SYNTHESIS OF SOME 1-(2-FLUORENYL)PIPERAZINES*

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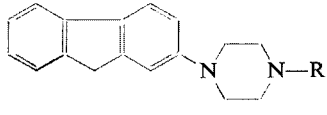
Reaction of N,N-bis(2-chloroethyl)-2-aminofluorene with n-butylamine, benzylamine and 3-aminopropanol led to 1,4-disubstituted piperazines *I*—*III*. Reaction of the benzyl derivative *II* with ethyl chloroformate yielded carbamate *IV* which was hydrolyzed to the secondary amine *V*, or reduced to the methyl derivative *VI*. Compounds *I* and *III* displayed a certain antimicrobial activity *in vitro* but none of the compounds tested possessed the expected neurotropic activity.

In a previous communication of this series[1], the synthesis of a series of 1-(naphthyl- and tetrahydronaphthyl)piperazines with neurotropic properties was described. The same objective was followed in the synthesis of several 1-(2-fluorenyl)piperazines as described in this communication.

The starting compound was 2-aminofluorene[2] which could not be converted directly to the piperazine derivative *V* by applying the method of Pollard and MacDowell[3]. For this reason the starting amine was transformed in a reaction with ethylene oxide and subsequent action of phosphorus oxychloride to the previously described[4] N,N-bis(2-chloroethyl)-2-aminofluorene. Heating this compound with n-butylamine, benzylamine or 3-aminopropanol in diphenyl ether yielded piperazines *I*—*III*. The benzyl derivative *II* was debenzylated by the action of ethyl chloroformate in boiling benzene which gave rise to carbamate *IV*. Alkaline hydrolysis of this compound led to the fundamental 1(2-fluorenyl)piperazine (*V*). Reduction of carbamate *IV* with sodium dihydridobis(2-methoxyethoxy)aluminate in benzene (for method see ref.[5]) led to the methyl derivative *VI*.



I, R = $(CH_2)_3CH_3$
II, R = $CH_2C_6H_5$
III, R = $(CH_2)_3OH$

IV, R = $COOC_2H_5$
V, R = H
VI, R = CH_3

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Compounds *I*—*III* were evaluated as hydrochlorides by Dr A. Dlabač and Dr J. Metyšová (pharmacological department of this institute) for their antireserpine (*i.e.* potentially antidepressant) and central depressant activity but with negative results. *I* was applied intraperitoneally to mice at a dose of 40 mg/kg (the doses shown refer to the bases) but it did not affect reserpine ptosis. Compounds *II* and *III* were evaluated in the rotating-rod test on mice when up to a dose of 50 mg/kg *i.v.* they did not bring about ataxia. The compounds were further tested by Dr J. Turi-rinová and Dr A. Čapek (bacteriological department of this institute) for their antimicrobial activity toward a standard set of microorganisms *in vitro*. While *II* was found to be inactive, *I* and *III* showed a certain inhibitory activity against a limited number of microorganisms (the minimum inhibitory concentrations in μg/ml are shown): *Mycobacterium tuberculosis* H37Rv, *III*, 50; *Saccharomyces pasterianus III*, 125; *Trichophyton mentagrophytes*, *I*, 125; *III*, 125; *Aspergillus niger*, *I*, 125; *III*, 125.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block and are not corrected. The samples were dried *in vacuo* at about 0·5 Torr over P_2O_5 at 100°C. The UV spectrum (in methanol) was recorded on a Unicam SP 700 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in a Unicam SP 200G spectrophotometer and the NMR spectra (in $CDCl_3$) in a ZKR 60 (Zeiss Jena) spectrometer. The homogeneity of the compounds was tested by chromatography on a thin layer of silica gel.

1-(n-Butyl)-4-(2-fluorenyl)piperazine (*I*)

A mixture of 10·0 g N,N-bis(2-chloroethyl)-2-aminofluorene[4] (m.p. 137—139°C), 7·2 g n-butylamine and 10 ml diphenyl ether was refluxed under stirring for 1 h at 110°C, the temperature was then raised in the course of 3 h to 200°C and at that temperature the mixture was kept for 8 h. After partial cooling, the mixture was combined with 50 ml light petroleum, the solid was filtered, dissolved in chloroform, the solution was washed with water, dried with $MgSO_4$ and evaporated. The residue was recrystallized from 170 ml ethanol. A total of 6·2 g (62%) crude base melting at 170—175°C was obtained. An analytical sample melted at 178—182°C (ethanol). ^{1}H-NMR spectrum: δ 6·80—7·80 (m, 7 H, aromatic protons), 3·80 (s, 2 H, $ArCH_2Ar$ of fluorene), 3·24 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·36 (t, 2 H, NCH_2 of butyl), 1·42 (m, 4 H, C—CH_2CH_2—C of butyl), 0·91 (t, 3 H, CH_3). For $C_{21}H_{26}N_2$ (306·4) calculated: 82·31% C, 8·55% H, 9·14% N; found: 82·50% C, 8·78% H, 9·03% N.

Dihydrochloride, m.p. 241—244°C, decomp. (ethanol–ether). For $C_{21}H_{28}Cl_2N_2$ (379·4) calculated: 66·48% C, 7·44% H, 18·70% Cl, 7·38% N; found: 66·74% C, 7·59% H, 18·61% Cl, 7·40% N.

1-Benzyl-4-(2-fluorenyl)piperazine (*II*)

In analogy to the preceding case, a mixture of 15·3 g N,N-bis (2-chloroethyl)-2-aminofluorene[4], 16·1 g benzylamine and 10 ml diphenyl ether was processed and heated finally for 22 h at 185 to 190°C. After cooling, it was diluted with 300 ml chloroform and washed with 100 ml water. Treatment of the organic phase led to a residue which was recrystallized from 150 ml ethanol; 8·5 g (50%), m.p. 142—146°C; analytical preparation melts at 149—151°C (ethanol–benzene). ^{1}H-NMR spectrum: δ 7·35 (s, 5 H, C_6H_5), 6·80—7·80 (m, 7 H, aromatic protons of fluorene), 3·78 (s, 2 H, $ArCH_2Ar$ of fluorene), 3·52 (s, 2 H, $ArCH_2N$), 3·18 (m, 4 H, $CH_2N^4CH_2$ of pipe-

razine), 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine). For $C_{24}H_{24}N_2$ (340·5) calculated: 84·66% C, 7·11% H, 8·23% N; found: 84·83% C, 7·05% H, 8·40% N.

Monohydrochloride, m.p. 244—250°C, decomp. (aqueous ethanol). For $C_{24}H_{25}ClN_2$ (376·2) calculated: 76·47% C, 6·69% H, 9·41% Cl, 7·43% N; found: 76·47% C, 6·75% H, 9·67% Cl, 7·41% N.

1-(2-Fluorenyl)-4-(3-hydroxypropyl)piperazine (*III*)

Like in the preceding cases, a mixture of 4·5 g N,N-bis(2-chloroethyl)-2-aminofluorene[4], 3·4 g 3-aminopropanol and 5·5 ml diphenyl ether was left to react and finally it was heated for 10 h at 185—195°C. The crude product was extracted with chloroform, the solution was washed with water, dried, evaporated and the residue recrystallized from 50 ml ethanol. A total of 4·0 g (87%) product melting at 152—156°C was obtained, the m.p. not changing on further crystallization from ethanol. On crystallization from a mixture of benzene and light petroleum it rises to 173 to 175°C (perhaps a crystal modification). IR spectrum: 735, 768, 818, 859 (4 and 2 adjacent and solitary Ar—H), 1070 (CH_2OH), 1491, 1571, 1610 (Ar), 3190 and 3415 cm^{-1} (OH). For $C_{20}H_{24}N_2O$ (308·4) calculated: 77·88% C, 7·84% H, 9·08% N; found: 77·84% C, 7·82% H, 8·86% N.

Monohydrochloride, m.p. 240—243°C, decomp. (ethanol–ether). For $C_{20}H_{25}ClN_2O$ (344·9) calculated: 69·65% C, 7·31% H, 10·28% Cl, 8·12% N; found: 69·58% C, 7·46% H, 10·58% Cl, 8·62% N.

1-(Ethoxycarbonyl)-4-(2-fluorenyl)piperazine (*IV*)

A solution of 24·5 g *II* in 280 ml benzene was added dropwise over a period of 30 min to a solution of 12·8 g ethyl chloroformate in 50 ml benzene refluxing at 70°C. The mixture was then refluxed for 3 h, cooled, shaken with 70 ml 1M-HCl to remove the more basic starting amine *II*, the benzene solution was washed with water, dried with K_2CO_3 and evaporated. The yield was 26·8 g (72%) product melting at 143—146°C (it softens from 135°C on); the analytical product melts at 146 to 147°C (benzene–light petroleum), while at 133—135°C a change in crystal modification occurs. UV spectrum: λ_{max} 293 nm (log ε 4·38). IR spectrum (Nujol): 740, 780, 836, 883 (4 and 2 adjacent and solitary Ar—H), 1228 (C—O), 1572, 1615 (Ar), 1695 cm^{-1} (NCOOR). NMR spectrum: δ 6·80—7·85 (m, 7 H, aromatic protons), 4·15 (q, 2 H, $NCOOCH_2$), 3·80 (s, 2 H, $ArCH_2Ar$ of fluorene), 3·40—3·80 and 2·95—3·40 (2 m, 8 H, 4 NCH_2 of piperazine), 1·28 (t, 3 H, CH_3).

1-(2-Fluorenyl)piperazine (*V*)

Solid KOH (6·1 g) was added to a mixture of 7·0 g *IV* and 7 ml ethanol and the mixture was refluxed under stirring for 3 h at 120°C. After cooling, it was decomposed with 70 ml water and extracted with 100 ml benzene. The extract was washed with water and shaken with 50 ml 4M-HCl. After separation, the aqueous layer was made alkaline with 5M-NaOH and the base was isolated by extraction with benzene; 4·0 g (73%). On standing in the refrigerator the crude product crystallized and was purified by crystallization either from ethanol or from a mixture of benzene and light petroleum; m.p. 179—181·5°C. For $C_{17}H_{18}N_2$ (250·3) calculated: 81·56% C, 7·25% H, 11·19% N; found: 81·45% C, 7·43% H, 11·30% N.

1-(2-Fluorenyl)-4-methylpiperazine (*VI*)

A 65% benzene solution (16·0 g) of sodium dihydridobis(2-methoxyethoxy)aluminate was added dropwise under stirring over a period of 20 min to a solution of 6·8 g *IV* in 90 ml benzene

at 40—60°C. The solution was stirred for 30 min at room temperature and left to stand overnight. Then it was decomposed under stirring by adding dropwise 50 ml 3M-NaOH, combined with 50 ml water and 100 ml benzene and well agitated. The benzene phase was washed with water, dried with $MgSO_4$ and evaporated. The residue (5·5 g, almost theoretical yield) is the crystalline base melting at 138—142°C. Crystallization from ethanol or from a mixture of benzene and light petroleum raises the m.p. until it reaches 230°C with decomposition. IR spectrum: 740, 768, 815, 870 (4 and 2 adjacent and solitary Ar—H), 1495, 1575, 1615 (Ar), 2780 cm^{-1} (N—CH_3). For $C_{18}H_{20}N_2$ (264·4) calculated: 81·78% C, 7·63% H, 10·60% N; found: 81·50% C, 7·08% H, 10·23% N. The conventionally prepared hydrochloride (m.p. 214—220°C with decomposition) is hygroscopic and, according to analysis, it is a mixture of the monohydrochloride and the dihydrochloride.

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