SEARCH FOR NEW ANALEPTICS: HOMOANALOGUES OF DIMEFLINE-TYPE DERIVATIVES

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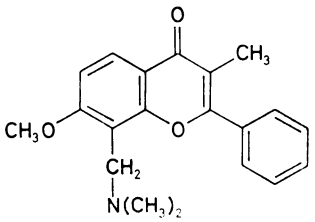
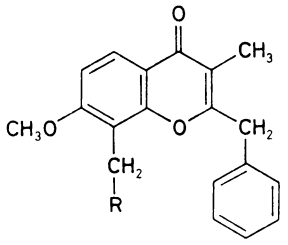
Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

The preparation and the pharmacological profile of a selected number of homologues at C_2 (homoflavones) of dimefline-type analeptics are described. The structural modification introduced in *I* seems to cause a remarkable alteration of the CNS stimulating pattern so that the new compounds are to be considered as minor analeptics.

As a further development of our preceeding research in the field of the centrally stimulating benzo-γ-pyrone derivatives related to dimefline (refs[1-7]), another aspect of the structure–activity relationships of this class of drugs has been examined. Here we describe the effect of the replacement of the 2-phenyl group of *I* with a benzyl one, i.e. by preparing and testing a number of selected homologues (homoflavones) *II*.



I



II

In formula *II*: *a*, R = $N(CH_3)_2$; *b*, R = $N(C_2H_5)_2$; *c*, R =  ; *d*, R =  ;

e, R = 

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The new compounds, collected with their pharmacological properties in Table I, have been prepared by standard procedures i.e., by chloromethylation of 3-methyl--7-methoxyhomoflavone and subsequent amination with selected secondary bases.

EXPERIMENTAL

All melting points were determined in open glass capillaries using a Büchi apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0·4% of the theoretical values.

3-Methyl-7-methoxyhomoflavone (*III*)

A mixture of 2-hydroxy-4-methoxypropiophenone (40 g, 0·22 mol), phenylacetyl chloride (80 g, 0·52 mol) and sodium phenylacetate (120 g) was heated at 180—190°C (oil bath) for 7—8 h. The reaction mixture was poured into water and extracted with chloroform; the organic layer was then washed with 10% NaOH and H_2O and dried. Removal of the solvent left a residue which on crystallizing from ligroin gave 24·6 g (40%) of white solid m.p. 121—122°C. Elemental analysis (C, H) gave satisfactory results.

TABLE I

N-Disubstituted 3-methyl-7-methoxy-8-aminoethylhomoflavones *IIa*—*IIe*

Compound	M.p., °C (yield, %)	Formula[a]	LD_{50} i.p.	Symptomatology
IIa	205—208 (70)	$C_{21}H_{24}ClNO_3$	66·7 (49—96)	2
IIb	165—168 (70)	$C_{23}H_{28}ClNO_3$	91·4 (63—143)	2
IIc	182—184 (65)	$C_{23}H_{26}ClNO_3$	70·1 (44—107)	2
IId	195—197 (80)	$C_{24}H_{28}ClNO_3$	75·0 (58—97)	2
IIe	211—213 (80)	$C_{23}H_{26}ClNO_4$	165·5 (99—198)	2
Dimefline	—	—	4·8 (2·0—7·2)	1

[a] All compounds, as hydrochloride salts, were analyzed for C, H, Cl, N and the analytical results obtained were within ±0·4% of the theoretical values.

3-Methyl-7-methoxy-8-chloromethylhomoflavone (*IV*)

To a solution of 3-methyl-7-methoxyhomoflavone (*III*) (2·8 g, 0·01 mol) in 30 ml acetic acid and 15 ml concentrated HCl, paraformaldehyde (0·9 g, 0·01 mol) were added and the mixture was stirred at 70–80°C for 5 h while a stream of HCl gas was introduced. The reaction mixture was then poured into water and the separated solid collected by filtration, washed with water and dried. On crystallizing the crude product from light petroleum, 2·3 g (70%) of white crystalline product m.p. 177–179°C were obtained. Elemental analysis (C, H, Cl) gave satisfactory results.

Preparation of the N-Disubstituted 8-Aminomethyl Derivatives (*IIa–IIe*). General Procedure

A solution of *IV* (0·01 mol) and a slight excess of the appropriate secondary amine in 300 ml benzene was stirred under reflux for 5–6 h. The reaction mixture after cooling was washed with water and the benzene layer dried over $MgSO_4$. Removing of the solvent left a residue which was converted in hydrochloride salt and crystallized from ethanol–ether (see Table I).

PHARMACOLOGY

The acute LD_{50}'s referred to the bases, were estimated following Lichfield and Wilcoxson method[8] and the behaviour pattern of animals was observed during one day in groups of mice after i.p. administration of four doses for each compound dissolved in saline as hydrochloride salt.

Groups ($n = 10$) of female mice (Swiss strain, 20–25 g) supplied by Charles River Italia, were housed at least for ten days, in groups of ten (Macrolon cage) on 12 h light-dark cycle (8 a.m.–8 p.m.) in a temperature controlled environment (21 ± 1°C) and allowed free access to food (Nossah GP-M pellets) and water until 1 h before the start of the experiment. The experiments were performed blind in that during the test the tester was unaware of the compound or dose each individual animal had received. All tests were performed at room temperature and they took place between 10·00 a.m. and 3 p.m. Each animal was only used once.

It is well known that the main acute toxic effects of the analeptics may be considered as result of general hyperexcitation of CNS, since these drugs cause both an increase in ventilation and in motor activity; the animal shows hyperpnea, hyperexcitability and tonic–clonic convulsions. While clonic convulsions seem mainly an expression of cortical stimulation[9–11], the tonic component usually prevails in the true analeptic brain-stem stimulants[12–14]. Therefore in screening tests two general considerations are valuable: (i) drugs which cause clonic convulsions without tonic extension generally exert little or no analeptic activity; (ii) the centrally acting drugs produce a particular type of convulsive patterns which are fairly characteristic of their analeptic properties[2,15]. Two different patterns can be outlined after overdosage of this kind of compounds:

1) The animals almost suddenly loose the control of the body posture and struggle vigorously. After one or two generalized clonic–tonic attacks, the tonic component prevails and highly characteristic rigidity occurs; the head is flexed on the chest,

the forelimbs are extended and rigid, adhering to the torax and hindlimbs too, are extended and rigid. Death usually occurs after paroxsysmal convulsive excitation or, occasionally, after a deep prostation. This pattern is typical of brain-stem stimulants such as pentylentetrazole and bemegride[15].

2) The animals maintain their posture during the first muscular twitches, but the whole body assumes exaggerated muscular tone; they sit down their hindlimbs which are rigid, extended and outstretched, whereas forelimbs are lifted up (kangaroo posture), then the animals struggle with poor coordination and became unable to mantain their posture, a natatory convulsive pattern is observed, associated with some gasps and a state of depression with respiratory failure, which leads to death, occurs. This picture resembles that described for niketamide and prethcamide[15].

RESULTS

The LD_{50} i.p. and the prelethal symptomatology of the dimefline *I* and of the new compounds *IIa–IIe* were reported in Table I. These derivatives exhibited an LD_{50} and 95% confidence limits significantly higher; compound *IIe* was the less toxic as compared to dimefline.

It was remarkable that the replacement of the 2-phenyl group of *I* with a benzyl one produces a shift of the prelethal symptomatology from type *I*, typical of major analeptic drugs such as dimefline, to type *II* as minor analeptics such as nikethamide.

REFERENCES

1. Da Re P., Verlicchi L., Setnikar I., Murmann W., Magistretti M. J.: Nature *184*, 362 (1959).
2. Setnikar I., Murmann W., Magistretti M. J., Da Re P., Verlicchi L.: J. Med. Chem. *3*, 471 (1962).
3. Da Re P., Bonola G., Setnikar I., Magistretti M. J.: Experientia *18*, 387 (1962).
4. Da Re P., Mancini V., Toth E., Cima L.: Arzneim. Forsch. *18*, 718 (1968).
5. Da Re P., Sagramora L., Mancini V., Valenti P., Cima L.: J. Med. Chem. *13*, 527 (1970).
6. Valenti P., Recanatini M., Da Re P., Cima L., Giusti P.: Arch. Pharm. *316*, 421 (1983).
7. Recanatini M., Valenti P., Da Re P., Giusti P.: Arch. Pharm. *322*, 257 (1989).
8. Litchfield J. T., Wilcoxon F.: J. Pharmacol. Exp. Ther. *96*, 99 (1949).
9. Cheymol J.: Actual. Pharmacol. *2*, 1 (1950).
10. Goodman L. S., Frawl M. S., Brown W. C., Swinyard E. A.: J. Pharmacol. *108*, 168 (1953).
11. Kreindler A., Zuckermann E., Stenade M., Chimoion D.: J. Neurophysiol. *21*, 430 (1958).
12. Setnikar I., Murmann W., Magistretti M. J.: Arzneim. Forsch. *11*, 1109 (1961).
13. Starzl T. E., Niemar W. T., Deil M.: J. Neuropathol. Exp. Neurol. *12*, 262 (1953).
14. Longo V. G.: *Electroencephalographic Atlas for Pharmacological Research.* Elsevier, Amsterdam 1962.
15. Setnikar I.: Res. Progresses Org. Biol. Med. Chem. *1964*, 423; Chem. Abstr. *63*, 18506 (1965).