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Letter to the Editors

A New Group of Tranquillizers: Derivatives of 2,3:6,7-Dibenzosuberane and 2,3:6,7-Dibenzo-4-suberene

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Sir:

The well-known similarity between the pharmacodynamic properties of compounds which differ only in the substitution of a sulphide sulphur atom —S— by a vinyl residue —CH=CH— has led us to study 2,3:6,7-dibenzo-4-suberene and 2,3:6,7-dibenzosuberane analogues of the very effective tranquillizer, chlorprothixene [*trans*-9-(3-dimethylaminopropylidene)-2-chlorothiaxanthene hydrochloride],[1] in continuation of a previous study of pharmacologically interesting substances of this type.[2] This preliminary communication of our results has been stimulated by the paper of Bodi *et al.*[3] on a new antihistaminic—cyproheptadine —which is a 2,3:6,7-dibenzo-4-suberene derivative, and further by the announcement of a Czechoslovak patent application by Rey-Bellet and Spiegelberg,[4] relating to a very broad area of structures including both the ring systems mentioned in the title.

We are now reporting the chemistry and pharmacology of a series of substances shown in Table I. The starting materials for the synthesis of these substances were: 2,3:6,7-dibenzosuberone (IV),[5] 2,3:6,7-dibenzosuber-4-en-1-one (V),[5] 2,3:6,7-dibenzosuberane (VI),[6] 2,3:6,7-dibenzo-4-suberene (VII),[5] together with three new compounds, 2′-chloro- and 2′-methyl-2,3:6,7-dibenzosuberone (VIII and IX), and finally 2′-chloro-2,3:6,7-dibenzosuber-4-en-1-one (X). The new ketones were obtained from the

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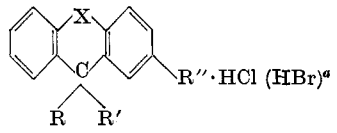
Table I. 2,3:6,7-Dibenzosuberane and



Compound no.	VÚFB no.	X	R	R'	R''	m.p., °C[b]	Formula
Ia	2794	CH_2CH_2	OH	$(CH_2)_3N(CH_3)_2$	H	211–212	$C_{20}H_{26}ClNO$
Ib	3087	CH_2CH_2	OH	$(CH_2)_3N(CH_3)_2$	Cl	234	$C_{20}H_{25}Cl_2NO$
IIa	2795	CH_2CH_2	=CH	$CH_2CH_2N(CH_3)_2$	H	196–7·5	$C_{20}H_{24}ClN$
IIb	3101A	CH_2CH_2	=CH	$CH_2CH_2N(CH_3)_2$	Cl	230–233	$C_{20}H_{23}Cl_2N$
IIc	3090	CH_2CH_2	=CH	$CH_2CH_2N(CH_3)_2$	CH_3	223–225	$C_{21}H_{26}ClN$
IId	3112	CH=CH	=CH	$CH_2CH_2N(CH_3)_2$	H	217	$C_{20}H_{22}ClN$
IIe	3127	CH=CH	=CH	$CH_2CH_2N(CH_3)_2$	Cl	227–230	$C_{20}H_{21}Cl_2N$
IIIa	3085	CH_2CH_2	H	$(CH_2)_2N(CH_3)_2$	H	202–205	$C_{19}H_{24}ClN$
IIIb	3086	CH_2CH_2	H	$(CH_2)_2NC_5H_{10}$	H	241–242	$C_{22}H_{28}ClN$
IIIc	3088	CH_2CH_2	H	$(CH_2)_2NC_4H_8O$	H	237–241	$C_{21}H_{26}ClNO$
IIId	2793	CH_2CH_2	H	$(CH_2)_3N(CH_3)_2$	H	187–189	$C_{20}H_{26}ClN$
IIIe	3102	CH_2CH_2	H	$(CH_2)_3N(CH_3)_2$	Cl	192–194	$C_{20}H_{25}Cl_2N$
IIIf	3111	CH_2CH_2	H	$(CH_2)_3N(CH_3)_2$	CH_3	204–207	$C_{21}H_{26}ClN$
IIIg	3128	CH=CH	H	$(CH_2)_3N(CH_3)_2$	H	173	$C_{20}H_{24}BrN$

[a] All substances with the exception of IIIg are hydrochlorides; IIIg is a hydrobromide.
[b] Analytical samples were crystallized from ethanol, ethanol–ether, acetone or ethanol–acetone.
[c] Intravenous toxicity in mice calculated according to the Litchfield–Wilcoxon method.
[d] Medium effective doses (ED_{50}) calculated according to the Litchfield–Wilcoxon method; 50 mice were used for one calculation.

2,3:6,7-dibenzo-4-suberene derivatives

Analysis, %				LD_{50}, mg/kg[c]	Rotating rod[d] test		Prolongation of thiopental sleep[e]	Hypothermia,[f] °C	Effect on pentazol toxicity %[g]
Calcd		Found			mg/kg	max. activity, min			
C	H	C	H						
72·38	7·89	72·05	7·91	54	20	15–45	1·3	0·1	92·1
65·58	6·88	65·34	6·91	54	17	5–10	3·2	1·6	78·3
76·53	7·71	76·45	7·96	31	6·6	5	5·08	0·8	87·5
68·96	6·66	68·88	6·85	43	4·3	10	15·8	2·8	73
76·92	7·99	76·65	8·09	35	10·5	10	2·1	1·4	61·1
77·03	7·11	76·84	7·17	36	6·6	30	7·6	1·1	89·3
69·37	6·11	69·62	6·15	28·5	1·9	10	4·6	2·7	94·1
75·60	8·01	75·49	8·21	31	9·7	10	1·6	0·7	100
77·28	8·25	77·05	8·12						
73·34	7·62	73·16	7·75	76	33·5	5	1·2	0·5	87·7
76·04	8·30	76·16	8·42	47	9·2	5–15	1·73	0·3	108·3
68·57	7·19	68·52	7·33	40	11·5	15	1·4	1·0	75·9
76·45	8·55	76·86	8·50	41·5	10·5	5–10	6·4	1·2	75·3
67·04	6·75	66·97	6·97	46	8·4	5	1·6		

[e] Prolongation of the duration of sleep after intravenous administration of a dose corresponding to 20 per cent LD_{50} of the tested compound 5–30 min before intravenous administration of thiopental (40 mg/kg).

[f] Maximal lowering of the body temperature in comparison with control group of mice after intravenous administration of the substance in a dose corresponding to 20 per cent LD_{50} (during 4 h testing period, groups of 10 mice).

[g] Changes in the acute intravenous toxicity of pentazol in mice in comparison with control group on administration of a dose corresponding to 20 per cent LD_{50} of tested compounds 5–30 min before administration of pentazol.

appropriate benzalphthalides by the application of methods described for the preparation of the unsubstituted compounds.[5, 7, 8]

The tertiary alcohols Ia and Ib were prepared from ketones IV and VIII by reaction with 3-dimethylaminopropylmagnesium chloride; they were dehydrated by the action of acetyl chloride in chloroform to the unsaturated compounds IIa and IIb. Similar reactions were also performed with ketones V, IX and X; in these cases, however, the dehydration mostly took place during the decomposition of the Grignard reaction mixtures, thus giving substances IIc–IIe directly. The compounds IIIa–IIIg were obtained (*a*) by aminoalkylation of VI and VII, metallized with phenyllithium, phenylsodium or sodium and naphthalene in tetrahydrofuran, and (*b*) by reduction of compounds of types I and II by means of hydriodic acid. Table I shows the melting points of crystalline salts, and empirical formulae which are in agreement with analytical data.

The pharmacological experiments were carried out to test anticipated tranquillizing effects on the central nervous system in white mice of the home strain. The following tests were used: prolongation of thiopental anaesthesia; discoordination of motor activity in the rotating rod test; effects on body temperature; influence on the acute toxicity of pentazol; and acute toxicity after intravenous administration. From the results shown in Table I it is possible to draw the following conclusions.

All the tested drugs have similar pharmacological properties. They prolong the duration of thiopental sleep, lower the body temperature, evoke discoordination of muscle activity on the rotating rod and have a slight antipentazol effect. Medium acute intravenous toxicity is within the range of 30–60 mg/kg. All compounds produce similar toxic effects, which are characterized by short-time excitation followed by sedation. Death is caused by acute respiratory arrest.

The most effective substances are the 3-dimethylaminopropylidene derivatives IIa–IIe. Chlorination in position 2′ of the dibenzosuberane system (compounds IIb and IIe) considerably increases the effect in the rota-rod test, prolongation of thiopental anaesthesia, and hypothermic activity. On the other hand methylation in the same position (substance IIc) decreases the activity in most tests. There is no great difference in pharmaco-

logical properties between the dibenzosuberane derivatives (IIa, IIb) and the corresponding dibenzosuberene derivatives (IId, IIe).

Aminoalkyl derivatives with a saturated side chain (compounds of type III) are less interesting in regard to tranquillizing activity. The tertiary alcohols (type I) did not show any noteworthy pharmacodynamic activity either. All the compounds were also tested for their anticholinergic activity (antagonism to methacholine in the lacrimation test in rats.) With the exception of IIIa all compounds were ineffective in this respect.

On the basis of these pharmacological results, the two most effective substances, i.e. IIb ('chlorproheptadiene') and IIe ('chlorproheptatriene'), have been chosen for further pharmacological as well as clinical trials.

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