ANTIDEPRESSANT FLUORINATED PROTHIADENE DERIVATIVES: 9-FLUORO AND 2,9-DIFLUORO DERIVATIVE OF 11-(3-DIMETHYLAMINOPROPYLIDENE)--6,11-DIHYDRODIBENZO[*b*,*e*]THIEPIN*

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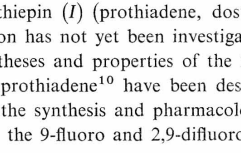
6-Fluorophthalide (*IV*), obtained from 6-aminophthalide by the Schiemann method, was transformed by reactions with potassium salts of thiophenol and 4-fluorothiophenol to the acids *V* and *VI*. Cyclization with polyphosphoric acid gave 9-fluoro- and 2,9-difluorodibenzo[*b*,*e*]thiepin--11(6*H*)-one (*VII*, *VIII*) which were treated with 3-dimethylaminopropylmagnesium chloride and afforded the tertiary alcohols *IX* and *X*. Dehydration by heating with dilute hydrochloric acid resulted in the title compounds *II* and *III* whose IR spectra indicated the *E*-configuration. Both compounds showed properties of tricyclic antidepressants being, however, less active than prothiadene (*I*) in the tests for the antireserpine activity.

It has been established that in the series of tricyclic neuroleptics the fluorination in some positions of the aromatic nuclei is connected with prolongation of the action and leads to deriving long-acting compounds which are suitable for oral use[1,2]. In the series of analogues of the antidepressant 11-(3-dimethylaminopropylidene)--6,11-dihydrodibenzo[*b*,*e*]thiepin (*I*) (prothiadene, dosulepin, dothiepin) (ref.[3–6]), the influence of fluorination has not yet been investigated systematically from this point of view though syntheses and properties of the 2-fluoro derivative[3,6–9] and 3,8-difluoro derivative of prothiadene[10] have been described. In the present communication we report on the synthesis and pharmacological properties of the title compound *II* and *III*, *i.e.* the 9-fluoro and 2,9-difluoro derivatives of prothiadene.



I, $R^1 = R^2 = H$
II, $R^1 = F$, $R^2 = H$
III, $R^1 = R^2 = F$

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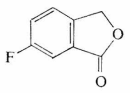
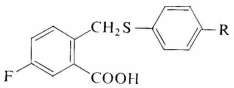
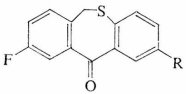
6-Aminophthalide[7,11] was converted by diazotization and treatment with fluoroboric acid to the diazonium fluoroborate which was processed by the Schiemann reaction[12], *i.e.* by the thermic decomposition to 6-fluorophthalide (*IV*) which was obtained in a rather poor yield. Its heating with thiophenol or 4-fluorothiophenol[13] in the presence of potassium carbonate to 120°C gave the acids *V* and *VI*. This modified procedure proved more suitable than the usual reaction of the phthalide *IV* with the sodium salt of the corresponding thiophenol, used in many cases heterofore[7]. The acids *V* and *VI* were cyclized by heating with polyphosphoric acid to 120–130°C; the ketones *VII* and *VIII* resulted in satisfactory yields and were



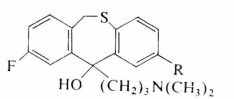
IV



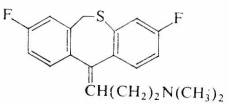
V, R = H
VI, R = F



VII, R = H
VIII, R = F



IX, R = H
X, R = F



XI

characterized by spectra. The following reactions with 3-dimethylaminopropylmagnesium chloride were carried out in tetrahydrofuran[14] and gave the tertiary alcohols *IX* and *X*. The final step of the syntheses was the acid-catalyzed dehydration, effected by heating with dilute hydrochloric acid. The olefinic bases (*II* and *III*) obtained were oily in the crude state and represented evidently mixtures of geometric isomers. One of the isomers predominated which enabled in both cases the preparation of crystalline maleates. In the case of compound *III*, a homogeneous and crystal-

line base was separated; the base *II* could not be obtained in crystalline state. The IR spectra of both bases were recorded in carbon disulfide and the area of out-of-plane vibrations of C—H bonds of aromatic nuclei was used for the assignment of configuration. We started here from the findings made with the geometric isomers of prothiadene (*I*) (ref.[5]) (*E*-configuration of the predominating isomer, assigned here on the basis of the IR spectrum, was confirmed in the meantime by the X-ray crystallographic study[15]) and its 2-methyl derivative[16]. For compound *II* with the unsubstituted ring A, the considered diagnostic symptom is the absence of a satellite band at 743–744 cm^{-1} which is typical for *Z*-prothiadene (*Z*–*I*) (ref.[5]). For this reason, *E*-configuration was assigned to compound *II*. For compound *III* the band at 879 cm^{-1} was considered crucial, which is attributed to the solitary C—H bond in the ring A. On the basis of a comparison with corresponding bands in the spectra of the *E*-isomer of the 2-methyl derivative of prothiadene (873 cm^{-1}) and the corresponding *Z*-isomer (894 cm^{-1}) (ref.[16]), the *E*-configuration was assigned also to compound *III*. These configuration assignments have to be considered tentative.

Compounds *II* and *III* were pharmacologically investigated and compared with prothiadene (*I*) (ref.[6]) and its 3,8-difluoro derivative (*XI*) (ref.[10]). The compounds were administered in the form of salts but the doses given were calculated for bases.

Compound II: Intravenous toxicity in mice, LD_{50} = 31·2 mg/kg. Rotarod test in mice, ED_{50} = = 7·2 mg/kg *i.v.* An intravenous dose of 6 mg/kg potentiated the thiopental effect in mice (prolongation of the thiopental sleeping time to 220% in comparison with 100% of the control group). An *i.p.* dose of 40 mg/kg antagonized significantly the reserpine ptosis in mice. An oral dose of 100 mg/kg antagonized significantly the ulcerogenic effect of reserpine in rats (simultaneous administration with reserpine); the effect of a dose of 50 mg/kg was statistically insignificant. An oral dose of 100 mg/kg did not antagonize the cataleptic action of perphenazine (administered 1 h or 24 h before perphenazine). A dose of 10 mg/kg *s.c.* did not influence the tremor in mice elicited with arecoline (20 mg/kg *s.c.*). The antinociceptive action of oxotremorine (0·15 mg/kg *s.c.*) in mice was antagonized with a dose of 10 mg/kg *s.c.* only in 20% animals.

Compound III: LD_{50} = 42·8 mg/kg *i.v.*; toxic doses brought about central depression and convulsions. Rotarod test in mice, ED_{50} = 30 mg/kg *i.v.* (maximum in 5 min after the administration). Thiopental potentiation, a dose of 8·5 mg/kg *i.v.* prolonged the thiopental sleeping time to 250%. Reserpine ptosis in mice was antagonized significantly by a dose of 40 mg/kg *i.p.* An oral dose of 50 mg/kg antagonized significantly the ulcerogenic effect of reserpine in rats (administered simultaneously with reserpine). An oral dose of 100 mg/kg antagonized the cataleptic effect of perphenazine in rats (administered 24 h before perphenazine). This anticataleptic effect is not related to a trihexyphenidyl-like anticholinergic-antiparkinsonic action. The nature and importance of the anticataleptic action of prothiadene has been investigated more thoroughly[17–19].

Compound XI (*cf.*[10]): LD_{50} = 39·4 mg/kg *i.v.* Rotarod test in mice, ED_{50} = 30 mg/kg *i.v.* (maximum activity in 10 min after the administration). Thiopental potentiation, a dose of 8 mg/kg *i.v.* prolonged the thiopental sleeping time to 220%. Reserpine ptosis in mice was not antagonized significantly by a dose of 40 mg/kg *i.p.* The ulcerogenic effect of reserpine in rats was not influenced by a dose of 50 mg/kg orally (administered simultaneously with reserpine or 24 h before reserpine). A dose of 100 mg/kg orally, however, antagonized significantly the cataleptic action of perphenazine (administered either 1 h of 24 h before perphenazine). Doses of 10 mg/kg *s.c.*

did influence neither the arecoline (20 mg/kg *s.c.*) tremor in mice nor the antinociceptive action of oxotremorine (0·15 mg/kg *s.c.*) in mice.

In conclusion, compounds *II*, *III* and *XI* have in general the character of tricyclic antidepressants with antireserpine and anticataleptic activities lower than those of prothiadene (*I*). Neither the central depressant nor the antireserpine effects did show reliable prolongation in time.

Compounds *II* and *III* were also tested for antimicrobial activity *in vitro* (Dr J. Turinová, bacteriological department of this institute); microorganisms and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus* β-*haemolyticus*, *III* 100; *Streptococcus faecalis*, *III* 100; *Staphylococcus pyogenes aureus*, *III* 50; *Pseudomonas aeruginosa*, *III* 100; *Proteus vulgaris*, *III* 100; *Mycobacterium tuberculosis* H37Rv, *II* 50, *III* 25; *Saccharomyces pasterianus*, *II* 50, *III* 100; *Trichophyton mentagrophytes*, *II* 50, *III* 50; *Candida albicans*, *II* 100, *III* 100; *Aspergillus niger*, *II* 100, *III* 100.

EXPERIMENTAL

The melting points of analytical preparations were determined in the Kofler's block and are not corrected; the samples were dried *in vacuo* of about 70 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 (KBr) with a Unicam SP 200G spectrophotometer and most of the ^{1}H-NMR spectra (in C^2HCl_3) with a ZKR 60 (Zeiss, Jena) spectrometer. The homogeneity of the compounds was checked by thin layer chromatography on silica gel.

6-Fluorophthalide (*IV*)

A mixture of 61·4 g 6-aminophthalide[7,11], 90 ml hydrochloric acid and 40 ml water was cooled to 0°C and diazotized under stirring with a solution of 31·0 g $NaNO_2$ in 60 ml water added dropwise over a period of 1 h. After further 30 min stirring at 0°C, a solution of fluoroboric acid (prepared from 111 g 40% H_2F_2 and 34 g H_3BO_3) was added under continual cooling. After 15 min of stirring and 30 min of standing at room temperature, the precipitated diazonium fluoroborate was filtered, washed with water, ethanol and ether, and dried *in vacuo* over P_2O_5. The product obtained (84·6 g) was divided into three parts and decomposed by heating using a direct flame (under reflux); the decomposition was considered complete when the gas formation ceased. The residues were extracted with boiling chloroform, the extracts were combined, filtered with charcoal and evaporated. The residue was chromatographed on a column of 550 g neutral Al_2O_3 (activity II). Benzene eluted some less polar impurities and elution with chloroform gave 10·9 g (18%) product, m.p. 106—108°C (benzene). IR spectrum: 835, 885 (2 adjacent and solitary Ar—H), 1 053 (C—O), 1 250 (Ar—F), 1 500, 1 612, 1 630 (Ar), 1 765 cm^{-1} (ArCOO of the lactone). ^{1}H-NMR spectrum: δ 7·30—7·80 (m, 3 H, Ar—H), 5·48 and 5·25 (2 d, J = 12·0 Hz, 2 H, $ArCH_2O$). For $C_8H_5FO_2$ (152·1) calculated: 63·16% C, 3·31% H; found: 63·36% C, 3·44% H.

5-Fluoro-2-(phenylthiomethyl)benzoic Acid (*V*)

A stirred mixture of 6·5 g *IV* and 5·2 g thiophenol was heated to 120°C and slowly treated with 6·0 g K_2CO_3. The solidified mixture was heated for 30 min to 120°C, cooled, dissolved in 250 ml warm water, the solution was filtered and the filtrate acidified with hydrochloric acid. The pre-

cipitated product was filtered after standing overnight, washed with water and dried *in vacuo*; 9·7 g (87%), m.p. 90–93°C. Analytical sample, m.p. 91–93°C (benzene–light petroleum). For $C_{14}H_{11}FO_2S$ (262·3) calculated: 64·10% C, 4·23% H, 7·24% F, 12·23% S; found: 64·15% C, 4·28 H, 7·16% F, 12·18% S.

5-Fluoro-2-(4-fluorophenylthiomethyl)benzoic Acid (*VI*)

A mixture of 5·1 g *IV*, 4·3 g 4-fluorothiophenol[13] and 4·6 g K_2CO_3 was slowly heated to 120°C and kept for 40 min at this temperature. Processing like in the preceding case gave 7·8 g (83%) crude product, m.p. 116–118°C. Analytical sample, m.p. 119–120°C (benzene–light petroleum). IR spectrum: 845, 885 (2 adjacent and solitary Ar—H), 925, 2 565, 2 585, 2 680 (COOH), 1 225 (Ar—F), 1 495, 1 590 (Ar), 1 690 cm^{-1} (ArCOOH). For $C_{14}H_{10}F_2O_2S$ (280·3) calculated: 59·99% C, 3·60% H, 13·56% F, 11·43% S; found: 60·06% C, 3·70% H, 13·33% F, 11·50% S.

9-Fluorodibenzo[*b*,*e*]thiepin-11(6*H*)-one (*VII*)

Polyphosphoric acid was prepared from 50 g P_2O_5 and 30 ml 85% H_3PO_4 and heated to 120 to 130°C. Under stirring, 9·7 g *V* were added and the mixture was heated for 1 h to 130°C. After partial cooling it was decomposed with ice and water, the product extracted with chloroform, the extract was washed with 5% NaOH, dried with K_2CO_3, filtered with charcoal and evaporated; 8·8 g (90%) crude product, m.p. 89–92°C. Analytical sample, m.p. 92–93°C (ethanol). UV spectrum: λ_{max} 240·5 nm (log ε 4·32), infl. 264·5 nm (4·00), 354 nm (3·58). IR spectrum: 731, 800, 852, 860, 888 (4 and 2 adjacent and solitary Ar—H), 1 291 (CO), 1 487, 1 585 (Ar), 1 650 cm^{-1} (ArCOAr). ^{1}H-NMR spectrum (Tesla BS 487C, 80 MHz): δ 8·15 (m, 1 H, 1-H), 7·00–7·40 (m, 6 H, remaining Ar—H), 3·97 (s, 2 H, $ArCH_2S$). ^{19}F-NMR spectrum (in $CHCl_3$, $\delta_{CFCl_3} = 0$): δ −114·8 (m). For $C_{14}H_9FOS$ (244·3) calculated: 68·83% C, 3·71% H, 7·78% F, 13·13% S; found: 68·73% C, 3·87% H, 7·58% F, 13·12% S.

2,9-Difluorodibenzo[*b*,*e*]thiepin-11(6*H*)-one (*VIII*)

Cyclization of 7·8 g *VI* with polyphosphoric acid (from 60 g P_2O_5 and 40 ml 85% H_3PO_4) by heating for 1·5 h to 120°C was carried out similarly like in the preceding case; processing gave 7·1 g (97%) crude product, m.p. 111–113°C. Analytical sample, m.p. 116–118°C (ethanol). UV spectrum: λ_{max} 239 nm (log ε 4·28), infl. 263·5 nm (3·96), 359 nm (3·61). IR spectrum: 840, 899 (2 adjacent and solitary Ar—H), 1 270 (Ar—F), 1 600 (Ar), 1 645 cm^{-1} (ArCOAr). ^{1}H-NMR spectrum: δ 6·90–8·05 (m, 6 H, Ar—H), 3·98 (s, 2 H, $ArCH_2S$). For $C_{14}H_8F_2OS$ (262·3) calculated: 64·11% C, 3·07% H, 14·49% F, 12·23% S; found: 64·34% C, 3·12% H, 14·38% F, 12·36% S.

9-Fluoro-11-(3-dimethylaminopropyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*IX*)

Grignard reagent was prepared by a reaction of 1·4 g Mg with 7·0 g 3-dimethylaminopropyl chloride in 20 ml tetrahydrofuran (the reaction was started with a small quantity of iodine and 2 drops 1,2-dibromoethane) and refluxed for 1 h. After cooling the stirred reagent was treated dropwise with a solution of 7·1 g *VII* in 15 ml tetrahydrofuran over 5 min (cooling with cold water). The mixture was stirred for 1 h at room temperature, cooled with ice and decomposed with 35 ml 20% solution of NH_4Cl. The product was extracted with chloroform, the extract was washed with water, dried with K_2CO_3 and evaporated. The residue was crystallized from 20 ml cyclohexane; 6·0 g (62%), m.p. 116–120°C. Analytical sample, m.p. 121–123°C (ethanol). IR spectrum: 752, 825, 885 (4 and 2 adjacent and solitary Ar—H), 1 122 (R_3C—OH), 1 253

(Ar—F), 1 482, 1 556, 1 583, 1 607 (Ar), 2 600 cm^{-1} (OH···N). ^{1}H-NMR spectrum (Tesla BS 487C, 80 MHz): δ 8·00 (m, 1 H, 1-H), 7·70 (q, J = 12·0 (H—F); 2·0 Hz, 1 H, 10-H), 6·70—7·20 (m, 5 H, remaining Ar—H), 4·56 and 3·75 (2 d, J = 14·0 Hz, 2 H, $ArCH_2S$), 1·30—2·50 (m, 6 H, 3 CH_2 of the side chain), 2·24 (s, 6 H, CH_3NCH_3). For $C_{19}H_{22}FNOS$ (331·5) calculated: 68·85% C, 6·69% H, 4·23% N, 9·67% S; found: 68·88% C, 6·68% H, 4·37% N, 9·38% S.

2,9-Difluoro-11-(3-dimethylaminopropyl)-6,11-dihydrodibenzo[*b,e*]thiepin-11-ol (*X*)

Similarly like in the preceding case, the Grignard reagent was prepared from 1·3 g Mg and 6·5 g 3-dimethylaminopropyl chloride in 20 ml tetrahydrofuran and was reacted with a solution of 7·0 g *VIII* in 35 ml tetrahydrofuran. Similar processing gave 6·6 g (71%) product, m.p. 112 to 114°C (cyclohexane). Analytical sample, m.p. 113—115°C (ethanol). IR spectrum: 820, 840, 900 (2 adjacent and solitary Ar—H), 1 125 (R_3C—OH), 1 268 (Ar—F), 1 495, 1 605 (Ar), 2 490 cm^{-1} (OH...N). ^{1}H-NMR spectrum: δ 6·50—8·00 (m, 6 H, Ar—H), 4·45 and 3·70 (2 d, J = = 14·0 Hz, 2 H, $ArCH_2S$), 2·12 (s, 6 H, CH_3NCH_3), 1·00—2·50 (m, 7 H, 3 CH_2 of the side chain and OH). For $C_{19}H_{21}F_2NOS$ (349·4) calculated: 65·30% C, 6·06% H, 10·87% F, 4·01% N, 9·18% S; found: 65·25% C, 5·99% H, 10·75% F, 3·78% N, 9·44% S.

9-Fluoro-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b,e*]thiepin (*III*)

A mixture of 6·0 g *IX* and 90 ml 1 : 2 dilute hydrochloric acid was refluxed for 30 min. After cooling it was diluted with water, made alkaline with NH_4OH and extracted with ether. The extract was filtered with charcoal, the filtrate dried with K_2CO_3 and evaporated. The oily mixture of bases (5·6 g) was dissolved in 24 ml ethanol and the solution was neutralized with a solution of 2·2 g maleic acid in 45 ml ether. Standing overnight afforded 6·0 g (77%) hydrogen maleate, m.p. 150—152°C (ethanol–ether). UV spectrum: infl. 226 nm (log ε 4·44), 260 nm (3·99), λ_{max} 306 nm (3·37). IR spectrum: 729, 755, 765, 824, 859, 865, 882 (4 and 2 adjacent and solitary Ar—H), 1 573,1 579, 1 610 (Ar), 1 695 (COO^-), 2 360 cm^{-1} (NH^+). ^{1}H-NMR spectrum (Tesla BS 487 C, 80 MHz, $C^2H_3SOC^2H_3$): δ 6·80—7·60 (m, 7 H, Ar—H), 6·00 (s, 2 H, CH=CH of maleic acid), 5·88 (t, J = 6·0 Hz, 1 H, C=CH), 4·75 and 3·70 (2 d, J = 14·0 Hz, 2 H, $ArCH_2S$), 3·16 (t, J = 6·0 Hz, 2 H, CH_2N), 2·68 (s, 6 H, CH_3NCH_3), 2·25 (m, 2 H, remaining CH_2 in the side chain). For $C_{23}H_{24}FNO_4S$ (429·5) calculated: 64·31% C, 5·63% H, 3·26% N; found: 64·57% C, 5·96% H, 3·24% N.

Decomposition of the pure maleate with NH_4OH and extraction with ether gave the homogeneous oily base *II* to which the *E*-configuration was assigned on the basis of the IR spectrum (CS_2): 692, 712, 730, 750, 763, 782, 820, 844, 866, 887 cm^{-1}.

2,9-Difluoro-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b,e*]thiepin (*III*)

Compound *X* (1·2 g) was dehydrated by refluxing with 20 ml 1 : 1 dilute hydrochloric acid for 30 min. Processing like in the preceding case gave 1·1 g (100%) base which crystallized from light petroleum, m.p. 62—66°C. Two recrystallizations from light petroleum gave a homogeneous base, m.p. 71—72°C, to which the *E*-configuration was assigned on the basis of the IR spectrum (CS_2): 719, 758, 764, 780, 806, 821, 866, 867, **879** cm^{-1}; in KBr: 815, 820, 838, 858, 888, 895 (2 adjacent and solitary Ar—H), 1 498, 1 574, 1 590, 1 604 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 6·60—7·50 (m, 6 H, Ar—H), 5·95 (t, 1 H, C=CH), 4·85 and 3·32 (2 d, J = 14·0 Hz, 2 H, Ar. CH_2S), *c* 2·25 (m, 4 H, 2 CH_2 of the side chain), 2·11 (s, 6 H, CH_3NCH_3). For $C_{19}H_{19}F_2NS$ (331·4) calculated: 68·85% C, 5·78% H, 11·47% F, 4·23% N, 9·67% S; found: 69·29% C, 5·84% H, 11·36% F, 4·25% N, 9·74% S.

Hydrogen maleate, m.p. 184–185°C with decomposition (aqueous ethanol). For $C_{23}H_{23}F_2NO_4S$ (447·5) calculated: 61·73% C, 5·18% H, 8·49% F, 3·13% N, 7·17% S; found: 61·94% C, 5·29% H, 8·20% F, 3·19% N, 6·90% S.

[1]H-NMR *spectra were recorded and interpreted by Dr J. Holubek (department of physical chemistry of this institute). The intermediates were prepared by Mr F. Mikšík. The analyses were carried out by Mrs J. Komancová, Mrs A. Slaviková, Mr M. Čech, Mr K. Havel and Mr J. Komínek (analytical department of this institute).*

REFERENCES

1. Protiva M.: 5th Conf. Org. Chem., Smolenice, Apr. 1976; Proc. Conf., p. 72 (Pub. 1976).
2. Protiva M.: Pharmazie *34*, 274 (1979).
3. Protiva M., Rajšner M., Seidlová V., Adlerová E., Vejdělek Z. J.: Experientia *18*, 326 (1962).
4. Rajšner M., Protiva M.: Česk. Farm. *11*, 404 (1962).
5. Rajšner M., Svátek E., Metyšová J., Protiva M.: This Journal *34*, 1963 (1969).
6. Metyšová J., Metyš J., Votava Z.: Arzneim.-Forsch. *13*, 1039 (1963).
7. Rajšner M., Seidlová V., Protiva M.: Česk. Farm. *11*, 451 (1962).
8. Protiva M., Rajšner M., Seidlová V., Vejdělek Z., Metyšová J.: Czech 107.632 (Appl. 24.03.62) Chem. Abstr. *60*, 1718 (1964).
9. Protiva M., Rajšner M., Votava Z., Metyšová J., Adlerová E., Seidlová V., Vejdělek Z. (Spofa): Fr. 1 332 145 (Czech. Appl. 08.06.61 and 24.03.62); Chem. Abstr. *60*, 2916 (1964).
10. Rajšner M., Protiva M.: This Journal *32*, 2021 (1967).
11. Hoenig M.: Ber. Deut. Chem. Ges. *18*, 3447 (1885).
12. Roe A.: Org. Reactions *5*, 193 (1949).
13. Rajšner M., Metyšová J., Svátek R., Mikšík F., Protiva M.: This Journal *40*, 719 (1975).
14. Protiva M., Rajšner M., Adlerová E., Seidlová V., Vejdělek Z. J.: This Journal *29*, 2161 (1964).
15. King T. J.: Unpublished results.
16. Rajšner M., Metyš J., Svátek E., Protiva M.: This Journal *34*, 1015 (1969).
17. Metyšová J., Metyš J., Dlabač A.: Activ. Nerv. Super. *20*, 55 (1978).
18. Metyšová J., Metyš J.: Česk. Fysiol. *27*, 53 (1978).
19. Valchář M., Metyš J., Metyšová J., Dlabač A.: Activ. Nerv. Super. *20*, 54 (1978).

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