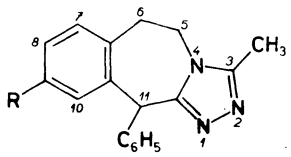


II, $R^1 = R^2 = H$
III, $R^1 = Cl$; $R^2 = H$
IV, $R^1 = H$; $R^2 = Cl$
V, $R^1 = R^2 = Cl$



VI, $R^1 = R^2 = H$
VII, $R^1 = Cl$; $R^2 = H$
VIII, $R^1 = H$; $R^2 = Cl$
IX, $R^1 = R^2 = Cl$

a, X = O
b, X = S



X, R = H
XI, R = Cl

EXPERIMENTAL

The melting points of analytical samples were determined in the Kofler block and were not corrected. The samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at a suitably elevated temperature. UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in NUJOL, ν in cm^{-1}) were recorded with the Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (mostly in CD_3SOCD_3, δ in ppm, J in Hz) with a CW-NMR TESLA BS 487C (80 MHz) spectrometer, and the mass spectra (m/z, %) with Varian MAT 44S (GC-MS) spectrometer. The homogeneity of the substances and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

2-(4-Chlorophenyl)ethylamine

A stirred solution of 30·0 g $LiAlH_4$ in 600 ml ether was treated dropwise over 35 min with a solution of 87 g $AlCl_3$ in 600 ml ether, a solution of 57 g (4-chlorophenyl)acetonitrile[12] in 200 ml

ether was added over 1 h to the stirred mixture, and the mixture was refluxed for 2 h. After cooling it was decomposed by addition of 130 ml 20% NaOH, stirred for 1 h, allowed to stand overnight, the solid was filtered off and washed with 500 ml benzene. It was then treated with a solution of 100 g NaOH in 400 ml water and the suspension was extracted three times with 250 ml of a mixture of benzene and ether (1 : 1). The organic layers were combined, filtered, and evaporated. The residue was dissolved in a mixture of 100 ml ether and 200 ml benzene and the solution was acidified with a solution of 70 ml hydrochloric acid in 110 ml water. The crystallized hydrochloride (58 g) was filtered, washed with benzene, and dried in vacuo. Processing of the mother liquor gave further 13 g of hydrochloride, the total yield being thus 71 g (98%), m.p. 216–217°C (ethanol–ethyl acetate). For $C_8H_{11}Cl_2N$ (192·1) calculated: 50·02% C, 5·77% H, 36·92% Cl, 7·29% N; found: 49·97% C, 5·78% H, 36·76% Cl, 7·18% N. Ref.[11], m.p. 208–209°C.

The oily base was released with diluted NaOH and isolated by extraction with benzene–ether (2 : 1); a sample was distilled, b.p. 115–118°C/2·1 kPa. Ref.[11], b.p. 114–120°C/2 kPa.

N-(2-Phenylethyl)-2-chloromandelamide (*IV*)

A mixture of 37·5 g 2-phenylethylamine, 360 ml xylene, and 54·1 g 2-chloromandelic acid[10] was slowly distilled for 9·5 h through a column with a separator of water and with continual return of the xylene distillate to the reaction flask. Xylene was then evaporated in vacuo and the residue crystallized after trituration with a mixture of 400 ml ether and 20 ml hexane. The crystalline *IV* (50 g) was filtered and the mother liquor was processed giving further 6·0 g of *IV*, the total yield being thus 56 g (67%) of *IV*, m.p. 88–89°C (aqueous ethanol). IR spectrum: 700, 766 (5 and 4 adjacent Ar–H); 1 071 (CHOH); 1 480, 1 493, 1 597, 3 020 (Ar); 1 560, 1 642 (CONH); 3 113, 3 320 (NH, OH). ^{1}H NMR spectrum ($CDCl_3$): 2·71 bt, 2 H ($ArCH_2$); 3·50 m, 2 H (CH_2N); 4·25 bs, 1 H (OH); 5·38 s, 1 H (Ar–CH–O); 6·25 bt, 1 H (NHCO); 6·80–7·40 m, 9 H (ArH). For $C_{16}H_{16}ClNO_2$ (289·8) calculated: 66·32% C, 5·57% H, 12·24% Cl, 4·83% N; found: 66·46% C, 5·52% H, 12·42% Cl, 4·80% N.

N-(2-(4-Chlorophenyl)ethyl)-2-chloromandelamide (*V*)

A similar reaction of 24·5 g 2-(4-chlorophenyl)ethylamine and 27·6 g 2-chloromandelic acid[10] in 200 ml xylene gave 34·0 g (71%) of *V* m.p. 79–80°C (aqueous ethanol). IR spectrum: 760, 890 (4 and 2 adjacent Ar–H); 1 063 (CHOH); 1 489, 1 591, 1 596, 3 018, 3 035, 3 060 (Ar); 1 543, 1 653 (CONH); 3 250, 3 410 (NH, OH). ^{1}H NMR spectrum ($CDCl_3$): 2·70 bt, 2 H ($ArCH_2$); 3·45 m, 2 H (CH_2N); 4·37 d, 1 H (OH, J = 4·0); 5·38 d, 1 H (Ar–CH–O, J = 4·0); 6·35 bt, 1 H (NH); 6·90 d, 2 H (H-2 and H-6 of 4-chlorophenyl, J = 9·0); 7·13 d, 2 H (H-3 and H-5 of 4-chlorophenyl, J = 9·0); 7·20 m, 4 H (remaining ArH). For $C_{16}H_{15}Cl_2NO_2$ (324·2) calculated: 59·27% C, 4·67% H, 21·88% Cl, 4·32% N; found: 59·54% C, 4·66% H, 22·08% Cl, 4·50% N.

1-(2-Chlorophenyl)-4,5-dihydro-3-benzazepin-2(1*H*,3*H*)-one (*VIIIa*)

Polyphosphoric acid was prepared by heating a mixture of 235 g 85% H_3PO_4 and 312 g P_2O_5 for 5 h to 145–155°C and by standing overnight at room temperature. Compound *IV* (55 g) was added and the mixture was stirred for 5 h at 70–75°C. It was poured to a mixture of 600 g ice and 700 ml water, the mixture was stirred for 3 h, the solid was filtered, washed with water, dissolved in 450 ml chloroform, the solution was washed with dilute NaCl solution, dried with $CaCl_2$, and evaporated in vacuo. The residue was crystallized from ethanol; 44·5 g (86%) of *VIIIa*, m.p. 191–192°C. UV spectrum: 260 (3·40), 300 (3·13). IR spectrum: 750, 761 (4 adjacent

Ar–H); 1 484, 1 570, 3 062, 3 098 (Ar); 1 635, 1 680 (CONH); 3 095, 3 200 (NH). ^{1}H NMR spectrum: 2·90—3·50 bm, 4 H (2 × H-4 and 2 × H-5); 5·50 s, 1 H (Ar_2CHCO); 6·80—7·60 m, 8 H (ArH); 7·70 bt, 1 H (CONH). For $C_{16}H_{14}ClNO$ (271·7) calculated: 70·72% C, 5·19% H, 13·05% Cl, 5·15% N; found: 70·91% C, 5·22% H, 13·35% Cl, 5·01% N.

8-Chloro-1-(2-chlorophenyl)-4,5-dihydro-3-benzazepin-2(1*H*,3*H*)-one (*IXa*)

A similar cyclization of 32·0 g *V* with polyphosphoric acid (from 135 g 85% H_3PO_4 and 180 g P_2O_5) at 80°C (5·5 h) gave 22·6 g (75%) of *IXa*, m.p. 162—163°C (ethanol). UV spectrum: 270 (3·47), 350 (3·20). IR spectrum: 749, 812, 902 (4 and 2 adjacent and solitary Ar–H); 1 569, 1 591, 3 042, 3 060 (Ar); 1 675 (CONH); 3 190, 3 310 (NH). ^{1}H NMR spectrum: 3·00—3·60 bm, 4 H (2 × H-4 and 2 × H-5); 5·60 s, 1 H (Ar_2CHCO); 5·96 bs, 1 H (H-9); 7·20—7·60 m, 6 H (remaining ArH); 7·80 bt, 1 H (NH). For $C_{16}H_{13}Cl_2NO$ (306·2) calculated: 62·76% C, 4·28% H, 23·16% Cl, 4·57% N; found: 62·62% C, 4·30% H, 22·91% Cl, 4·46% N.

1-Phenyl-4,5-dihydro-3-benzazepin-2(1*H*,3*H*)-thione (*VIb*)

A mixture of 40·5 g *VIa* (ref.[5]), 310 ml pyridine, and 32 g P_4S_{10} was stirred and refluxed for 60 min under nitrogen. After cooling to 35°C the mixture was poured to a solution of 520 g NaCl in 1·8 l water at 3°C under stirring. The suspension formed was stirred under cooling for 50 min, the solid was filtered and washed with water. The product was dissolved in 850 ml dichloromethane, the solution was washed with a solution of 50 ml hydrochloric acid in 150 ml water, dried with Na_2SO_4, and filtered through a column of 50 g Al_2O_3. The column was washed with 200 ml dichloromethane, and the combined filtrates were evaporated. The crude product (37·6 g) was extracted with 120 ml boiling ethanol, the suspension formed was allowed to stand for 48 h in a refrigerator, the product was filtered, washed with 60 ml ethanol and 60 ml ether, and dried in vacuo; 33·2 g of *VIb*, m.p. 207—208°C. Processing of the mother liquor gave further 3·0 g of the product, the total yield being 36·2 g (84%) of *VIb*. Analytical sample, m.p. 210—211°C (benzene). IR spectrum: 700, 741, 758 (5 and 4 adjacent Ar–H); 1 490, 1 580, 1 598, 3 016, 3 053 (Ar); 1 567 (N—C=S); 3 150 (NH). ^{1}H NMR spectrum: 2·70—3·50 m, 4 H (2 × H-4 and 2 × H-5); 5·70 s, 1 H (H-1); 7·00—7·50 m, 9 H (ArH); 10·60 bs, 1 H (NH). For $C_{16}H_{15}NS$ (253·4) calculated: 75·85% C, 5·97% H, 5·53% N, 12·65% S; found: 76·12% C, 6·02% H, 5·27% N, 12·20% S.

8-Chloro-1-phenyl-4,5-dihydro-3-benzazepin-2(1*H*,3*H*)-thione (*VIIb*)

Similar reaction of 11·7 g *VIIa* (ref.[9]) and 10·0 g P_4S_{10} in 120 ml boiling pyridine gave 10·0 g (81%) of *VIIb*, m.p. 201—202°C (ethyl acetate). IR spectrum: 700, 731, 751, 800, 819, 884 (5 and 2 adjacent and solitary Ar–H); 1 490, 1 580, 1 590, 3 010, 3 052 (Ar); 1 560 (N—C=S). ^{1}H NMR spectrum: 2·70—3·80 m, 4 H (2 × H-4 and 2 × H-5); 5·76 s, 1 H (H-1); 7·00—7·50 m, 8 H (ArH); 10·60 bs, 1 H (NH). For $C_{16}H_{14}ClNS$ (287·8) calculated: 66·77% C, 4·90% H, 12·32% Cl, 4·87% N, 11·14% S; found: 66·60% C, 4·95% H, 12·42% Cl, 4·79% N, 10·97% S.

1-(2-Chlorophenyl)-4,5-dihydro-3-benzazepin-2(1*H*,3*H*)-thione (*VIIIb*)

Similar reaction of 44·0 g *VIIIa* and 35 g P_4S_{10} in 350 ml boiling pyridine gave 35·0 g (75%) of *VIIIb*, m.p. 175—176°C (ethanol–chloroform). IR spectrum: 751, 760 (4 adjacent Ar–H); 1 489, 1 589, 1 600, 3 015, 3 048 (Ar); 1 560 (N—C=S); 3 140 (NH). ^{1}H NMR spectrum ($CDCl_3$): 2·50—4·00 m, 4 H (2 × H-4 and 2 × H-5); 5·90 s, 1 H (H-1); 6·90—7·50 m, 8 H (ArH); 9·55 bs,

1 H (NH). For $C_{16}H_{14}ClNS$ (287·8) calculated: 66·77% C, 4·90% H, 12·32% Cl, 4·87% N, 11·14% S; found: 66·47% C, 4·84% H, 12·65% Cl, 4·86% N, 11·21% S.

8-Chloro-1-(2-chlorophenyl)-4,5-dihydro-3-benzazepin-2(1*H*,3*H*)-thione (*IXb*)

Similar reaction of 20·4 g *IXa* and 14 g P_4S_{10} in 140 ml boiling pyridine afforded 17·3 g (81%) of *IXb*, m.p. 171—172°C (ethyl acetate. UV spectrum: 286 (4·15). IR spectrum: 752, 829: 879 (4 and 2 adjacent and solitary Ar–H); 1 493, 1 600, 3 010, 3 040, 3 060, 3 080 (Ar); 1 585 (N—C=S); 3 105 (NH). ^{1}H NMR spectrum: 2·70—3·70 m, 4 H (2 × H-4 and 2 × H-5); 5·80 s, 1 H (H-1); 7·00—7·60 m, 7 H (ArH); 10·35 bt, 1 H (NH). For $C_{16}H_{13}CL_2NS$ (322·2) calculated: 59·63% C, 4·06% H, 22·01% Cl, 4·35% N, 9·95% S; found: 59·64% C, 4·13% H, 22·17% Cl, 4·25% N, 10·12% S.

3-Methyl-11-phenyl-5,6-dihydro-11*H*-*s*-triazolo[3,4-*b*]-3-benzazepine (*X*)

A mixture of 3·3 g *VIb*, 4·25 g acethydrazide[7], and 100 ml 2-(ethoxy)ethanol was refluxed for 25 h and evaporated in vacuo. The residue was distributed between dichloromethane and water, the organic layer was washed with dilute NaCl, dried, and evaporated. The residue was extracted with 10 ml boiling ethanol and the undissolved part was crystallized from a mixture of ethyl acetate and chloroform; 1·5 g (42%) of *X*, m.p. 264—265°C. Mass spectrum: 275 (M^+, $C_{18}H_{17}N_3$, 100), 274 (80), 260 (40), 219 (10), 198 (20), 192 (20), 191 (15), 184 (20), 178 (10), 165 (10). UV spectrum: infl. 255 (2·68), 259 (2·74), infl. 264·8 (2·69). IR spectrum: 706, 741, 760, 775 (5 and 4 adjacent Ar–H); 1 493, 1 530, 1 597, 3 020, 3 052, 3 080 (Ar); 1 611 (C=N). Fo $C_{18}H_{12}N_3$ (275·3) calculated: 78·51% C, 6·23% H, 15·26% N; found: 78·31% C, 6·35% H, 14·96% N.

9-Chloro-3-methyl-11-phenyl-5,6-dihydro-11*H*-*s*-triazolo[3,4-*b*]-3-benzazepine (*XI*)

A mixture of 5·0 g *VIIb*, 4·25 g acethydrazide[7], and 150 ml butanol was refluxed for 62 h under nitrogen. After the addition of 10 ml pyridine and 4·0 g acethydrazide[7] the refluxing was continued for 32 h and the mixture was evaporated in vacuo. From the residue acethydrazide was removed by extraction with water. The undissolved solid was refluxed for 15 min with 30 ml ethyl acetate. Standing and cooling of the solution led to recovery of 3·2 g *VIIb*. The mother liquor was evaporated and the residue was repeatedly crystallized from a mixture of chloroform and ethyl acetate giving a small amount (0·2 g) of *XI*, m.p. 294—296°C. Mass spectrum: 309 (M^+, $C_{18}H_{16}ClN_3$, 100), 294 (33·3). For $C_{18}H_{16}ClN_3$ (309·8) calculated: 69·78% C, 5·21% H, 11·44% Cl; found: 69·47% C, 5·21% H, 11·61% Cl.

The spectra were recorded and interpreted by Drs J. Holubek, E. Svátek, M. Ryska, I. Koruna, O. Matoušová, Mrs A. Hrádková, and Mrs Z. Janová. The elemental analyses were carried out by Mrs J. Komancová, Mrs V. Šmídová, and Mrs A. Svatošová.

REFERENCES

1. Weinstock J., Hieble J. P., Wilson J. W., III: Drugs Future *10*, 645 (1985).
2. Kametani T., Fukumoto K.: Heterocycles *3*, 931 (1975).
3. Shapiro S. L., Rose I. M., Freedman L.: J. Am. Chem. Soc. *81*, 6322 (1959).
4. Hamon M.: C. R. Acad. Sci. *255*, 1619 (1962); Chem. Abstr. *58*, 5637 (1963).
5. Hamon M.: Ann. Chim. (Paris) *10*, 213 (1965); Chem. Abstr. *63*, 18027 (1965).
6. Kametani T., Hirata S., Shibuya S., Fukumoto K.: J. Chem. Soc., C *1971*, 1927.

7. Curtius T., Hofmann T. S.: J. Prakt. Chem. [2] *53*, 524 (1896).
8. Vejdělek Z. J., Metyš J., Protiva M.: Collect. Czech. Chem. Commun. *48*, 123 (1983).
9. Mull R. P., De Stevens G. (Ciba Corp.): U.S. 3,496,166; Chem. Abstr. *73*, 14724 (1970).
10. Jenkins S. S.: J. Am. Chem. Soc. *53*, 2341 (1931).
11. Benington F., Morin R. D., Clark L. C., Jr., Fox R. P.: J. Org. Chem. *23*, 1979 (1958).
12. Rorig K., Johnston J. D., Hamilton R. W., Telinski T. J.: Org. Synth., Coll. Vol. *4*, 578 (1963).

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