# NEUROTROPIC AND PSYCHOTROPIC AGENTS. LX.*

## 2-ACETYL-6*H*,11*H*-DIBENZO[*b*,*e*]THIEPIN AND SOME RELATED COMPOUNDS

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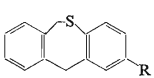
Received August 11th, 1972

Friedel-Crafts reaction of 6*H*,11*H*-dibenzo[*b*,*e*]thiepin (*I*) with acetyl chloride gives rise to the monoacetyl derivative *II*. Analogously, the 2-propionyl derivative *III* is formed. Willgerodt's reaction of these ketones was studied and thioamides *V* and *VI* and acids *VII* and *VIII* were obtained. Beckmann's rearrangement of oxime *IX* gave rise to the 2-acetamido derivative *X*. Oxidation of ketone *II* and acid *VII* yielded the sulfoxides *XIII* and *XIV* and further the sulfones *XV* and *XVI*. The methylpiperazine derivative *VI* displayed spasmolytic and hypotensive acticity while acids *VII*, *VIII*, *XIV* and *XVI* are clearly antiinflammatory in several tests.

The dibenzo[*b*,*e*]thiepin system[1,2] has proved to be a useful structural basis of compounds with neurotropic and psychotropic activity. Thus, in particular the various 11-(aminoalkylidene) and 11-(aminoalkyl) derivatives displayed a therapeutically applicable antidepressant (antireserpine), centrally depressant, antihistamine and antiserotonin activity[2-7]. Until recently, nothing has been known about the derivatives of this system with a functional group attached either directly or by a chain to one of the aromatic rings. The aim of the present communication is to fill partly this gap.

Reaction of 6*H*,11*H*-dibenzo[*b*,*e*]thiepin[3,8] (*I*) with acetyl chloride and aluminium chloride in dichloromethane gave a high yield of homogeneous monoacetyl derivative for which the structure of 2-acetyl derivative *II* was assumed. The structure was verified by comparing with the previously described and unequivocally synthesized 2-ethyl-6*H*-dibenzo[*b*,*e*]thiepin-11-one[2,9] (*XI*). Both ketones are reduced to the same 2-ethyl-6*H*,11*H*-dibenzo[*b*,*e*]thiepin (*IV*); ketone *II* was reduced for this

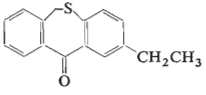


*I*, R = H
*II*, R = $COCH_3$
*III*, R = $COCH_2CH_3$
*IV*, R = $CH_2CH_3$
*V*, R = $CH_2CSN$ (O)

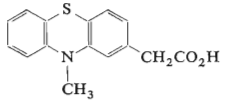
*VI*, R = $CH_2CSN$ ($NCH_3$)
*VII*, R = $CH_2COOH$
*VIII*, R = $CH_2CH_2COOH$
*IX*, R = $C(=NOH)CH_3$
*X*, R = $NHCOCH_3$

* Part LIX: This Journal *38*, 1596 (1973).

purpose by Clemmensen's method, ketone *XI* was reduced with zinc in boiling acetic acid. Similar Friedel–Crafts reaction of *I* with propionyl chloride gave a product which is assumed on the basis of analogy to have the structure of the 2-propionyl derivative *III*.



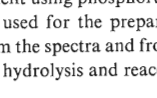
*XI*



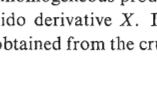
*XII*

In further work we took up Willgerodt's reaction[10,11] of ketones *II* and *III*. Reaction of ketone *II* with sulfur and morpholine or with 1-methylpiperazine at 150°C yielded the thioamides *V* and *VI*. Alkaline hydrolysis of the thiomorpholide *V* resulted in 6*H*,11*H*-dibenzo[*b*,*e*]thiepin-2-ylacetic acid (*VII*). By an analogous procedure from propionyl derivative *III*, *via* the noncrystalline thiomorpholide, the acid *VIII* was obtained. Both these acids, in particular *VII*, were of potential pharmacodynamic interest as structural analogous of methiazinic acid (*XII*) which has important antiinflammatory activity and is derived from phenothiazine, *i.e.* another tricyclic system which attained wide application as a carrier system in the molecules of psychotropic substances[12,13].

Oxidation of ketone *II* and acid *VII* with hydrogen peroxide in acetic acid under gentle or more rigorous conditions produced sulfoxides *XIII* and *XIV*, and sulfones *XV* and *XVI*. The oxime *IX* prepared from ketone *II* was subjected to a Beckmann rearrangement using phosphorus pentachloride. A nonhomogeneous product resulted which was used for the preparation of the 2-acetamido derivative *X*. Its structure follows from the spectra and from the fact that it was obtained from the crude product by alkaline hydrolysis and reacetylation.



*XIII*, R = $COCH_3$
*XIV*, R = $CH_2COOH$



*XV*, R = $COCH_3$
*XVI*, R = $CH_2COOH$

Thiomorpholide *V* ($LD_{50} > 2500$ mg/kg in mice on oral application, dose tested 300 mg/kg *p.o.*) and hydrochloride of thioamide *VI* ($LD_{50} = 100$ mg/kg on *i.v.* application, dose tested 20 mg/kg *i.v.*) were tested pharmacologically by screening methods at the unit of this institute at Rosice n/L under the direction of Dr F. Hradil and Dr J. Němec. While the water-insoluble and nontoxic thiomorpholide V showed only traces of antiarrhythmic effects toward chloroform arrhythmias in mice, the piperazine derivative *VI* is spasmolytic toward barium chloride spasm in isolated rat duodenum, resembling in intensity papaverine; further it has a negatively inotropic effect in the isolated rabbit auricle and finally, at the dose tested, brings about in rats a pronounced drop of blood pressure with a slow return to the initial value.

Acids *VII*, *VIII*, *XIV* and *XVI* were evaluated from the point of view of assumed antiinflammatory activity. To evaluate the toxicity and the activity, they were applied *per os* as an aqueous suspension in gum arabic. The antiinflammatory activity was examined on two models of acute inflammation (rat foot oedema after injection of kaolin and, with one of the compounds, the test of the intrapleural fluid) and on two models of subchronic inflammation (test of implanted pellets and, with one of the compounds, rat foot oedema after an injection of adjuvant; for pharmacological methods see also ref.[14-16]). The activity of the compounds was compared with phenylbutazone in the same tests[17]. The results of the tests are shown in Table I, the numbers shown giving the percentage of inflammation inhibition as compared with an untreated control. It may be stated that the acids tested display a certain degree of antiinflammatory activity. Their activity is, however, much weaker than that of phenylbutazone.

TABLE I

Antiinflammatory Activity of Compounds Described

| Compound | Toxicity | | Dose mg/kg | Antiinflammatory activity | | | |
|---|---|---|---|---|---|---|---|
| | *p.o.*[a] mortality | *i.v.*[b] $LD_{50}$ | | kaolin | pleuritis | pellets | adjuvant |
| *VII* | 0/5 | 225 | 100 | 13[c] | | 6 | |
| *VIII* | 2/10 | | 100 | 2 | | 24 | 12 |
| | | | 200 | | 24[c] | | |
| *XIV* | 0/5 | 200 | 100 | 16[c] | | 0 | |
| *XVI* | 0/5 | 200 | 100 | 3 | | 0 | |
| Phenylbutazone | | 540[d] | 75 | 27[c] | | | 29[c] |
| | | | 100 | | 29[c] | 82[c] | |

[a] Orientation acute toxicity after a single dose of 1 g/kg for mice. The numerator shows the number of deaths, the denominator the total number of animals in group. [b] Intravenous application of aqueous solutions of sodium salts. [c] Statistically significant. [d] Oral toxicity.

## EXPERIMENTAL

The melting points of the analytical preparations were determined in a capillary (uncorrected); they were dried in the usual way. The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol) in a Unicam SP 200 G spectrophotometer and the NMR spectra (in $CDCl_3$ unless shown otherwise) in a ZKR 60 (Zeiss, Jena) spectrometer.

2-Acetyl-6*H*,11*H*-dibenzo[*b*,*e*]thiepin (*II*)

Acetyl chloride (4·3 ml) was added to a solution of 7·6 g anhydrous $AlCl_3$ in 25 ml dichloromethane and the solution formed was added dropwise over 20 min under stirring to a solution of 10·6 g 6*H*,11*H*-dibenzo[*b*,*e*]thiepin[3,8] (*I*) in 30 ml dichloromethane. The mixture was stirred for 1 h at room temperature and poured into 130 ml HCl (1 : 10). On adding chloroform the precipitate dissolved, the organic phase was separated, dried with $MgSO_4$ and evaporated. Re-

crystallization of the residue from 80 ml acetic acid yielded 11·0 g (87%) product melting at 201 to 203°C. UV spectrum: $\lambda_{max}$ 231 nm (log $\varepsilon$ 3·87), 317 nm (4·22). IR spectrum: 757 (1,2-$C_6H_4$). 827 and 916 (1,2,4-$C_6H_3$), 1 592 (Ar), 1 667 (in $CCl_4$ 1 685) $cm^{-1}$ (Ar—CO). For $C_{16}H_{14}OS$ (254·3) calculated: 75·55% C, 5·55% H, 12·61% S; found: 75·35% C, 5·55% H, 12·72% S. *Oxime* IX was prepared from ketone *II* and hydroxylamine hydrochloride by heating in pyridine; m.p. 214—216°C (acetic acid). For $C_{16}H_{15}NOS$ (269·4) calculated: 71·34% C, 5·61% H, 5·20% N, 11·91% S; found: 70·98% C, 5·72% H, 4·77% N, 11·68% S.

2-Propionyl-6*H*,11*H*-dibenzo[*b*,*e*]thiepin (*III*)

In analogy to the preceding case, reaction of 21·2 g *I*, 10·4 g propionyl chloride and 14·8 g $AlCl_3$ in 120 ml dichloromethane yielded 26 g crude product. After recrystallization from benzene, 19·0 g (71%) compound melting at 156—158°C was obtained. UV spectrum: $\lambda_{max}$ 241 nm (log $\varepsilon$ 3·86), 315 nm (4·21). IR spectrum: 755 (1,2-$C_6H_4$), 800 and 875 (1,2,4-$C_6H_3$), 1 550 and 1 590 (Ar) 1 670 $cm^{-1}$ (Ar—CO). NMR spectrum: $\delta$ 6·90—7·95 (m, 7 H, aromatic protons), 4·29 (s, 2 H) and 4·16 (s, 2 H), of $CH_2S$ and $ArCH_2Ar$, 2·90 (q, $J$ = 8·0 Hz, 2 H, $COCH_2$), 1·17 (t, $J$ = 8·0 Hz, 3 H of C—$CH_3$). For $C_{17}H_{16}OS$ (268·4) calculated: 76·08% C, 6·01% H, 11·95% S; found: 75·88% C, 6·10% H, 11·78% S.

2-Ethyl-6*H*,11*H*-dibenzo[*b*,*e*]thiepin (*IV*)

*A*. A mixture of 0·45 g ketone[2,9] *XI* and 1·6 g zinc powder in 8 ml acetic acid was refluxed under stirring for 2 h. After filtration, the filtrate was diluted with water and the precipitated compound was extracted with dichloromethane. The extract was dried with $K_2CO_3$ and evaporated. The residue (0·3 g oil) crystallized after dissolving in 1·5 ml light petroleum; m.p. 46—48°C (ethanol). NMR spectrum: $\delta$ 7·14 (s, 5 H, aromatic protons in positions 4, 7, 8, 9, 10), 6·70—7·05 (m, 2 H, aromatic protons in positions 1 and 3), 4·17 (s, 2 H, $CH_2S$), 4·05 (s, 2 H, $ArCH_2Ar$), 2·50 (q, 2 H, $CH_2$ in ethyl), 1·14 (t, 3 H, $CH_3$). For $C_{16}H_{16}S$ (240·4) calculated: 79·95% C, 6·71% H, 13·34% S; found: 80·27% C, 6·80% H, 13·19% S.

*B*. A mixture of 2·4 g ketone *II*, 30 ml acetic acid, 50 g amalgamated zinc and 5 ml HCl was refluxed for 4 h. The remaining zinc was separated by decanting, the liquid was filtered and the filtrate diluted with water. The precipitated product was isolated by extraction with benzene; 2·19 g oil which crystallized from ethanol, m.p. 46°C. In mixture with the compound obtained under *A* it melts without depression and in chromatography on a thin layer of alumina the products of *A* and *B* give identical spots.

2-(Morpholinothiocarbonylmethyl)-6*H*,11*H*-dibenzo[*b*,*e*]thiepin (*V*)

A mixture of 60·6 g ketone *II*, 11·4 g sulfur and 31·8 ml morpholine was heated under stirring for 5 h to 150°C. The solidified melt was recrystallized from 700 ml acetic acid; 78·0 g (92%), m.p. 174—176°C. Further recrystallization from the same solvent yielded the analytical product in the form of yellow needles melting at 180—182°C. For $C_{20}H_{21}NOS_2$ (355·5) calculated: 67·56% C, 5·96% H, 3·94% N, 18·04% S; found: 67·54% C, 6·02% H, 3·67% N, 17·94% S.

2-(4-Methylpiperazinothiocarbonylmethyl)-6*H*,11*H*-dibenzo[*b*,*e*]thiepin (*VI*)

A mixture of 2·5 g ketone *II*, 0·5 g sulfur and 1·5 g 1-methylpiperazine was heated for 4 h to 150°C. The solidified melt was boiled with 30 ml acetone, cooled and filtered; 1·9 g (52%), m.p. 160 to 162°C. For analysis it was recrystallized from benzene, m.p. 164—165°C. NMR spectrum: $\delta$ 7·18 (s, 4 H, aromatic protons in positions 7, 8, 9, 10), 7·11 (s, 1 H, aromatic proton in position 1),

6·90 (s, 2 H, aromatic protons in positions 3, 4), 4·20 (s, 2 H, $CH_2CS$), 4·16 (s, 2 H, $CH_2S$), 4·05 (s, 2 H, $ArCH_2Ar$), 4·25 and 3·52 (t, $J$ = 5·0 Hz, 4 H, $CH_2NCH_2$ with nonbasic N), 2·56 (s, 3 H, N—$CH_3$), 2·40 and 2·05 (t, $J$ = 5·0 Hz, 4 H, $CH_2N^4CH_2$). For $C_{21}H_{24}N_2S_2$ (368·6) calculated: 68·43% C, 6·56% H, 7·60% N, 17·40% S; found: 68·65% C, 6·72% H, 7·31% N, 17·02% S.

*Hydrochloride*, m.p. 217—218°C (95% ethanol). For $C_{21}H_{25}ClN_2S_2$ (405·0) calculated: 62·27% C, 6·22% H, 8·75% Cl, 6·92% N, 15·84% S; found: 62·34% C, 6·21% H, 9·03% Cl, 7·06% N, 15·55% S.

6*H*,11*H*-Dibenzo[*b*,*e*]thiepin-2-ylacetic Acid (*VII*)

KOH (4 g) was added to a mixture of 3·6 g thiomorpholide *V* and 5 ml ethanol and the whole was refluxed for 2 h at 120°C. After cooling, it was dissolved in 25 ml water, the solution was filtered with charcoal and the filtrate made acid with dilute hydrochloric acid. Filtration yielded 2·3 g (85%) crude product which was recrystallized for analysis from acetic acid, m.p. 202—204°C. According to chromatographic check the compound is completely homogeneous but analysis shows the presence of an oxygen-containing contaminant (probably acetic acid) which could not be removed even by drying *in vacuo* at 100°C. IR spectrum: 745 (1,2-$C_6H_4$), 820 and 870 (1,2,4-$C_6H_3$), 933, 1212, 1230, 1713 and 2720 $cm^{-1}$ (COOH). NMR spectrum ($CD_3SOCD_3$): $\delta$ 11·44 (bs, 1 H, COOH), 7·27 (m, 5 H, aromatic protons in positions 4, 7, 8, 9, 10), 6·95 (s, 2 H, aromatic protons in positions 1 and 3), 4·37 and 4·11 (2 s, 4 H, $ArCH_2Ar$ and $CH_2S$), 3·45 (s, 2 H, $CH_2COO$). For $C_{16}H_{14}O_2S$ (270·3) calculated: 71·08% C, 5·22% H, 11·86% S; found: 70·30% C, 5·44% H, 11·59% S.

3-[6*H*,11*H*-Dibenzo[*b*,*e*]thiepin-2-yl]propionic Acid (*VIII*)

A mixture of 5·4 g ketone *III*, 0·96 g sulfur and 2·68 ml morpholine was heated for 15 h at 150°C. After cooling, the melt was combined with 12 ml ethanol and 9 g KOH and the mixture was heated for 2 h to 100°C. Treatment as before yielded 3·8 g (67%) crude product which was purified by crystallization from acetone, m.p. 186—188°C. NMR spectrum ($CD_3SOCD_3$ : $\delta$ 12·28 (bs, 1 H, COOH), 7·26 (m, 4 H, aromatic protons in positions 7, 8, 9, 10), 7·12 (s, 1 H, aromatic proton in position 1), 6·90 (s, 2 H, aromatic protons in position 3 and 4), 4·34 (s, 2 H, $ArCH_2Ar$), 4·08 (s, 2 H, $CH_2S$), 2·40—2·80 (m, 4 H, $CH_2CH_2$). For $C_{17}H_{16}O_2S$ (284·4) calculated: 71·80% C, 5·67% H, 11·28% S; found: 71·64% C, 5·86% H, 11·24% S.

2-Acetyl-6*H*,11*H*-dibenzo[*b*,*e*]thiepin 5-Oxide (*XIII*)

$H_2O_2$ (1·3 ml 30%) was added to a solution of 2·54 g ketone *II* in 25 ml acetic acid. After cessation of the exothermic reaction, it was left for 30 min at room temperature, then diluted with 40 ml water and the precipitated product was filtered after some standing; 2·1 g (78%), m.p. 187—189°C (benzene). IR spectrum: 745 and 767 (1,2-$C_6H_4$), 830 and 870 (1,2,4-$C_6H_3$), 1040 and 1052 (SO), 1573 and 1594 (Ar), 1679 $cm^{-1}$ (ArCO). NMR spectrum: $\delta$ 7·95 (m, 3 H, aromatic protons in positions 1, 3, 4), 7·25 (m, 4 H, aromatic protons in positions 7, 8, 9, 10), 4·64 and 4·33 (ABq, $J$ = 14·0 Hz, 2 H) and 4·35 and 3·95 (ABq, $J$ = 15·0 Hz, 2 H), $ArCH_2Ar$ and $CH_2S$, 2·59 (s, 3 H, $COCH_3$). For $C_{16}H_{14}O_2S$ (270·3) calculated: 71·08% C, 5·22% H, 11·86% S; found: 71·32% C, 5·13% H, 11·84% S.

2-Acetyl-6*H*,11*H*-dibenzo[*b*,*e*]thiepin 5,5-Dioxide (*XV*)

$H_2O_2$ (2·7 ml 30%) was added to a suspension of 2·5 g ketone *II* in 25 ml acetic acid and the mixture was refluxed until dissolving of the solid. On standing overnight, 2·3 g (80%) product

precipitated: m.p. 194–196°C (acetic acid). IR spectrum: 760 (1,2-$C_6H_4$), 830 and 890 (1,2,4-$C_6H_3$), 1120 and 1300 ($SO_2$), 1565 and 1590 (Ar), 1680 $cm^{-1}$ (ArCO). NMR spectrum ($CD_3$.$SOCD_3$): $\delta$ 7·90–8·25 (m, 3 H, aromatic protons in positions 1, 3, 4), 7·00–7·75 (m, 4 H, aromatic protons in positions 7, 8, 9, 10), 5·26 (s, 2 H, $CH_2SO_2$), 4·48 (s, 2 H, $ArCH_2Ar$), 2·60 (s, 3 H, $COCH_3$). For $C_{16}H_{14}O_3S$ (286·3) calculated: 67·11% C, 4·93% H, 11·20% S; found: 66·93% C, 5·10% H, 11·01% S.

6*H*,11*H*-Dibenzo[*b*,*e*]thiepin-5-oxide-2-ylacetic Acid (*XIV*)

$H_2O_2$ (0·5 ml 30%) was added to a solution of 1·0 g acid *VII* in 10 ml acetic acid and the mixture was briefly boiled. On cooling, 0·75 g (71%) product precipitated, m.p. 197–198°C under decomposition (acetic acid). For $C_{16}H_{14}O_3S$ (286·3) calculated: 67·11% C, 4·93% H, 11·20% S; found: 66·78% C, 5·19% H, 11·16% S.

6*H*,11*H*-Dibenzo[*b*,*e*]thiepin-5,5-dioxide-2-ylacetic Acid (*XVI*)

A mixture of 1·0 g *VII*, 10 ml acetic acid and 1 ml 30% $H_2O_2$ was refluxed for 15 min. On standing and cooling, a product precipitated which was filtered and recrystallized from acetic acid; 0·8 g (72%), m.p. 225–227°C. IR spectrum: 751 (1,2-$C_6H_4$), 793, 828 and 880 (1,2,4-$C_6H_3$), 945, 1692 and 1710 (COOH), 1145 and 1300 ($SO_2$), 1605 $cm^{-1}$ (Ar). NMR spectrum ($CD_3SOCD_3$): $\delta$ about 7·50 (m, 7 H, aromatic protons), 5·15 (s, 2 H, $CH_2SO_2$), 4·34 (s, 2 H, $ArCH_2Ar$), 3·64 (s, 2 H, $CH_2COO$). For $C_{16}H_{14}O_4S$ (302·3) calculated: 63·56% C, 4·67% H, 10·60% S; found: 63·34% C, 4·71% H, 10·77% S.

2-Acetamido-6*H*,11*H*-dibenzo[*b*,*e*]thiepin (*X*)

A mixture of 5·0 g oxime *IX*, 80 ml benzene and 5·0 g $PCl_5$ was refluxed for 15 min. After cooling, it was washed with water, the solution was dried with $MgSO_4$, filtered with charcoal and evaporated. The noncrystalline residue (4·1 g) was hydrolyzed for 90 min by boiling with 8 ml ethanol and 5 g KOH. After cooling it was diluted with water and extracted with chloroform. The extract was dried, filtered and evaporated. The inhomogeneous residue was chromatographed on a column of 80 g $Al_2O_3$. Evaporation of the benzene eluate yielded an oil which was reacylated for 5 min by heating with 2 ml acetic anhydride. The product crystallized from acetic acid; m.p. 204–207°C. UV spectrum: $\lambda_{max}$ 280 nm (log $\varepsilon$ 4·24). IR spectrum: 741 and 765 (1,2-$C_6H_4$), 811 and 899 (1,2,4-$C_6H_3$), 1537, 1590, 1611, 1656 (CONH), 3245 and 3288 $cm^{-1}$ (NH). NMR spectrum ($CD_3SOCD_3$): $\delta$ 9·93 (bs, 1 H, NH), 7·10–7·60 (m, 6 H, aromatic protons in positions 1, 3, 7, 8, 9, 10), 6·92 (d, $J$ = 9·0 Hz, 1 H, aromatic proton in position 4), 4·34 (s, 2 H, $ArCH_2Ar$), 4·08 (s, 2 H, $CH_2S$), 2·02 (s, 3 H, $COCH_3$). For $C_{16}H_{15}NOS$ (269·4) calculated: 71·34% C, 5·61% H, 5·20% N, 11·91% S; found: 70·65% C, 5·56% H, 5·11% N, 11·69% S.

*The UV, IR and NMR spectra were kindly measured and interpreted by Dr B. Kakáč, Dr E. Svátek and Dr J. Holubek from the physico-chemical department of this institute. The analytical estimations were done by Mr K. Havel, Mrs V. Šmídová and Mrs J. Komancová from the analytical department of this institute.*

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Translated by A. Kotyk.