SYNTHESIS AND PHARMACOLOGICAL SCREENING OF 1-[2-TERT-AMINOETHYL]-8-FLUORO-5-[4-FLUOROPHENYL]--2,3,4,5-TETRAHYDRO-1*H*-1-BENZAZEPINES, THEIR 1-[AMINOACETYL] ANALOGUES AND 1-SUBSTITUTED 9-FLUORO-6-[4-FLUOROPHENYL]--5,6-DIHYDRO-4*H*-*s*-TRIAZOLO[4,3-*a*]-1-BENZAZEPINES*

Zdeněk VEJDĚLEK, Emil SVÁTEK, Jiří HOLUBEK, Jan METYŠ, Marie BARTOŠOVÁ and Miroslav PROTIVA

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

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7-Fluoro-4-(4-fluorophenyl)-1-naphthylamine (*III*) was identified as a by-product in the transformation of 7-fluoro-4-(4-fluorophenyl)-1-tetralone oxime to the lactam *I*. Reaction of 8-fluoro--5-(4-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (*V*) with chloroacetyl chloride gave the chloroamide *VI* which was treated with secondary amines to give the aminoacetamides *VII*, *VIII*, *XI* and *XII*. Reduction with lithium aluminium hydride afforded the amines *IX*, *X*, *XIV* and *XV*. Acylation of the piperazinoethanols *XII* and *XV* led to the esters *XIII*, *XVI* and *XVII*. Reaction of the lactam *I* with phosphorus pentasulfide gave the thiolactam *II* which was treated with a series of acid hydrazides and gave the title compounds *XVIII*—*XXIV*. Some of the compounds exhibited only in relatively high doses anticonvulsant and central depressant effects in various tests.

The important psychotropic activity of some 1,4-benzodiazepine derivatives[1,2] evokes attention to the corresponding 4-deaza analogues, *i.e.* 1-benzazepine derivatives. Tranquillizing and anticonvulsant[3], antiarrhythmic[4] and antiinflammatory activity[5,6] were reported for some members of this series; additional ones were prepared as potential analgetics[7]. Two papers were devoted to 5-aryl-1-benzazepine derivatives which can be considered analogues of chlordiazepoxide[8] and diazepam[9], respectively; whereas the former were described as being devoid of any significant activity in the central nervous system, no biological data were reported for the latter ones. The syntheses of 8-fluoro-5-(4-fluorophenyl)-1,3,4,5-tetrahydro-1-benzazepin--2-one (*I*) and 8-fluoro-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (*V*) have been described[10]. In the present communication we are describing the transformations of these two compounds to a series of further potential neurotropic agents containing the 1-benzazepine fragment in their molecules.

The starting lactam *I* was obtained by the Beckmann rearrangement of 7-fluoro-

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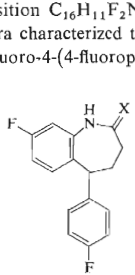
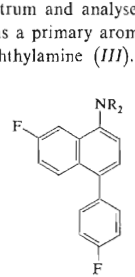
-4-(4-fluorophenyl)-1-tetralone oxime with polyphosphoric acid at 130°C, similarly as described in our previous communication[10]; the pure lactam was obtained in a yield of 68%. Working in larger batches made possible to search after the by-products of the reaction. Whereas we were not able to isolate the expected isomeric 8-fluoro--5-(4-fluorophenyl)-2,3,4,5-tetrahydro-2-benzazepin-1-one (obtained formerly[10] by the Schmidt reaction from the corresponding tetralone), we isolated from the mother liquors in a yield of about 4% phosphate of an oxygen-free base, for which the elemental composition $C_{16}H_{11}F_2N$ (mass spectrum and analyses) has been determined. The spectra characterized the product as a primary aromatic amine, finally identified as 7-fluoro-4-(4-fluorophenyl)-1-naphthylamine (*III*). Its formation is



I, X = O
II, X = S

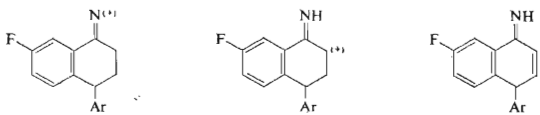


III, R = H
IV, R = $COCH_3$

a new example of a reaction, designed as the Semmler–Wolff aromatization[11,12], consisting in transformation of the cyclohexenone oximes[11,12], 1-tetralone oximes[13–16] and 1- or 4-oxo-1,2,3,4-tetrahydrophenanthrene oximes[17,18] to the corresponding aromatic amines by treatment with a mixture of acetic acid and acetic anhydride saturated with hydrogen chloride[13,15] or hydrogen bromide[17,18], with polyphosphoric acid[14] or with a mixture of acetic anhydride and phosphoric acid[16]. Whereas the mechanism of the reaction, suggested by Schroeter[13], is too complicated and probably not correct, another paper[14] indicates a more probable explanation by postulating the imine cation as the first short-lived intermediate. In our case it would be the cation *A*, formed by cleavage of the hydroxyl anion. A shift of the charge and of one hydrogen atom could lead to the cation B being stabilized to intermediate *C* by the loss of a proton; the final step is the tautomeric shift of the double bonds leading to the isolated product *III*. For its characterization, it was acetylated with boiling acetic anhydride resulting in the N,N-diacetyl derivative *IV*.

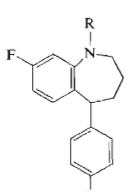
The lactam *I* was transformed to the amine *V* by reduction with lithium aluminium hydride[10]. The following reaction with chloroacetyl chloride in chloroform in the presence of potassium carbonate gave the chloroacetyl derivative *VI*, transformed by substitution reactions with an excess of diethylamine, pyrrolidine, 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine in benzene (method *A*) to the aminoacetamides

VII, *VIII*, *XI* and *XII*. These amides were then reduced with lithium aluminium hydride in a mixture of ether and benzene (method *B*) to the amines *IX*, *X*, *XIV* and *XV*. Acylation of the piperazinoethanol derivatives *XII* and *XV* with propionyl chlo-

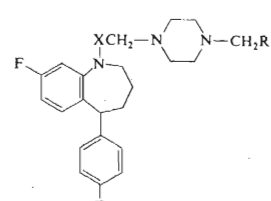


A *B* *C*

ride and 2-chlorobenzoyl chloride in chloroform in the presence of potassium carbonate (method *C*) afforded the esters *XIII*, *XVI* and *XVII*.



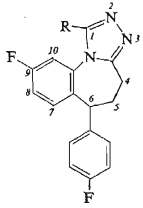
V, R = H
VI, R = $COCH_2Cl$
VII, R = $COCH_2N(C_2H_5)_2$
VIII, R = $COCH_2N$ 
IX, R = $CH_2CH_2N(C_2H_5)_2$
X, R = CH_2CH_2N 



XI, X = CO, R = H
XII, X = CO, R = CH_2OH
XIII, X = CO, R = $CH_2OCOC_2H_5$
XIV, X = CH_2, R = H
XV, X = CH_2, R = CH_2OH
XVI, X = CH_2, R = $CH_2OCOC_2H_5$
XVII, X = CH_2, R = CH_2OCO 

Reaction of the lactam *I* with phosphorus pentasulfide in pyridine led to the thiolactam *II*. Its reactions with acetic[19], propionic[20], methoxacetic[21], methylthioacetic[22], benzoic[23], phenylacetic[24] and nicotinic[25] acid hydrazides in boiling 1-butanol (method *D*) resulted in the corresponding 1-substituted derivatives of 9-fluoro-6-(4-fluorophenyl)-5,6-dihydro-4*H*-s-triazolo[4,3-*a*]-1-benzazepine (*XVIII*–*XXIV*) containing in their molecules the new tricyclic system (for the similar annelation of the triazole ring to the 1,4-benzodiazepine system, *cf.*[26]). Isolation of the pure

substances requested in most of the cases the use of chromatography on columns of alumina; in two cases the N,N'-diacylhydrazines (N,N'-diacetylhydrazine[27], N,N'-bis(phenylacetyl)hydrazine[28]) were separated as by-products, formed evidently by a thermic reaction of the starting monoacylhydrazines[28], used in excess. The compounds which were prepared using the general methods *A*–*D* are assembled in Table I with the usual experimental data; the Experimental describes the preparation of the remaining substances and presents examples of syntheses using the general methods *A* – *D*.



XVIII, R = CH_3
XX, R = CH_2OCH_3
XXII, R = C_6H_5

XIX, R = C_2H_5
XXI, R = CH_2SCH_3
XXIII, R = $CH_2C_6H_5$

XXIV, R = 

The compounds prepared were pharmacologically evaluated using the methods of the general screening with oral and parenteral administration and with the main emphasis to the central effects (central depressant and anticonvulsant). Table II presents the values of acute toxicity in mice (LD_{50}), the basic doses D used in the screening (compounds which did not show activity in the dose D were considered inactive in the respective line), and finally the character of effects of doses higher than D which were observed during the toxicity tests. Positive results obtained in the individual tests are presented in the following paragraph (the way of administration no more mentioned if it was in agreement with the statement in the Table II, the doses in mg/kg).

Central excitation (dose eliciting a 50% increase of motility in mice in comparison with the control group): *II* 100; *VII*, 10; *VIII*, 5–10; *XIX*, D. Antireserpine effect (dose antagonizing significantly the reserpine ptosis in mice; for amphetamine, ED = 0·5 mg/kg *i.p.*): *IX*, 12 *i.p.*; *XIX*, D *p.o.* Inhibition of locomotor activity (D_{50} in the photo-cell method in mice): *XIV*, D; *XVIII*, D; *XXII*, D. Ataxia in mice (ED_{50} in the rotarod test): *XVIII*, >D; *XX*, >D; *XXIV*, >D. Thiopental potentiation (dose prolonging significantly the duration of the thiopental sleeping-time

in mice; for chlorpromazine a dose of 1 mg/kg *p.o.* prolongs to 200% of the control value): *XIV*, D; *XVIII*, 7·5 (200%); *XX*, 7 (250%); *XXIV*, D (480%). Hypothermic, effect (dose decreasing the rectal temperature of rats by 1·0°C; for chlorpromazine ED = 5–10 mg/kg *p.o.*): *VII*, D.

Anticonvulsant effect – pentetrazole (dose prolonging significantly the latency of clonic convulsions in mice elicited by pentetrazole; for phenytoine, ED = 100 mg/kg *p.o.*): *II*, D; *VIII*, 2·5–5; *XX*, 30; *XXII*, D. Anticonvulsant effect – electroshock (dose protecting 50% mice from the tonic-extensor convulsions of the hind extremities elicited by electroshock; for phenytoine, ED = 100 mg/kg *p.o.*): *VII*, D *VIII*, D; *XIV*, D; *XVIII*, 15·9; *XX*, D protects only 20% animals; *XXIV*, D. Anti-inflammatory effect (dose inhibiting significantly over 24 h the development of the rat hind limb oedema elicited by subplantar administration of 0·1 ml 10% kaolin suspension; for phenylbutazone, ED = 75 mg/kg *p.o.*): *VIII*, 25. Spasmolytic (parasympatholytic) effect (concentration in μg/ml exhibiting a reduction of the acetylcholine contractions of the isolated rat duodenum by 50%; for atropine, ED = = 0·05 μg/ml): *IX*, 1–10. Spasmolytic (musculotropic) effect (concentration in μg/ml exhibiting a reduction of barium chloride contractions of the isolated rat duodenum by 50%; for papaverine, ED = 5 μg/ml): *IX*, 1–10. Local anaesthetic effect (concentration bringing about anaesthesia in 50% guinea-pigs in the test of infiltration anaesthesia; for procaine, ED = 1%): *XII*, 1% (slight effect). Heart inotropy and frequency: *XII*, a concentration of 50 μg/ml increased the inotropy of the isolated rabbit heart atrium by 25% and decreased the frequency by 25%. Hypotensive effect in normotensive rats: *VIII*, D decreased the blood pressure within 24 h after the administration by 12%; *IX*, D decreased the pressure by 20% for at least 10 min; *XII*, D decreased the pressure by 20–30% for several min, the effect is accompanied by bradycardia and cardiotoxic ECG effects; *XIII*, D brought about brief and deep reduction of the pressure; *XV*, like the preceding compound. Adrenolytic effect (dose *i.v.* inhiting the adrenaline pressor reaction in rats by 50%): *XII*, D.

In conclusion, the compounds prepared display indications of central activities typical for the 1,4-benzodiazepine and *s*-triazolo[4,3-*a*]-1,4-benzodiazepine derivatives[1,2,26]; the difference in the intensity of effects, however, is very important – our compounds being much less active. It might be caused – at least partly – by the location of the fluorine atoms in our compounds which would be unfavourable (for the effects) even in the mentioned series.

The compounds prepared were also tested for antimicrobial activity *in vitro* (Dr L. Langšádl and Dr J. Turinová, bacteriological department of this institute). The used microorganisms, numbers of compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *II* 25, *VII* 50, *IX* 25, *X* 12·5, *XII* 100, *XIV* 25, *XVI* 50, *XXIII* 100: *Streptococcus faecalis*, *IX* 50, *X* 50, *XIV* 25, *XV* 25, *XVI* 50; *Staphylococcus pyogenes aureus*, *IX* 50, *X* 25, *XIV* 25, *XV* 25, *XXII* 100, *XXIII* 50; *Escherichia coli*, *IX* 50, *X* 25, *XIV* 25, *XV* 25, *XVI* 50; *Proteus vulgaris*, *X* 100; *Mycobacterium tuberculosis* H37Rv, *VIII* 100, *IX* 6·25, *X* 50, *XI* 100, *XIV* 12·5, *XV* 50, *XVI* 100, *XVII* 50, *XXII* 100; *Saccharomyces pasterianus*,

TABLE I
Compounds *VII*—*XXIV* and Salts

Compound	Method (yield, %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
				% C	% H	% F	% N	% Cl(S)
VII	*A* (79)	104—105[a] (cyclohexane)	$C_{22}H_{26}F_2N_2O$ (372·4)	70·94 70·99	7·04 6·94	10·20 10·11	7·52 7·01	— —
VII-HOx[b]		206—207 (aqueous ethanol–ether)	$C_{24}H_{28}F_2N_2O_5$ (462·5)	62·32 62·44	6·10 6·39	8·22 8·04	6·06 6·14	— —
VIII[c]	*A* (93)	97—98[d] (cyclohexane–pentane)	$C_{22}H_{24}F_2N_2O$ + 1/3 C_6H_{12} (398·5)	72·33 72·73	7·08 6·97	9·54 9·85	7·03 7·51	— —
VIII-HOx[b]		211—212 (aqueous ethanol–ether	$C_{24}H_{26}F_2N_2O_5$ (460·5)	62·60 62·98	5·59 5·96	8·25 7·96	6·08 5·89	— —
IX-HCl	*B* (86)	196—197 (ethanol–ether)	$C_{22}H_{29}ClF_2N_2$ (394·9)	66·89 66·54	7·42 7·43	9·62 9·58	7·09 6·80	8·98 8·92
X-1·5 HCl[e]	*B*[f] (100)	195—196 (ethanol–ether)	$C_{22}H_{26}F_2N_2$ + 1·5 HCl + 0·5 H_2O (420·2)	62·92 63·26	6·83 7·16	9·02 8·69	6·68 6·49	12·65 12·57
X-Ox[g]		199—200 (aqueous ethanol–ether)	$C_{24}H_{28}F_2N_2O_4$ (446·5)	64·56 64·51	6·33 6·48	8·51 8·47	6·27 6·31	— —
XI	*A*[f] (92)	164—165 (ethanol)	$C_{23}H_{27}F_2N_3O$ (399·5)	69·15 69·38	6·81 6·87	9·51 9·70	10·52 10·34	— —
XI·2 HCl		244—245 (aqueous ethanol)	$C_{23}H_{29}Cl_2F_2N_3O$ (472·4)	58·47 58·61	6·19 6·34	8·04 7·99	8·90 8·41	15·01 14·82
XII	*A* (93)	150—151[h] (benzene–hexane)	$C_{24}H_{29}F_2N_3O_2$ (429·5)	67·11 67·36	6·81 6·85	8·85 8·94	9·78 9·52	— —
XII·2 HCl[e]		226—227 (aqueous ethanol–ether)	$C_{24}H_{31}Cl_2F_2N_3O_2$ + 0·5 H_2O (511·4)	56·35 56·18	6·29 6·00	7·43 7·52	8·21 8·01	13·88 13·66
XIII·2 HCl	*C* (100)	190—191 (ethanol–ether)	$C_{27}H_{35}Cl_2F_2N_3O_3$ (558·5)	58·06 57·92	6·32 6·08	6·80 7·10	7·53 7·53	12·70 12·37
XIV·2HCl	*B* (98)	239—240 (aqueous ethanol)	$C_{23}H_{31}Cl_2F_2N_3$ (458·4)	60·26 60·63	6·83 6·71	8·29 8·63	9·15 8·54	15·47 15·22
XV·2 HCl	*B* (100)	225—226 (aqueous ethanol–ether)	$C_{24}H_{33}Cl_2F_2N_3O$ (488·5)	59·00 59·32	6·81 6·75	7·79 7·99	8·60 8·75	14·52 14·70

TABLE I
(*Continued*)

Compound	Method (yield, %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found % C	% H	% F	% N	% Cl(S)
XVI·2 HCl	*C*[f] (100)	191—192 (aqueous ethanol–ether)	$C_{27}H_{37}Cl_2F_2N_3O_2$ (544·5)	59·55 59·72	6·85 6·77	6·98 7·33	7·72 7·95	13·02 13·21
XVII·2 HCl	*C* (90)	199—200[i] (aqueous ethanol–ether)	$C_{31}H_{36}Cl_3F_2N_3O_2$ (627·0)	59·38 59·70	5·79 5·68	6·06 6·16	6·70 6·97	16·97 17·34
XVIII	*D*[f] (70)	215—216 (benzene–hexane)	$C_{18}H_{15}F_2N_3$ (311·3)	69·43 69·70	4·86 5·02	12·21 11·94	13·50 13·70	— —
XIX	*D* (82)	182—183[j] (benzene–hexane)	$C_{19}H_{17}F_2N_3$ (325·4)	70·13 70·18	5·27 5·40	11·68 11·83	12·92 12·97	— —
XX	*D* (77)	159—160[k] (benzene–hexane)	$C_{19}H_{17}F_2N_3O$ (341·4)	66·85 67·01	5·02 4·96	11·13 11·34	12·31 12·51	— —
XXI	*D* (85)	193—194[l] (ethyl acetate)	$C_{19}H_{17}F_2N_3S$ (357·4)	63·85 64·24	4·79 4·66	10·63 10·83	11·76 11·51	8·97 8·89
XXII	*D* (71)	206—207[m] (benzene–hexane)	$C_{23}H_{17}F_2N_3$ (373·4)	73·98 74·56	4·59 4·60	10·18 10·08	11·25 11·21	— —
XXIII	*D*[n] (79)	182—183[o] (benzene–hexane)	$C_{24}H_{19}F_2N_3$ (387·4)	74·40 74·39	4·94 5·06	9·81 10·00	10·85 10·52	— —
XXIV·C_6H_6	*D* (80)	117—118[p] (benzene–hexane)	$C_{22}H_{16}F_2N_4 + C_6H_6$ (452·5)	74·32 74·87	4·90 4·80	8·40 8·30	12·38 12·27	— —

[a] UV spectrum: λ_{max} 266·5 nm (log ε 3·36), 272 nm (3·34); IR spectrum: 790, 821, 840, 900 (2 adjacent and solitary Ar—H), 1 490, 1 510, 1 587, 1 601, 3 020 (Ar), 1 668 cm^{-1} (ArNCOR); ^{1}H-NMR spectrum: δ 6·30—7·20 (m, 7 H, Ar—H), 4·20 and 4·70 (2 m, 2 H, $CONCH_2$), 3·21 and 2·98 (ABq, J = 14·0 Hz, 2 H, $COCH_2N$), 1·60—3·20 (m, 9 H, CH_2NCH_2 of diethylamino and $Ar_2CHCH_2CH_2$), 0·89 (t, J = 7·0 Hz, 6 H, 2 CH_3). [b] Hydrogen oxalate. [c] Solvate with 1/3 molecule of cyclohexane. [d] IR spectrum: 826, 831, 896 (2 adjacent and solitary Ar—H), 1200, 1229, 1 303 (Ar—F), 1 497, 1 514, 1 596, 1 604, 3 010, 3 030 (Ar), 1 669 cm^{-1} (ArNCOR); ^{1}H-NMR spectrum: δ 6·30—7·40 (m, 7 H, Ar—H), 4·70 and 4·10 (2 m, 2 H, $CONCH_2$), 3·18 and 2·98 (ABq, J = 15·0 Hz, 2 H, $COCH_2N$), 1·50—2·90 (m, 9 H, remaining CH and CH_2), 1·35 (s, 4 H, CH_2CH_2 of cyclohexane). [e] Hemihydrate. [f] See Experimental. [g] Oxalate. [h] IR spectrum: 819, 841, 900 (2 adjacent and solitary Ar—H), 1 058 (CH_2OH), 1 200, 1 225, 1 305 (Ar—F), 1 498, 1 515, 1 595, 1 606, 2 995, 3 015 (Ar), 1 687 (ArNCOR), 2 740, 2 780 (NCH_2), 3 460 cm^{-1} (OH); ^{1}H-NMR, spectrum: δ 6·30—7·30 (m, 7 H, Ar—H), 4·70 and 4·10 (2 m, 2 H, $CONCH_2$), 3·59 (t, J = 5·0 Hz, 2 H, CH_2O), 2·90 (bt, disappears after D_2O, 1 H, OH), 3·15 and 2·80 (ABq, J = 15·0 Hz, 2 H, $COCH_2N$), 2·52 (s, 8 H, 4 NCH_2 of piperazine), 1·60—3·00 (m, 7 H, remaining CH and CH_2).

XIV 50; *Trichophyton mentagrophytes*, *II* 25, *IX* 50, *X* 50, *XIV* 12·5, *XV* 50, *XVI* 12·5, *XX* 50; *Candida albicans*, *XIV* 50.

EXPERIMENTAL

The melting points of analytical preparations were determined on Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (in $CDCl_3$) with a Tesla BS 487C (80 MHz) spectrometer, ^{19}F-NMR spectra (in $CHCl_3$, $\delta_{CFCl_3} = 0$) with the same instrument, and the mass spectra with the MCH-1320 or Varian MAT 311 spectrometers. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol). The column chromatography was carried out on neutral Al_2O_3 (activity II).

[i] UV spectrum: λ_{max} 249 nm (infl.) (log ε 3·90); IR spectrum: 756, 822 (Ar—H), 1253, 1729 (ArCOOR), 1 500, 1 514, 1 592, 1607, 3 045, 3 092 (Ar), 2 300, 2 330, 2466 cm^{-1} (NH^+). [j] UV spectrum: λ_{max} 225 nm (infl.) (log ε 4·11), 267 nm (3·38), 270·5 nm (3·40), 276·5 nm (3·34); IR spectrum: 833, 845, 866, 889 (2 adjacent and solitary Ar—H), 1 200, 1 229 (Ar—F), 1 498, 1 503, 1 513, 1528, 1540, 1602, 3015, 3040 (Ar), 1610 cm^{-1} (C=N); ^{1}H-NMR spectrum: δ 6·80—7·20 (m, 7 H, Ar—H), 3·85 (bs, 1 H, Ar_2CH), 2·40—3·40 (m, 6 H, 3 CH_2), 1·23 (t, J = 7·0 Hz, CH_3). [k] UV spectrum: λ_{max} 267 nm (infl.) (log ε 3·35), 270·5 nm (3·37), 276·5 nm (3·32); IR spectrum: 802, 839 860, 885, 895, 905 (2 adjacent and solitary Ar—H), 1 090, 1 197, 1 232 (CH_3OR), 1 500, 1 514, 1540, 1 600, 3035, 3065 (Ar), 1614 cm^{-1} (C=N); ^{1}H-NMR spectrum: δ 7·48 (mcd, J_{H-F} = = 9·0 Hz, J_{H-H} = 2·0 Hz, 1 H, 10-H), 6·80—7·30 (m, 6 H, remaining Ar— H), 4·66 and 4·41 (ABq, J = 13·0 Hz, 2 H, CH_2O), 3·80 (bt, 1 H, Ar_2CH), 3·45 (s, 3 H, OCH_3), 2·40—3·40 (m, 4 H, CH_2CH_2 in the ring). [l] UV spectrum: λ_{max} 225 nm (infl.) (log ε 4·10), 266 nm (infl). (3·38), 271 nm (3·42), 277 nm (3·35); IR spectrum: 790, 830, 840, 860, 880, 889, 896 (2 adjacent and solitary Ar—H), 1 190, 1 232 (Ar—F), 1 486, 1 500, 1 512, 1 543, 1 600, 3 030, 3 060 (Ar), 1 613 cm^{-1} (C—N); ^{1}H-NMR spectrum: δ 7·45 (mcd, J_{H-F} = 9·0 Hz, J_{H-H} = 2·0 Hz, 1 H, 10-H), 6·70 to 7·20 (m, 6 H, remaining Ar—H), 3·80 (m, 3 H, Ar_2CH and CH_2S), 2·40—3·50 (m, 7 H, SCH_3 and CH_2CH_2 in the ring). [m] UV spectrum: λ_{max} 250 nm (infl.) (log ε 4·04), infl. 276 nm (3·64); IR spectrum: 698, 760, 836, 859, 866, 893 (5 and 2 adjacent and solitary Ar—H), 1192, 1220, 1 237 (Ar—F), 1 480, 1 500, 1 513, 1 540, 1 600, 3 020, 3 055 (Ar), 1612 cm^{-1} (C=N); ^{1}H-NMR spectrum: δ 7·35 (s, 5 H, C_6H_5), 6·80—7·30 (m, 6 H, 7,8-H_2 and 4 Ar H of *p*-phenylene), 6·51 (mcd, J_{H-F} = 9·0 Hz, J_{H-H} = 2·0 Hz, 1 H, 10-H), 4·18 (bt, 1 H, Ar_2CH), 2·40—3·40 (m, 4 H, CH_2CH_2 in the ring). [n] N,N'-Bis(phenylacetyl)hydrazine, m.p. 235—237°C (ethanol), was obtained as a by-product (lit.[28], m.p. 236—237°C). [o] UV spectrum: λ_{max} 225 nm (infl.) (log ε 4·08), 266 nm (3·37), 271 nm (3·39), 277 nm (3·33); IR spectrum: 700, 725, 821, 831, 863, 889, 892 (5 and 2 adjacent and solitary Ar—H), 1 200, 1 223 (Ar—F), 1 494, 1 512, 1 540, 1 600, 3035, 3050 (Ar), 1610 cm^{-1} (C=N); ^{1}H-NMR spectrum: δ 6·60—7·30 (m, 12 H, Ar—H), 4·40 and 4·12 (ABq, J = 16·0 Hz, 2 H, $ArCH_2$), 2·30—3·60 (m, 5 H, $Ar_2CHCH_2CH_2$). [p] Mass spectrum, *m/e*: 374 (M^+, $C_{22}H_{16}F_2N_4$), 252, 241, 201; UV spectrum: λ_{max} 240 nm (infl.) (log ε 4·01), infl. 270 nm (3·88), infl. 277 nm (3·78); IR spectrum: 699, 719, 775 (3 adjacent Ar—H in the pyridine nucleus), 820, 860, 881, 898 (2 adjacent and solitary Ar—H), 1498, 1512, 1540, 1573, 1 600, 3010, 3040, 3060 (Ar), 1615 cm^{-1} (C=N); ^{1}H-NMR spectrum: δ 8·59 (mcs, J = = 5·0; 2·0 Hz, 1 H, 6-H of pyridine), 8·48 (bs, 1 H, 2-H of pyridine), 6·80—7·20 (m, 8 H, 4,5-H_2 of pyridine, 7,8-H_2 of the tricycle and 4 H of *p*-phenylene), 7·29 (s, 6 H of benzene), 6·50 (bd, 1 H, 10-H), 4·15 (bt, 1 H, Ar_2CH), 2·40—3·40 (m, 4 H, CH_2CH_2 in the tricycle).

8-Fluoro-5-(4-fluorophenyl)-1,3,4,5-tetrahydro-1-benzazepin-2-one (*I*)

7-Fluoro-4-(4-fluorophenyl)-1-tetralone oxine[10] (355 g) was processed by treatment with polyphosphoric acid[10] and gave 332 g (94%) crude product, m.p. 175—180°C. Crystallization from ethanol gave 240 g (68%) pure compound *I*, m.p. 189—191°C (lit.[10], m.p. 191—192°C).

TABLE II

Survey of Compounds Which Were Pharmacologically Tested; Acute Toxicities, Administration, Doses (in mg/kg)

Compound	Code number	Administration	LD_{50}	D	Effects of >D
II	VÚFB-14.044	oral	>2 500	300	—
VII[a]	VÚFB-14.063	oral	400	80	[b]
VIII[a]	VÚFB-14.126	oral	400	80	[c]
IX[d]	VÚFB-14.043	*i.v.*	60	12	[e]
X[f]	VÚFB-14.129	*i.v.*	40	8	[g]
XI[h]	VÚFB-14.041	oral	1 000	200	[g]
XII[i]	VÚFB-14.127	*i.v.*	100	20	[j]
XIII[h]	VÚFB-14.128	*i.v.*	50	10	[k]
XIV[h]	VÚFB-14.042	oral	335	50	[l]
XV[h]	VÚFB-14.130	*i.v.*	50	10	[m]
XVI[h]	VÚFB-14.132	*i.v.*	62	12	[n]
XVII[h]	VÚFB-14.131	oral	>2 500	300	[o]
XVIII	VÚFB-14.034	oral	754	50	[p]
XIX	VÚFB-14.035	oral	1000	200	[q]
XX	VÚFB-14.040	oral	710	50	[r]
XXI	VÚFB-14.039	oral	>2 500	300	—
XXII	VÚFB-14.037	oral	>2 500	300	—
XXIII	VÚFB-14.036	oral	>2 500	300	—
XXIV[s]	VÚFB-14.038	oral	>1 000	50	[o]

[a] Oxalate. [b] Lower doses increase significantly the activity, less significantly the reactivity, elicit ataxia, tremor and Straub phenomenon; higher doses bring about hypothermia. [c] Lower doses increase the activity in the interval of 5 h; higher doses reduce activity and reactivity and lower the body temperature. [d] Hydrochloride. [e] Central excitation with higher activity and reactivity followed by ataxia and convulsions. [f] Sesquihydrochloride hemihydrate. [g] Mild inhibition of activity, ataxia and convulsions. [h] Dihydrochloride. [i] Dihydrochloride hemihydrate. [j] Increase of activity of short duration followed by convulsions. [k] In higher doses ataxia and convulsions. [l] After a dose of 200 mg/kg central depression and convulsive phenomena. [m] Excitation of short duration followed by mild inhibition of activity; after higher doses ataxia, tremor and Straub phenomenon. [n] Excitation followed by central depression, ataxia, tremor, convulsions and Straub phenomenon. [o] Mild central depression. [p] Toxic symptoms starting from a dose of 200 mg/kg; ataxia, restlessness, tremor, convulsions. [q] Ataxia, tremor, convulsions. [r] Central depression. [s] Solvate with benzene.

7-Fluoro-4-(4-fluorophenyl)-1-naphthylamine (*III*)

The ethanolic mother liquors after the crystallization of *I* were evaporated *in vacuo* and the solid residue was extracted with 350 ml boiling benzene. The insoluble fraction was filtered, washed with benzene and dried; 19·4 g (4%) phosphate of *III*, m.p. 182—185°C. Analytical sample, m.p. 182—183°C (ethanol). For $C_{16}H_{14}F_2NO_4P$ (353·3) calculated: 54·39% C, 4·00% H, 3·96% N; found: 54·21% C, 4·09% H, 3·81% N.

Decomposition of the phosphate with dilute NH_4OH and extraction with benzene gave the base *III*, m.p. 118—119°C (cyclohexane). The compound displays yellow coloration by a reaction with 4-dimethylaminobenzaldehyde. Mass spectrum, *m/e*: 255 (M^+ corresponding to $C_{16}H_{11}F_2N$), 127·5 (2 charges). UV spectrum: λ_{max} 261 nm (log ε 4·62), 330 nm (3·80). IR spectrum: 838 (2 adjacent Ar—H), 1 515, 1 577, 1 600, 1 610 (Ar), 1 633 cm^{-1} ($ArNH_2$). ^{1}H-NMR spectrum: δ 6·80—7·90 (m, 9 H, Ar—H), 4·02 (s, disappears after D_2O, 2 H, NH_2). For $C_{16}H_{11}F_2N$ (255·3) calculated: 75·28% C, 4·34% H, 14·89% F, 5·49% N; found: 75·45% C, 4·55% H, 14·70% F, 5·38% N.

N-[7-Fluoro-4-(4-fluorophenyl)-1-naphthyl]diacetamide (*IV*)

A mixture of 0·60 g *III* and 3·5 ml acetic anhydride was refluxed for 20 min, cooled and poured into 50 ml water. It was neutralized with K_2CO_3 and the mixture allowed to stand overnight. The solid was filtered and crystallized from 15 ml 75% aqueous ethanol, m.p. 172—173°C. Mass spectrum, *m/e* (%): 339 (M^+ corresponding to $C_{20}H_{15}F_2NO_2$, 18), 297 (50, M — CH_2=C=O), 281 (5), 255 (100, M — 2 CH_2=C=O), 238 (7), 43 (45, CH_3CO^+). For $C_{20}H_{15}F_2NO_2$ (339·3) calculated: 70·80% C, 4·46% H, 11·19% F, 4·12% N; found: 70·77% C, 4·45% H, 11·19% F, 4·14% N.

8-Fluoro-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (*V*)

I (32·5 g) was reduced by refluxing with 7·0 g $LiAlH_4$ in a mixture of 200 ml ether and 50 ml benzene for 8 h. Processing the mixture according to ref.[10] recovered 6·3 g starting *I* and gave 20·5 g (83% per conversion) oily *V* (ref.[10]), which is chromatographically homogeneous and was used for further work without purification.

1-(Chloroacetyl)-8-fluoro-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (*VI*)

A mixture of 20·0 g *V*, 14·0 g K_2CO_3 and 50 ml chloroform was stirred and treated dropwise with a solution of 12·0 g chloroacetyl chloride in 50 ml chloroform over 20 min. The mixture was refluxed for 1 h, allowed to stand overnight at room temperature, decomposed with 120 ml water and stirred for 20 min. The organic layer was then separated, dried with Na_2SO_4 and evaporated *in vacuo*. The remaining oil crystallized after mixing with 100 ml hexane; 21·0 g (79%), m.p. 130—132°C. Analytical sample, m.p. 133—134°C (benzene–hexane). UV spectrum: λ_{max} 266·5 nm (log ε 3·36), 272 nm (3·33). IR spectrum: 787, 795, 839, 889 (2 adjacent and solitary Ar—H), 1496, 1512, 1595, 1610, 3015, 3034 (Ar), 1678 cm^{-1} (Ar—N—COR). ^{1}H-NMR spectrum: δ 6·40—7·30 (m, 7 H, Ar—H), 4·10—4·80 (m, 2 H, $CONCH_2$), 3·99 (s, 2 H, $COCH_2Cl$), 1·50—3·00 (m, 5 H, $Ar_2CHCH_2CH_2$). For $C_{18}H_{16}ClF_2NO$ (335·8) calculated: 64·38% C, 4·80% H, 10·56% Cl, 4·17% N; found: 65·00% C, 4·74% H, 10·15% Cl, 4·58% N.

8-Fluoro-5-(4-fluorophenyl)-1-(4-methylpiperazinoacetyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (*XI*) (Method *A*)

A mixture of 10·1 g *VI*, 7·5 g 1-methylpiperazine and 70 ml benzene was refluxed for 9 h and allowed to stand overnight at room temperature. The suspension was decomposed with dilute NH_4OH and extracted with benzene. The extract was washed with water, dried and evaporated; 11·0 g (92%) base *XI* which crystallized on standing, m.p. 163—165°C, Analytical sample, m.p. 164—165°C (ethanol). UV spectrum: λ_{max} 266·8 nm (log ε 3·33), 272 nm (3·30). IR spectrum: 792, 818, 825, 836, 850, 900 (2 adjacent and solitary Ar—H), 1495, 1517, 1592, 1605, 2980, 3000, 3020 (Ar), 1682 cm^{-1} (ArNCOR). ^{1}H-NMR spectrum: δ 6·30—7·30 (m, 7 H, Ar—H), 4·68 and 4·05 (2 m, 2 H, CO—N—CH_2), 3·12 and 2·78 (ABq, J = 14·0 Hz, 2 H, $COCH_2N$), 2·48 (s, 8 H, 4 NCH_2 of piperazine), 2·20 (s, 3 H, NCH_3), 1·70—3·00 (m, 5 H, $Ar_2CHCH_2CH_2$). Dihydrochloride, m.p. 244—245°C (aqueous ethanol). Analyses in Table I.

8-Fluoro-5-(4-fluorophenyl)-1-(2-pyrrolidinoethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (*X*) (Method *B*)

A solution of 5·0 g *VIII* in 70 ml benzene was dropped into a stirred suspension of 2·5 g $LiAlH_4$ in 70 ml ether and the mixture was refluxed for 7 h. After cooling, it was decomposed with 10 ml 20% NaOH, stirred for 30 min, the solid filtered off, washed with benzene and the filtrate evaporated; 4·9 g (100%) oil. Neutralization with anhydrous HCl in a mixture of ethanol and ether gave the sesquihydrochloride crystallizing with 0·5 H_2O, m.p. 195—196°C (ethanol–ether). Oxalate, m.p. 199—200°C (ethanol–ether). Analyses in Table I. A sample of the hydrochloride was decomposed with NH_4OH and the purified base isolated by extraction with ether, oil. ^{1}H-NMR spectrum: δ 6·30—7·30 (m, 7 H, Ar—H), 4·30 (m, 1 H, Ar_2CH), 3·28 and 2·73 (2 t, J = = 7·0 Hz, 4 H, $ArNCH_2CH_2N$), 2·40—3·60 (m, 6 H, 3 NCH_2 in the rings), 1·50—2·20 (m, 8 H, remaining 4 CH_2).

8-Fluoro-5-(4-fluorophenyl)-1-(2-[4-(2-propionoxyethyl)piperazino]ethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (*XVI*) (Method *C*)

A mixture of 5·0 g *XV*, 2·0 g K_2CO_3 and 20 ml chloroform was stirred and treated dropwise with a solution of 1·52 g propionyl chloride in 15 ml chloroform over 30 min. The mixture was refluxed for 1 h, cooled, decomposed with 50 ml water and extracted with chloroform. The extract was washed with 10% Na_2CO_3 and water, dried (Na_2SO_4) and evaporated; 5·67 g (100%) oily *XVI*. Dihydrochloride, m.p. 191—192°C (95% ethanol–ether). UV spectrum: λ_{max} 253 nm (log ε 4·15). IR spectrum: 810, 836, 878 (2 adjacent and solitary Ar—H), 1190, 1740 (RCOOR'), 1500, 1517, 1593, 1610 (Ar), 2290, 2380 cm^{-1} (NH^+). Analysis in Table I.

8-Fluoro-5-(4-fluorophenyl)-1,3,4,5-tetrahydro-1-benzazepin-2-thione (*II*)

A mixture of 17·9 g *I*, 16·0 g P_2S_5 and 130 ml pyridine was refluxed for 45 min under nitrogen and poured into a solution of 215 g NaCl in 720 ml water at 4°C. The product was extracted with chloroform and the extract evaporated *in vacuo*. The residue (19·7 g oil) was dissolved in benzene and chromatographed on a column of 500 g Al_2O_3. Elution with benzene gave 7·3 g (39%) crude product, m.p. 154—156°C. Analytical sample, m.p. 166—167°C (ethanol). UV spectrum: λ_{max} 303 nm (log ε 4·38). IR spectrum (KBr): 830, 835, 870 (2 adjacent and solitary Ar—H), 1490, 1515 (CSNH), 1590, 1610 (Ar), 3140 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 10·62 (bs, 1 H, CSNH), 6·50—7·40 (m, 7 H, Ar—H), 4·25 (m, 1 H, Ar_2CH), 2·30—3·20 (m, 4 H,

remaining 2 CH_2). ^{19}F-NMR spectrum: δ —114·6 (dt, 1 F, 8-F). —115·7 (m, 1 F, 4-fluorophenyl). For $C_{16}H_{13}F_2NS$ (289·3) calculated: 66·42% C, 4·53% H, 13·13% F, 4·84% N, 11·08% S; found: 66·19% C, 4·56% H, 12·94% F, 4·76% N, 11·31% S.

9-Fluoro-6-(4-fluorophenyl)-1-methyl-5,6-dihydro-4*H*-s-triazolo[4,3-*a*]-1-benzazepine (*XVIII*) (Method *D*)

A solution of 6·0 g *II* and 5·0 g acethydrazide[19] in 120 ml 1-butanol was refluxed for 34 h under nitrogen. It was then filtered with charcoal, the filtrate evaporated *in vacuo*, the residue suspended in 100 ml water, the solid filtered, washed with water and dried *in vacuo*. Extraction with 30 ml chloroform led to 0·4 g insoluble solid identified as N,N'-diacetylhydrazine, m.p. 138—139°C (ethanol–hexane) (lit.[27], m.p. 138°C). The chloroform solution was evaporated and the residue was chromatographed on a column of 250 g Al_2O_3. Elution with benzene removed the less polar impurities (mainly the starting *II*) and elution with chloroform gave 4·5 g (70%) crude *XVIII*, m.p. 216—217°C. Analytical sample, m.p. 216—217°C (benzene–hexane). Mass spectrum, *m/e*: 311 (M^+ corresponding to $C_{18}H_{15}F_2N_3$, base peak), 296 (M — CH_3), 293 (M — 28), 255 (M — 56), 241 (M — 70), 216, 202, 201. UV spectrum: λ_{max} 225 nm (infl.) (log ε 4·08), 270 nm (3·36), 276 nm (3·31). IR spectrum: 795, 820, 843, 890 (2 adjacent and solitary Ar—H), 1491, 1500, 1510, 1585, 1595, 3030, 3050 (Ar), 1600 cm^{-1} (C=N). ^{1}H-NMR spectrum: δ 6·80—7·30 (m, 7 H, Ar—H), 3·85 (m, 1 H, Ar_2CH), 2·20—3·40 (m, 4 H, CH_2CH_2 in the ring), 2·48 (s, 3 H, CH_3). ^{19}F-NMR spectrum: δ —114·2 (dt, 1 F, 9-F), —115·7 (m, 1 F, 4-fluorophenyl). Analysis in Table I.

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REFERENCES

1. Sternbach L. H., Randall L. O., Gustafson S. R. in the book: *Medicinal Chemistry*. 4. *Psychopharmacological Agents* (M. Gordon, Ed.), Vol. 1, p. 137. Academic Press, New York and London 1964.
2. Randall L. O., Schallek W., Sternbach L. G., Ning R. Y. in the book: *Medicinal Chemistry*. 4. *Psychopharmacological Agents* (M. Gordon, Ed.), Vol. 3, p. 175. Academic Press, New York 1974.
3. Societa Farmaceutici Italia: Brit. 1 359 285 (Ital. Appl. 03.02.72); Chem. Abstr. *81*, 152 031 (1974).
4. Huet J., Sado-Odeye M., Martin N., Guibet P., Linee P., Lacroix P., Quiniou P., Laurent J.: Eur. J. Med. Chem.-Chim. Therap. *9*, 376 (1974).
5. Rodriguez H. R. (Ciba-Geigy Corp.): U.S. 3 949 081 (Appl. 08.04.74); Chem. Abstr. *85*, 46 440 (1976).
6. Rodriguez H. R. (Ciba-Geigy Corp.): U.S. 3 989 689 (Appl. 08.04.74); Chem. Abstr. *86*, 89 641 (1977).
7. Sawa Y., Kato T., Masuda T., Hori M., Fujimura H.: Chem. Pharm. Bull. *23*, 1917 (1975).
8. Kukla M. J.: J. Heterocycl. Chem. *14*, 933 (1977).

9. Vogel A., Troxler F., Lindenmann A.: Helv. Chim. Acta *52*, 1929 (1969).
10. Rajšner M., Kopicová Z., Holubek J., Svátek E., Metyš J., Bartošová M., Mikšík F., Protiva M.: This Journal *43*, 1760 (1978).
11. Semmler W.: Ber. Deut. Chem. Ges. *25*, 3352 (1892).
12. Wolff L.: Justus Liebigs Ann. Chem. *322*, 351 (1902).
13. Schroeter G.: Ber. Deut. Chem. Ges. *63*, 1308 (1930).
14. Hardy A., Ward E. R., Day L. A.: J. Chem. Soc. *1956*, 1979.
15. Adcock W., Dewar M. J. S.: J. Amer. Chem. Soc. *89*, 386 (1967).
16. Newman M. S., Hung W. M.: J. Org. Chem. *38*, 4073 (1973).
17. Langenbeck W., Weissenborn K.: Ber. Deut. Chem. Ges. *72*, 724 (1939); Chem. Zentralbl. *1939*, I, 4973.
18. Beringer F. M., Chang L. L., Fenster A. N., Rossi R. R.: Tetrahedron *25*, 4339 (1969).
19. Curtius T., Hofmann T. S.: J. Prakt. Chem. [2] *53*, 524 (1896).
20. Curtius T.: J. Prakt. Chem. [2] *64*, 404 (1901).
21. Browne E. J., Polya J. B.: J. Chem. Soc. *1962*, 5149.
22. Rose F. L., Wilson B. R. (Imperial Chemical Industries Ltd.): Brit. 782 420 (04.09.57); Chem. Abstr. *52*, 2907 (1958).
23. Curtius T.: J. Prakt. Chem. [2] *50*, 278 (1894).
24. Curtius T., Boetzelen E.: J. Prakt. Chem. [2] *64*, 314 (1901).
25. Curtius T., Mohr E.: Ber. Deut. Chem. Ges. *31*, 2493 (1898).
26. Hester J. B. jr, Rudzik A. D., Kamdar B. V.: J. Med. Chem. *14*, 1078 (1971).
27. Stollé R.: Ber. Deut. Chem. Ges. *32*, 796 (1899).
28. Klein G., Fuchs W.: Biochem. Z. *213*, 40 (1929).

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