NEUROTROPIC AND PSYCHOTROPIC SUBSTANCES. XLVII.*

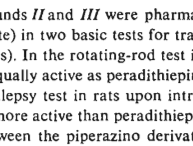
PIPERAZINE ENAMINES DERIVED FROM BENZO[*b*]THIENO[3,2-*f*]THIEPIN

K. ŠINDELÁŘ, J. METYŠOVÁ and M. PROTIVA

Research Institute of Pharmacy and Biochemistry, Prague 3

Received October 29th, 1970

After the establishment of the high neuroleptic activity of derivatives of 10-piperazinodibenzo-[*b*,*f*]thiepin[1-4], *i.e.* of piperazine enamines corresponding to the 10,11-dihydro-analogues of the "perathiepin" type[5] and "octoclothepin" type[6] it appeared suitable to study enamines corresponding in their neuroleptic and tranquilizing effect to "peradithiepin", *i.e.* 4-(4-methylpiperazino)-4,5-dihydrobenzo[*b*]thieno[3,2-*f*]thiepin[7] (*I*). For this reason we prepared now compounds *II* and *III*. During their synthesis we proceeded from the corresponding ketone, 4,5-dihydrobenzo-[*b*]thieno[3,2-*f*]thiepin-4-one[7], for the transformation of which into enamines we employed the titanium tetrachloride method[8], successfully used in the dibenzo[*b*,*f*]thiepin series[2,4].



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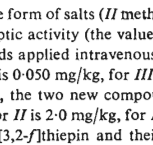

II, R = CH_3
III, R = $CH_2CH_2CH_2OH$

Compounds *II* and *III* were pharmacologically tested in the form of salts (*II* methanesulfonate, *III* fumarate) in two basic tests for tranquilizing and neuroleptic activity (the values shown refer to the bases). In the rotating-rod test in mice, both compounds applied intravenously are approximately equally active as peradithiepin *I* (ref.[7]). ED_{50} for *II* is 0·050 mg/kg, for *III* 0·078 mg/kg. In the catalepsy test in rats upon intraperitoneal application, the two new compounds are substantially more active than peradithiepin *I* (see ref.[9]): ED_{50} for *II* is 2·0 mg/kg, for *III* 2·1 mg/kg. Hence between the piperazino derivatives of benzo[*b*]thieno[3,2-*f*]thiepin and their 4,5-dihydro derivatives there exists a similar relationship as to their tranquilizing and neuroleptic activity as in the series of dibenzo[*b*,*f*]thiepin derivatives.

Compound *II* was further tested by Dr J. Turinová at the bacteriological department of this institute (headed by Dr A. Šimek) as to its inhibitory effects toward several microbial species *in vitro*. It was found that at a concentration of 25 μg/ml it inhibits the growth of *Streptococcus* β-*haemolyticus* and *Staphylococcus pyogenes aureus* (including the penicillin-resistant strain).

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block. The samples were dried for 8 h *in vacuo* (about 0·2 Torr) over phosphorus pentoxide at a temperature adequate to the melting points of the substances (100°C at most). The NMR spectra were recorded in a ZKR-60 (Zeiss Jena) apparatus in deuteriochloroform. As reference standard we used hexamethyldisiloxane; the values shown in the paper are referred to tetramethylsilane.

* Part XLVI: This Journal *36*, 2824 (1971).

4-(4-Methylpiperazino)benzo[*b*]thieno[3,2-*f*]thiepin (*II*)

A solution of 3·0 g titanium tetrachloride in 20 ml benzene was added dropwise under stirring over a period of 5 min to a mixture of 6·0 g 4,5-dihydrobenzo[*b*]thieno[3,2-*f*]thiepin-4-one[7], 15·0 g 1-methylpiperazine and 80 ml benzene. The mixture was left to stand overnight at room temperature, then it was refluxed under stirring for 16 h. After cooling, the mixture was decomposed with 30 ml water, the precipitated hydrate of titanium dioxide was filtered and washed with water and benzene. The benzene layer was separated from the filtrate and evaporated: 6·7 g (83%), m.p. 151–153°C (ethanol). NMR spectrum: δ 7·25 (mult. 4 H of benzene ring), 7·21 (doublet, 1 H in position 2 of the thiophene nucleus, $J = 7{\cdot}0$ Hz), 7·04 (doublet, 1 H in position 3 of the thiophene ring, $J = 7{\cdot}0$ Hz), 6·27 (singlet, 1 H in position 5 of the skeleton), 3·04 (multiplet, 4 H of CH_2 groups adjacent to enamine N), 2·55 (mult., 4 H of CH_2 groups adjacent to NCH_3), 2·35 (singlet, 3 H of methyl). For $C_{17}H_{18}N_2S_2$ (314·3) calculated: 64·95% C, 5·77% H, 8,91% N, 20·36% S; found: 65·03% C, 5·89% H, 8·78% N, 20·26% S.

Monomethanesulfonate monohydrate, m.p. 203–205°C (ethanol–ether). For $C_{18}H_{24}N_2O_4S_3$ (428·4) calculated: 50·46% C, 5·65% H, 6·54% N; found: 50·16% C, 6·08% H, 6·63% N.

4-[4-(3-Hydroxypropyl)piperazino]benzo[*b*]thieno[3,2-*f*] thiepin (*III*)

As in the previous case, 6·0 g 4,5-dihydrobenzo[*b*]thieno[3,2-*f*]thiepin-4-one[7] reacted with 21·6 g 1-(3-hydroxypropyl)piperazine[10] and 3·0 g titanium tetrachloride in 100 ml benzene. A similar treatment of the reaction mixture yielded 5·9 g substance which was recrystallized from ethanol to recover 3·2 g of the starting ketone, melting at 123–126°C (ref.[7] gives 122–124°C). Evaporation of the mother liquor yielded 2·42 g (56%) crude base *III* which was purified by conversion to the crystalline maleate (m.p. 95–97°C) and its decomposition by alkalization to give back the pure base, m.p. 121–3°C (ethanol). NMR spectrum: δ 7·26 (multiplet, 4 H of the benzene ring), 7·21 (doublet, 1 H in position 2 of the thiophene ring, $J = 7{\cdot}0$ Hz), 7·04 (doublet, 1 H in position 3 of the thiophene ring, $J = 7{\cdot}0$ Hz), 6·25 (singlet, 1 H in position 5 of the system), 4·20 (wide singlet, 1 H of the OH group), 3·80 (triplet, 2 H of the CH_2 group in CH_2OH, $J = 5{\cdot}0$ Hz), 3·02 (multiplet, 4 H of the CH_2 groups adjacent to the enamine N), 2·65 (multiplet, 6 H of the CH_2 groups adjacent to the second N atom), 1·76 (multiplet, 2 H of the central CH_2 group of the propane chain). For $C_{19}H_{22}N_2OS_2$ (358·4) calculated: 63·67% C, 6·19% H, 7·82% N, 17·86% S; found: 63·34% C, 6·35% H, 7·55% N, 17·92% S.

Fumarate, m.p. 213–214°C under decomposition (ethanol). For $C_{19}H_{22}N_2OS_2 \cdot 0{\cdot}5\ C_4H_4O_4$ (416·4) calculated: 60·56% C, 5·81% H, 6·73% N, 15·40% S; found: 60·25% C, 5·86% H, 6·57% N, 15·45% S.

The authors are indebted to Dr M. Rajšner of this laboratory for the starting 4,5-*dihydrobenzo*[*b*]-*thieno*[3,2-*f*]*thiepin*-4-*one. The NMR spectra were recorded and interpreted by Dr J. Holubek of the physico-chemical department of this institute (headed by Dr B. Kakáč). The analytical determinations were done at the analytical department of this institute (headed by Dr J. Kőrbl) by Mr K. Havel and Mrs V. Šmídová.*

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Translated by A. Kotyk.

ON PHTHALIDES AND INDANDIONES. XLII.*
ALKYLATION OF 2-(1-NAPHTHYL-)-1,3-INDANDIONE

P. Hrnčiar and M. Sladková

Department of Organic Chemistry,
Komenský University, Bratislava

Received October 19th, 1970

When the anions of 2-phenyl-1,3-indandione and 2-(2-naphthyl)-1,3-indandione are alkylated with primary alkyl halides in various solvents C-alkyl derivatives[1,2] are formed exclusively. In a previous work[3] Hrnčiar found that on methylation of the anion of 2-(1-naphthyl)-1,3-indandione (*I*) with methyl iodide in ethanol O-methyl derivative is formed in addition to the C-methyl derivative. Therefore we were interested in the question to what extent the sterical effect (drop in nucleophilicity) at the C-atom in the position 2 of *I* would be observable during the alkylations with other alkyl halides, in comparison with 2-phenyl-1,3-indandione and 2-(2-naphthyl)-1,3-indandione. The alkylations were carried out in protic and in aprotic solvents having various dielectrical constants (methanol, ethanol, dimethylformamide, dimethyl sulfoxide, acetone, dichloromethane). For the formation of anion *I* in alcoholic medium we made use of alcoholate, while in other solvents potassium carbonate was employed.

From the results given in Table I it is evident that the anion of compound *I* affords in all solvents on alkylation with methyl iodide, benzyl chloride, benzyl iodide, allyl bromide, and allyl chloride a mixture of C-alkyl and O-alkyl derivatives. After ethylation with ethyl bromide and ethyl iodide only the O-ethyl derivative *VI* could be isolated. In alkylations of the anion of 2-phenyl-1,3-indandione and 2-(2-naphthyl)-1,3-indandione with the mentioned primary halo hydrocarbons C-alkyl derivatives were obtained exclusively. When anion *I* reacted with isopropyl iodide, again O-isopropyl derivative *VII* is formed exclusively.

* Part XLI: This Journal *36*, 2775 (1971).