# SYNTHESIS OF 1-ACYL- AND 1-(THIOACYL)-4-BENZYLPIPERAZINES AS POTENTIAL ANTIDEPRESSANTS

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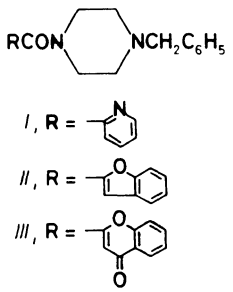
2-Nitro, 3-nitro- and 4-nitrobenzoyl chloride were reacted with 1-benzylpiperazine in benzene in the presence of triethylamine and gave the amides *IV*—*VI*, the first of which is considered a bioisostere of the antidepressant agent piberaline (*I*). 2-Dimethylamino-, 3-dimethylamino- and 4-dimethylaminobenzoic acid were treated with thionyl chloride in benzene in the presence of triethylamine or pyridine, and the acid chlorides formed were reacted in situ with 1-benzylpiperazine affording the amides *VII*—*IX*. The amides *I* and *IV*—*VI* were transformed by treatment with phosphorus pentasulfide in pyridine to the thioamides *X*—*XIII*. 4-(Dimethylaminomethyl)benzoic acid was reacted with 1-benzylpiperazine in dimethylformamide in the presence of N,N′-carbonyldiimidazole and afforded the amide *XIV*. Heating of ethyl 5-methylimidazole-4-carboxylate with 1-benzylpiperazine to 200—210°C gave the amide *XV* together with the unexpected 1-benzyl-4-ethylpiperazine (*XVI*). The oily or crystalline bases of the amino amides or thioamides were mostly transformed to crystalline salts and characterized by spectra. Out of the compounds prepared only *X* (VÚFB-17070) and *XIV* (VÚFB-17114) showed indications of efficacy in tests which are considered indicative of antidepressant activity. Compounds *VII*, *VIII*, and *X* appeared to be mildly antidopaminergic — similarly like piberaline (*I*), and compounds *IV*, *V*, *XI*, *XIV*, and *XV* on the contrary showed signs of dopaminominetic activity.

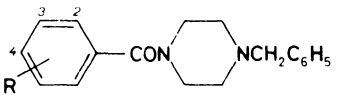
Some 1-acyl-4-benzylpiperazines were described in the literature as antidepressants. In the first line it was the 2-picolinoyl derivative *I* ("piberaline", EGYT 475, refs[1–4]) which was introduced to therapeutic practice as Trelibet[R]. The papers published deal mainly with biochemical mechanisms[5–7] of the piberaline actions, some[8,9] with its activity in behavioural tests but its clinical efficacy was not yet sufficiently documented. The bicyclic compound *II* ("befuraline", DIV 154, refs[10,11]) is an experimental antidepressant which was clinically tested[12,13] but whose development was probably discontinued because of the psychostimulant effects. A further experimental agent "BC" (*III*) was described in a single paper[14] as having antireserpine and anticataleptic activity in combination with a rather strong central depressant effect, which probably led to discontinuation of its development.

In order to contribute to the knowledge of the structural field of antidepressant activity in this area, our team synthesized title compounds for pharmacological testing.

In the first line it was the 2-nitrobenzoyl derivative *IV* which may be considered bioisosteric with piberaline (*I*) on the basis of the Erlenmeyer's concept of bioisosterism between pyridine and nitrobenzene[15,16]. This compound was followed by the position isomers *V* and *VI*. These compounds were prepared by reactions of 2-nitro-, 3-nitro-, and 4-nitrobenzoyl chloride with 1-benzylpiperazine[17] in benzene in the



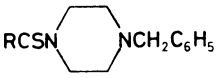

presence of triethylamine at 40–60°C (method *A*, for analogy, cf. ref.[18]). The bases (crystalline with the exception of *VI*) were transformed to crystalline hydrochlorides and the identity of the products was corroborated by spectra.

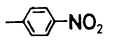



*IV*, R = 2-$NO_2$ *V*, R = 3-$NO_2$
*VI*, R = 4-$NO_2$ *VII*, R = 2-$N(CH_3)_2$
*VIII*, R = 3-$N(CH_3)_2$ *IX*, R = 4-$N(CH_3)_2$

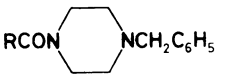
With the intention to keep a slightly basic group in the acyl of the title compounds, the dimethylaminobenzoyl derivatives *VII*–*IX* were prepared. They were obtained from 2-dimethylaminobenzoic acid[19], 3-dimethylaminobenzoic acid[20], and 4-dimethylaminobenzoic acid[21,22] which were treated with thionyl chloride in benzene in the presence of triethylamine or pyridine and the acid chlorides formed were reacted in situ with 1-benzylpiperazine[17] (method *B*, for analogy, cf. ref.[23]). Like in the preceding case, the bases (crystalline with the exception of *VIII*) were transformed to crystalline salts with fumaric and maleic acid and structures were confirmed by spectra.

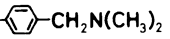
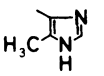
The nitrobenzamides *IV*–*VI* and the 2-picolinamide *I* (refs[1–3]) were transformed to the thioamides *X*–*XIII* by tratment with phosphorus pentasulfide in boiling pyridine (method *C*, for analogy, cf. ref.[24]). The bases (partly crystalline) were transformed to hydrochlorides and the spectra were recorded.

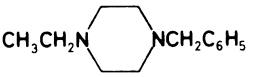



*X*, R = 
*XI*, R = 
*XII*, R = 
*XIII*, R = 

4-(Dimethylaminomethyl)benzoic acid, which was released from the known hydrochloride[25,26], was reacted with 1-benzylpiperazine[17] in dimethylformamide in the presence of N,N'-carbonyldiimidazole (method, cf. ref.[27]) affording *XIV*. The product was characterized in the form of the hydrochloride. Heating of ethyl 5-methylimidazole-4-carboxylate with 1-benzylpiperazine[17] and a small amount of sodium (cf. ref.[28]) to 200–210°C gave a mixture which was separated by chromatography on aluminium oxide. The less polar component of the mixture was isolated as the crystalline hydrochloride corresponding to $C_{13}H_{20}N_2.2\,HCl$ (mass spectrum and analysis) and was identified as 1-benzyl-4-ethylpiperazine (*XVI*) dihydrochloride (cf. ref.[29]). A similar unusual "transfer of ethyl from the oxygen of the starting ester to nitrogen of the piperazine component" has recently been mentioned by us[30] in a different case. The more polar fraction from the chromatography was identified as the desired *XV*: it was isolated as the dihydrochloride monohydrate and characterized by spectra. The compounds prepared by the general methods *A*, *B*, and *C* are assembled in Table I with the usual experimental data. Syntheses of *VI*, *VII*, and *XII* are being described in the Experimental as examples. The spectra of compounds *IV*–*XIII* are assembled in Table II.




*XIV*, R = 
*XV*, R = 




*XVI*

Compounds *IV*–*XV* were tested in the form of salts described in the Experimental and in Table I as potential antidepressants. The doses (in mg/kg) were calculated

TABLE I

1-Acyl- and 1-(thioacyl)-4-benzylpiperazines and their salts

| Compound Method; yield, % | M.p., °C Solvent | Formula (M.w.) | Calculated/Found | | |
|---|---|---|---|---|---|
| | | | % C | % H | % N |
| *IV* | 102—104 | $C_{18}H_{19}N_3O_3$ | 66·44 | 5·89 | 12·92 |
| *A*; 96 | ethanol | (325·4) | 66·25 | 5·95 | 12·85 |
| *IV*-HCl | 223—225 | $C_{18}H_{20}ClN_3O_3$[a] | 59·75 | 5·57 | 11·61 |
| | ethanol–ether | (361·8) | 59·45 | 5·65 | 11·62 |
| *V* | 115—117 | $C_{18}H_{19}N_3O_3$ | 66·44 | 5·89 | 12·92 |
| *A*; 93 | ethanol | (325·4) | 66·63 | 5·99 | 12·88 |
| *V*-HCl | 218—220 | $C_{18}H_{20}ClN_3O_3$[b] | 59·75 | 5·57 | 11·61 |
| | ethanol | (361·8) | 59·82 | 5·66 | 11·40 |
| *VI*-HCl | 246—248 | $C_{18}H_{20}ClN_3O$[c] | 59·75 | 5·57 | 11·61 |
| *A*[d]; 95 | ethanol | (361·8) | 59·52 | 5·65 | 11·68 |
| *VII* | 83—85 | $C_{20}H_{25}N_3O$ | 74·27 | 7·79 | 12·99 |
| *B*[d]; 92 | cyclohexane | (323·4) | 73·94 | 7·77 | 12·95 |
| *VII*-F[e] | 143—145 | $C_{24}H_{29}N_3O_5$ | 65·59 | 6·65 | 9·56 |
| | acetone–ether | (439·5) | 65·30 | 6·72 | 9·30 |
| *VIII*-M[f] | 168—170 | $C_{24}H_{29}N_3O_5$ | 65·59 | 6·65 | 9·56 |
| *B*[g]; 68 | ethanol | (439·5) | 65·32 | 6·80 | 9·51 |
| *IX* | 105—107 | $C_{20}H_{25}N_3O$ | 74·27 | 7·79 | 12·99 |
| *B*; 74 | cyclohexane | (323·4) | 74·09 | 7·87 | 12·76 |
| *IX*-M[f] | 175—177 | $C_{24}H_{29}N_3O_5$ | 65·59 | 6·65 | 9·56 |
| | ethanol–ether | (439·5) | 65·47 | 6·73 | 9·42 |
| *X*-HCl | 234—236 | $C_{18}H_{20}ClN_3O_2S$[h] | 57·21 | 5·33 | 11·12 |
| *C*; 79 | ethanol–ether | (377·9) | 57·32 | 5·51 | 11·05 |
| *XI* | 102—104 | $C_{18}H_{19}N_3O_2S$[i] | 63·32 | 5·61 | 12·31 |
| *C*; 73 | methanol | (341·4) | 63·12 | 5·49 | 12·06 |
| *XI*-HCl | 211—213 | $C_{18}H_{20}ClN_3O_2S$[j] | 57·21 | 5·33 | 11·12 |
| | ethanol | (377·9) | 57·00 | 5·59 | 10·87 |
| *XII* | 182—184 | $C_{18}H_{19}N_3O_2S$[k] | 63·32 | 5·61 | 12·31 |
| *C*[d]; 93 | ethanol | (341·4) | 63·05 | 5·77 | 12·27 |
| *XII*-HCl | 198—200 | $C_{18}H_{20}ClN_3O_2S$[l] | 57·21 | 5·33 | 11·12 |
| | ethanol–ether | (377·9) | 57·46 | 5·39 | 10·86 |

TABLE I
(*Continued*)

| Compound Method; yield, % | M.p., °C Solvent | Formula (M.w.) | Calculated/Found % C | % H | % N |
|---|---|---|---|---|---|
| *XIII*-2 HCl[m] | 150–152 and | $C_{17}H_{21}Cl_2N_3S$[n] | 52·57 | 5·97 | 10·82 |
| *C*; 70 | 215–217 | $+ H_2O$ | 52·71 | 5·97 | 10·82 |
| | ethanol–ether | (388·4) | | | |
| *XIII*-2 P[o] | 213–215 | $C_{29}H_{25}N_9O_{14}S$[p] | 46·09 | 3·34 | 16·68 |
| | ethyl acetate | (755·6) | 45·89 | 3·25 | 16·44 |

[a] Calculated: 9·80% Cl, found: 9·93% Cl; [b] calculated: 9·80% Cl, found: 10·05% Cl; [c] calculated: 9·80% Cl, found: 9·95% Cl; [d] see Experimental; [e] fumarate; [f] maleate; [g] pyridine was used instead of triethylamine; [h] calculated: 9·38% Cl, 8·49% S; found: 9·37% Cl, 8·29% S; [i] calculated:9·39% S, found: 9·68% S; [j] calculated: 9·38% Cl, 8·49% S; found: 9·58% Cl, 8·29% S; [k] calculated:9·39% S, found: 9·34% S; [l] calculated: 9·38% Cl, 8·49% S; found: 9·32% Cl, 8·62% S; [m] monohydrate; [n] calculated: 18·26% Cl, 8·25% S; found: 17·62% Cl, 8·25% S; [o] dipicrate; [p] calculated: 4·24% S, found: 4·27% S.

per base and the compounds were administered in the in vivo tests orally. Acute toxicity in mice was studied only with two compounds: *X*, the dose of 700 mg/kg was not toxic (no lethality and no influence on behaviour); *XIV*, $LD_{50}$ = 170 mg/kg. In concentrations of 100 nmol $l^{-1}$ the compounds did not inhibit the binding of 4 nM [$^3$H]imipramine and 4 nM [$^3$H]desipramine to the imipramine and desipramine binding sites in hypothalamus of the rat brain. In doses of 25 mg/kg only *XIV* showed a significant antireserpine effect in the test of ptosis in mice. In doses of 50 mg/kg only *X* showed a mild but significant antagonistic effect against the ulcerogenic action of reserpine in rats. In doses of 10 mg/kg only *VI*, *X*, *XI*, and *XII* inhibited the spontaneous locomotor activity in mice (photo-cell method of Dews). In doses of 80 mg/kg the compounds altered the homovanillic acid level in the rat brain striatum (per cent of the control value given; increase above 100% indicates antidopaminergic activity, decrease bellow 100% indicates dopaminomimetic activity): *IV*, 63; *V*, 91; *VI*, 85; *VII*, 113; *VIII*, 132; *IX*, 68; *X*, 153; *XI*, 58; *XII*, 73; *XIII*, 85; *XIV*, 73; *XV*, 76. In the same dose *I* increased significantly the homovanillic acid level in the striatum.

In conclusion: only *X* (VÚFB-17070) and *XIV* (VÚFB-17114) showed indications of antireserpine activity (i.e. effect considered indicative of antidepressant profile), the former being significantly antidopaminergic and the latter slightly dopaminomimetic.

TABLE II

Spectra of 1-acyl- and 1-(thioacyl)-4-benzylpiperazines

| Compound | Spectrum | Data |
|---|---|---|
| *IV* | UV | infl. 256 (3·77) |
| | IR | 700, 744 (4 and 5 adjacent Ar–H); 1 350, 1 520 ($ArNO_2$); 1 610, 3 020, 3 060, 3 080 (Ar); 1 640 (CON); 2 765, 2 810 ($CH_2$–N) |
| | $^1$H NMR | 2·35 bm and 2·60 bm, 2 and 2 H ($CH_2N^4CH_2$ of piperazine); 3·51 s, 2 H ($ArCH_2N$); 3·20 bt and 3·82 bt, 2 and 2 H ($CH_2N^1CH_2$ of piperazine); 7·26 s, 5 H ($C_6H_5$); 7·60 m, 3 H (H-4, H-5, and H-6 of nitrobenzoyl); 8·15 bd, 1 H (H-3 of nitrobenzoyl, $J$ = 8·5) |
| *V* | UV | infl. 236 (4·01) |
| | IR | 675, 693, 733, 766, 823, 854 (3 and 5 adjacent and solitary Ar–H); 1 353, 1 526 ($ArNO_2$); 1 586, 3 025, 3 080 (Ar); 1 630 (CON); 2 764 ($CH_2$–N) |
| | $^1$H NMR | 2·50 bs, 4 H ($CH_2N^4CH_2$ of piperazine); 3·52 s, 2 H ($ArCH_2N$); 3·40 bs and 3·75 bs, 2 and 2 H ($CH_2N^1CH_2$ of piperazine); 7·26 s, 5 H ($C_6H_5$); 7·60 m, 2 H (H-5 and H-6 of nitrobenzoyl); 8·35 m, 2 H (H-2 and H-4 of nitrobenzoyl) |
| *VI*-HCl | MS | 325 ($M^+$, $C_{18}H_{19}N_3O_3$, 1), 248 (0·3), 234 (1), 150 (12), 146 (4), 134 (26), 132 (22), 104 (13), 91 (100) |
| | UV | 263 (4·04) |
| | IR | 702, 754, 869 (5 and 2 adjacent Ar–H); 1 346, 1 515 ($ArNO_2$); 1 602, 3 088, 3 105 (Ar); 1 635 (ArCON); 2 440, 2 520 ($NH^+$) |
| *VII* | UV | infl. 224 (4·12), 260 (3·75), 293 (3·27) |
| | IR | 703, 740, 761 (5 and 4 adjacent Ar–H); 1 490, 1 570, 1 598, 3 025, 3 055 (Ar); 1 618 (CON); 2 795 ($CH_2$–N) |
| | $^1$H NMR | 2·50 m, 4 H ($CH_2N^4CH_2$ of piperazine); 2·78 s, 6 H ($N(CH_3)_2$); 3·50 s, 2 H ($ArCH_2N$); 3·20 m and 3·80 m, 2 and 2 H ($CH_2N^1CH_2$ of piperazine); 6·70–7·20 m, 4 H (H-3, H-4, H-5, and H-6 of nitrobenzoyl); 7·25 s, 5 H ($C_6H_5$) |
| *VIII*-M[a] | MS | 323 ($M^+$, $C_{20}H_{25}N_3O$, 3), 308 (0·2), 190 (15), 185 (5), 148 (27), 146 (39), 134 (8), 132 (32), 120 (18), 91 (100), 42 (40) |
| *IX* | UV | 289 (4·22) |
| | IR | 710, 761, 822 (5 and 2 adjacent Ar–H); 1 522, 3 020, 3 080 (Ar); 1 605 (ArCON); 2 740, 2 810 ($CH_2$–N) |
| | $^1$H NMR | 2·48 bt, 4 H ($CH_2N^4CH_2$ of piperazine); 2·95 s, 6 H ($N(CH_3)_2$); 3·51 s, 2 H ($ArCH_2N$); 3·62 bt, 4 H ($CH_2N^1CH_2$ of piperazine); 6·62 d, 2 H (H-3 and H-5 of aminobenzoyl, $J$ = 8·5); 7·28 s, 5 H ($C_6H_5$); 7·38 d, 2 H (H-2 and H-6 of aminobenzoyl, $J$ = 8·5) |

TABLE II
(*Continued*)

| Compound | Spectrum | Data |
|---|---|---|
| *X*-HCl | MS | 341 ($M^+$, $C_{18}H_{19}N_3O_2S$, 0·03), 308 (0·4), 290 (0·2), 146 (4), 91 (100) |
| | UV | infl. 265 (4·11), 280 (4·13) |
| | IR | 700, 745, 755, 792 (5 and 4 adjacent Ar–H); 1 340, 1 520 ($ArNO_2$); 1 510 (N–C=S); 1 570, 1 608, 3 040, 3 060, 3 100 (Ar); 2 370, 2 400, 2 438 ($NH^+$) |
| *XI* | UV | 254 (4·19), infl. 277 (4·12) |
| | IR | 700, 745, 798, 886 (5 and 3 adjacent and solitary Ar–H); 1 350, 1 527 ($ArNO_2$); 1 493 (N—C=S); 1 575, 3 030 (Ar); 2 770 ($CH_2$–N) |
| | $^1$H NMR | 2·40 bt and 2·62 bt, 2 and 2 H ($CH_2N^4CH_2$ of piperazine); 3·50 s, 2 H ($ArCH_2N$); 3·50 bt and 4·40 bt, 2 and 2 H ($CH_2N^1CH_2$ of piperazine); 7·25 s, 5 H ($C_6H_5$); 7·50 m, 2 H (H-5 and H-6 of nitrophenyl); 8·10 m, 2 H (H-2 and H-4 of nitrophenyl) |
| *XII* | UV | 260 (4·20), infl. 300 (3·84) |
| | IR | 698, 738, 748, 800 (5 and 2 adjacent Ar–H); 995, 1 293, 1 510 (ArCSN); 1 342, 1 510 ($ArNO_2$); 1 592, 3 025, 3 050, 3 085 (Ar); 2 765, 2 810 ($CH_2$–N) |
| | $^1$H NMR | 2·31 bt and 2·58 bt, 2 and 2 H ($CH_2N^4CH_2$ of piperazine); 3·48 s, 2 H ($ArCH_2N$); 3·41 bt and 4·33 bt, 2 and 2 H ($CH_2N^1CH_2$ of piperazine); 7·23 s, 5 H ($C_6H_5$); 7·30 d, 2 H (H-2 and H-6 of nitrophenyl, $J$ = 8·5); 8·11 d, 2 H (H-3 and H-5 of nitrophenyl, $J$ = 8·5) |
| *XII*-HCl | MS | 341 ($M^+$, $C_{18}H_{19}N_3O_2S$, 0·5), 308 (0·5), 159 (13), 150 (3), 146 (30), 91 (100), 65 (8) |
| | UV | 260 (4·16), infl. 300 (3·84), infl. 379 (3·06) |
| | IR | 700, 750, 852 (5 and 2 adjacent Ar–H); 1 348, 1 518 ($ArNO_2$); 1 493 (N–C=S); 1 598, 3 085 (Ar), 2 400, 2 510 ($NH^+$) |
| *XIII*-2 HCl[b] | MS | 297 ($M^+$, $C_{17}H_{19}B_3S$, 3), 264 (1), 226 (3), 176 (6), 146 (18), 134 (20), 91 (70), 36 (HCl, 100) |
| | UV | 278 (4·02) |
| | IR | 700, 759 (5 and 4 adjacent Ar–H); 1 274, 1 451 (ArCSN); 1 515, 1 600, 3 035, 3 085 (Ar); 1 619, 3 430, 3 510 ($H_2O$); 2 380, 2 500, 2 645 ($NH^+$) |

[a] Maleate; [b] monohydrate.

The compounds were also tested for antimicrobial activity in vitro (microorganisms and minimum inhibitory concentrations in mg/l given unless it exceeded 100 mg/l): *Streptococcus pyogenes*, *X* 25, *XI* 25, *XIII* 50; *Staphylococcus aureus*, *X* 3·1, *XIII* 50; *Proteus vulgaris*, *XIII* 50; *Saccharomyces pasterianus*, *X* 25; *Trichophyton mentagrophytes*, *VII* 50, *VIII* 50, *X* 0·03, *XI* 12·5, *XIII* 50.

## 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 suibly elevated temperature. UV spectra (in methanol, $\lambda_{max}$ in nm ($\log \varepsilon$)) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in NUJOL, $\nu$ in $cm^{-1}$) were recorded with the Perkin–Elmer 298 spectrophotometer, $^1H$ NMR spectra (in $CDCl_3$, $\delta$ in ppm, $J$ in Hz) with a CW-NMR Tesla BS 497C (80 MHz) spectrometer, and the mass spectra ($m/z$ and %) 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). The extracts were dried with $MgSO_4$ or $K_2CO_3$ and evaporated under reduced pressure on a rotary evaporator.

1-Benzyl-4-(4-nitrobenzoyl)piperazine (*VI*) (Method *A*)

A stirred solution of 8·8 g 1-benzylpiperazine[17] and 5·2 g triethylamine in 40 ml benzene was slowly treated (under external cooling with ice and water) with a solution of 9·3 g 4-nitrobenzoyl chloride in 50 ml benzene. It was diluted with 50 ml benzene and stirred for 2 h at 40°C. After standing overnight it was decomposed with 50 ml 20% NaOH, the benzene layer was washed several times with water, dried, and evaporated. The residue (15·4 g, 95%) was the crude oily *VI*. It was dissolved in 150 ml ethanol and the solution was neutralized with HCl in ether giving 13·6 g hydrochloride melting at 246–248°C (ethanol). Analysis and spectra are included in Tables I and II.

1-Benzyl-4-(2-dimethylaminobenzoyl)piperazine (*VII*) (Method *B*)

A stirred solution of 3·3 g 2-dimethylaminobenzoic acid[19] and 2·1 g triethylamine in 30 ml benzene was treated with a solution of 2·4 g $SOCl_2$ in 20 ml benzene, added dropwise at 0°C. The mixture was stirred for 20 min at 0°C and then for 1 h at 35–40°C. After cooling the separated solid was filtered off and the filtrate was dropped at 0°C into a stirred solution of 3·6 g 1-benzylpiperazine[17] and 2·1 g triethylamine in 20 ml benzene over 30 min. The mixture was then stirred for 5 h at 40°C, after cooling washed with 5% NaOH and water. Processing of the benzene solution gave 6·0 g (92%) of oily *VII* which crystallized from cyclohexane, m.p. 83 to 85°C.

*Fumarate*, m.p. 143–145°C (acetone–ether). Analyses and spectra are included in Tables I and II.

1-Benzyl-4-(4-nitrothiobenzoyl)piperazine (*XII*) (Method *C*)

A mixture of 8·5 g *VI*, 6·0 g $P_4S_{10}$, and 30 ml pyridine was refluxed in nitrogen atmosphere for 2 h, poured into a mixture of 80 ml 20% NaCl, 120 ml water and 250 ml toluene. The mixture

obtained was refluxed under stirring for 10 h. After cooling the toluene layer was separated, dried, and evaporated in vacuo. The residue (8·3 g, 93%) was the crystalline base *XII*, m.p. 182—184°C (ethanol).

*Hydrochloride*, m.p. 198—200°C (ethanol–ether). The analyses and spectra are included in Tables I and II.

4-(Dimethylaminomethyl)benzoic Acid

A warm solution of 3·06 g 4-(dimethylaminomethyl)benzoic acid hydrochloride[25,26] in 100 ml ethanol was treated with sodium ethoxide, prepared from 0·33 g Na and 10 ml ethanol. After 5 min standing the precipitated NaCl was filtered off and the filtrate was allowed to crystallize on standing; 2·40 g of free acid, m.p. 238—240°C (ethanol). Mass spectrum: 179 ($M^+$, $C_{10}H_{13}\cdot NO_2$), 162, 135, 118, 91, 77, 58 (100). UV spectrum: 278 (2·83), 270 (2·98). IR spectrum (KBr): 809 (2 adjacent Ar–H); 1 060, 1 218 (C–N); 1 566, 3 000, 3 030, 3 050 (Ar); 1 625 ($COO^-$); 2 110 ($NH^+$). For $C_{10}H_{13}NO_2$ (179·2) calculated: 67·01% C, 7·31% H, 7·82% N; found: 66·74% C, 7·46% H, 7·64% N.

1-Benzyl-4-(4-(dimethylaminomethyl)benzoyl)piperazine (*XIV*)

A mixture of 3·8 g 4-(dimethylaminomethyl)benzoic acid, 4·05 g N,N′-carbonyldiimidazole, and 400 ml dimethylformamide was heated for 3 h to 70°C. After cooling to 25°C, 3·8 g 1-benzylpiperazine[17] were added, the mixture was stirred for 4 h at room temperature and then allowed to stand for 4 days. Dimethylformamide was evaporated in vacuo, the residue was dissolved in 50 ml benzene, the solution was washed with water, dried, and evaporated. The residue was dissolved in 20 ml ethanol and the solution was neutralized with HCl in ethanol. The crude dihydrochloride was filtered and recrystallized from a mixture of ethanol and ether; 3·7 g (43%) of *XIV*.2 HCl, m.p. 245—250 and 275—278°C. Mass spectrum: 337 ($M^+$, $C_{21}H_{27}N_3O$, 5), 294 (3), 246 (1), 205 (8), 204 (10), 175 (5), 162 (20), 159 (20), 146 (65), 132 (42), 105 (15), 91 (100), 58 (25). UV spectrum: infl. 270 (3·64), 303 (3·35). IR spectrum: 701, 751, 761, 825 (5 a 2 adjacent Ar–H); 1 481, 1 573, 3 010, 3 028, 3 070 (Ar); 1 646 (ArCON); 2 400, 2 445, 2 520, 2 562 ($NH^+$). For $C_{21}H_{29}Cl_2N_3O$ (410·4) calculated: 61·48% C, 7·12% H, 17·28% Cl, 10·24% N; found: 61·21% C, 7·21% H, 17·34% Cl, 10·15% N.

1-Benzyl-4-(5-methyl-4-imidazolylcarbonyl) piperazine

A mixture of 8·9 g 1-benzylpiperazine[17], 8·1 g ethyl 5-methylimidazole-4-carboxylate (commercial product, BASF), and 0·2 g Na was stirred and heated for 16 h to 200—210°C. After cooling the melt was dissolved in 100 ml ether, the solution was filtered, and the filtrate was evaporated. The residue (15·7 g) was chromatographed on 300 g neutral $Al_2O_3$ (activity II). Elution with 1,2-dichloroethane gave 4·7 g of oil which was identified as 1-benzyl-4-ethylpiperazine (*XVI*). It was transformed to the dihydrochloride, m.p. 250—252°C (ethanol). Mass spectrum: 204 ($M^+$, $C_{13}H_{20}N_2$, 25), 189 (4), 175 (7), 161 (6), 146 (13), 91 (80), 58 (50), 36 (HCl, 100). IR spectrum: 702, 753 (5 adjacent Ar–H); 1 500, 3 040 (Ar); 2 340 ($NH^+$). The analysis is in agreement with the elemental composition $C_{13}H_{22}Cl_2N_2$. Ref.[29], m.p. 250—252°C.

The chromatography was continued by elution with chloroform which led to 2·6 g of mixtures. Elution with chloroform containing 5% of ethanol gave 5·5 g (36%) of crude *XV* which was transformed to dihydrochloride crystallizing from a mixture of 95% ethanol and ether as the monohydrate, m.p. 172—174°C. Mass spectrum: 294 ($M^+$, $C_{16}H_{20}N_4O$), 269 (0·3), 193

(2), 175 (4), 146 (45), 109 (46), 91 (100). IR spectrum: 698, 750 (5 adjacent Ar–H); 1 496, 1 595, 3 085 (Ar); 1 633 (ArCON); 2 500 ($NH^+$); 3 310 (NH, $H_2O$). For $C_{16}H_{22}Cl_2N_4O.H_2O$ (375·3) calculated: 51·21% C, 6·45% H, 18·89% Cl, 14·92% N; found: 51·18% C, 6·48% H, 18·69% Cl, 14·64% N.

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