ANTIHISTAMINE SUBSTANCES. LIII.*

ortho-SUBSTITUTED DERIVATIVES OF 1,1-DIPHENYL-1-(2-DIMETHYLAMINOETHOXY)ETHANE

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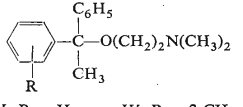
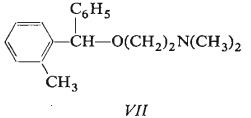
Some time ago[1] we described the synthesis of a series of *p*- and *m*-substituted derivatives of 1,1-diphenyl-1-(2-dimethylaminoethoxy)ethane ("mephenhydramine", *I*), particularly the *p*-halogen derivatives of which proved to be highly active antihistaminics[2,3]. Literature data[4,5] on the anticholinergic activity of *o*-methylbenzhydryl 2-dimethylaminoethyl ether ("orphenadrine", *VII*) attracted the attention to the hitherto unknown *o*-substituted derivatives of mephenhydramine, the synthesis and pharmacology of which are described in the present communication.

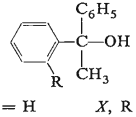
Grignard reagents from *o*-bromotoluene, *o*-bromochlorobenzene, *o*-bromothioanisol[6] and *o*-bromoanisol[7] reacted with acetophenone to the corresponding *o*-substituted 1,1-diphenylethanols (*IX*—*XII*). The reaction of the first three compounds with sodium amide and 2-dimethylaminoethyl chloride in benzene yielded without difficulty the desired ethers *IV*—*VI*. On the other hand, when attempting a similar reaction of 1-phenyl-1-(2-methoxyphenyl)ethanol (*XII*) no ether was formed and the starting alcohol was recovered. To exclude the possibility that the ether is formed but is split during isolation, water was eliminated from the isolation procedure but the result was the same. After prolonged boiling of the reaction mixture in toluene the formation of a small amount of a new substance was demonstrated chromatographically but the substance could not be isolated. In this case, too, a prevalent amount of the starting alcohol *XII* was recovered. A possible explanation of this anomaly was indicated by IR spectrum



I, R = H
II, R = 4-Br
III, R = 4-F
IV, R = 2-CH_3
V, R = 2-Cl
VI, R = 2-SCH_3



VII



VIII, R = H
IX, R = CH_3
X, R = Cl
XI, R = SCH_3
XII, R = OCH_3

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of alcohol *XII*: the band at 3560 cm^{-1} (at great dilution) indicates that the hydroxyl group is firmly bound by an intramolecular hydrogen bond apparently to the oxygen of the methoxyl group. The band of a free hydroxyl group (occurring with the unsubstituted alcohol *VIII* at 3610 cm^{-1}) is completely missing. The hydrogen bond is in this case so stable that it results in a decreased reactivity of the hydroxyl group.

In the experimental section we describe further a crystalline substance* which was obtained as a by-product of preparation of 1,1-diphenyl-1-(2-dimethylaminoethoxy)ethane (*I*) (ref.[8]) by a reaction of 1,1-diphenylethanol (*VIII*) with 2-dimethylaminoethyl chloride hydrochloride in benzene in the presence of solid sodium hydroxide (for the procedure see ref.[9]). The compound was identified as a molecular complex of base *I* with the starting alcohol *VIII*. Further we describe some new salts of bases *II* and *III*, an interesting substance being the molecular compound of base *II* with 8-chlorotheophylline[10]. This compound ("mebrophenhydrinate") shows a fine antiemetic activity and, at the same time, an acceptable central depressant activity and was introduced into clinical practice as a drug against kinetoses (Medrin^{R})[11,12].

Compounds *IV*—*VI* were pharmacologically tested in the form of hydrochlorides. Intravenous toxicity for mice (LD_{50}): *IV* 34·0 mg/kg, *V* 44·0 mg/kg, *VI* 26·0 mg/kg. The central activity in the rotating-rod test in mice upon intravenous administration is very low (ED_{50} max values are shown): *IV* 12·7 mg/kg, *V* 14·0 mg/kg, *VI* 7·6 mg/kg. All the three compounds showed a very weak hypothermic effect in mice after intravenous administration of a dose equalling 20% LD_{50} (temperature drop by 0·3—0·8°C). In the same dose, they were practically without effect on the duration of the narcotic effect of thiopental in mice. Similarly, the antihistamine effect was of a low degree. In the histamine aerosol test in guinea pigs only doses of 5 mg/kg showed a partly protective effect and in the histamine detoxication test in guinea pigs all the three compounds were without effect after subcutaneous injection of 1 mg/kg. All three compounds were without effect on lachrymation in rats brought about by methacholine upon intravenous administration of a dose equalling 40% LD_{50} (for mice). Similarly, the test of arecoline analgesia had a negative outcome (subcutaneous doses of 40—100 mg/kg of *IV*—*VI* are without effect) and in the tremorine analgesia in mice only *V* and *VI* had a slight antagonistic effect in doses of 50 mg/kg intraperitoneally. All the three compounds displayed a relatively low spasmolytic activity in the test of isolated rat duodenum toward acetylcholine spasms. They are thus practically ineffective in tests applied with antiparkinsonics, differing in this respect from orphenadrine (*VII*) (ref.[4,5]).

EXPERIMENTAL**

The melting points of analytical preparations were estimated in a Kofler block. The samples were dried for 8 h in *vacuo* (c. 0·2 Torr) over phosphorus pentoxide at temperatures adequate to the melting point of the substance (at most 100°C). The IR spectra were recorded on a Zeiss UR-10 spectrometer.

1-Phenyl-1-(2-methylthiophenyl)ethanol (*XI*)

Reaction of 40·6 g *o*-bromothioanisol (b.p. 156—159°C/30 Torr) (ref.[6]) with 4·9 g magnesium in 100 ml ether yielded the Grignard reagent (the reaction was initiated with a crystal of iodine and two drops of ethyl bromide and the mixture was refluxed for 90 min). The reagent was treated dropwise with 24 g acetophenone and the mixture was refluxed for 5 h. After cooling it was decomposed with a 20% solution of ammonium chloride, extracted with benzene and the combined organic phases were distilled: 27·8 g (61%), b.p. 165°C/2 Torr. For $C_{15}H_{16}OS$ (244·3) calculated: 73·75% C, 6·60% H, 13·10% S; found: 74·06% C, 6·70% H, 12·83% S.

* The compound was obtained from Mr J. Lukáč, Léčiva, Prague.

** The experiments were carried out in 1960—1963.

1-Phenyl-1-(2-tolyl)ethanol (*IX*)

This was prepared similarly to compound *XI* in a 35% yield; b.p. 165—175°C/15 Torr. For $C_{15}H_{16}O$ (212·3) calculated: 84·87% C, 7·60% H; found: 85·06% C, 7·56% H.

1-Phenyl-1-(2-chlorophenyl)ethanol (*X*)

It was prepared similarly to the foregoing compounds. In a yield of 50% a crude product was obtained, boiling at 132—139°C/1·5 Torr which was treated further in this state.

1-Phenyl-1-(2-methoxyphenyl)ethanol (*XII*)

Similarly to the preparation of *XI*, a total of 18·7 g *o*-bromoanisol (b.p. 215—220°C/760 Torr) (ref.[7]) and 12 g acetophenone were used in the reaction. The yield was 9·6 g (27%) of a product boiling at 140—145°C/1·5 Torr, m.p. 76—78°C (light petroleum). IR spectrum (chloroform): 697 (monosubstituted benzene), 763 (monosubstituted and 1,2-disubstituted benzene), 1240 and 2839 (OCH_3), 1129, 1359 (tert OH), 1495, 1590, 1607 (Ar), 3560 cm^{-1} (OH in intramolecular hydrogen bond).

1-Phenyl-1-(2-tolyl)-1-(2-dimethylaminoethoxy)ethane (*IV*)

A mixture of 14·8 g alcohol *IX*, 110 ml benzene and 6·0 g sodium amide was refluxed for 2 h. After partial cooling, 22·0 g 2-dimethylaminoethyl chloride was added dropwise and the mixture was refluxed under stirring for 8 h. After cooling, it was decomposed with 250 ml ice-cold water and extracted with benzene. Distillation of the extract yielded 8·7 g (44%) product boiling at 135—145°C/2 Torr. For $C_{19}H_{25}NO$ (283·4) calculated: 80·52% C, 8·89% H, 4·94% N; found: 80·03% C, 8·98% H, 5·15% N.

The *hydrochloride* was prepared from the base by treatment with hydrogen chloride in ether; m.p. 162—163°C (acetone). For $C_{19}H_{26}ClNO$ (319·8) calculated: 71·35% C, 8·19% H, 4·36% N, 11·10% Cl; found: 71·37% C, 8·41% H, 4·39% N, 11·11% Cl.

1-Phenyl-1-(2-chlorophenyl)-1-(2-dimethylaminoethoxy)ethane (*V*)

Similarly to the preceding case, 10·3 g alcohol *X* reacted with 3·9 g sodium amide and 9·7 g 2-dimethylaminoethyl chloride in 50 ml benzene to yield 10·4 g (75%) of a base with an unsharp boiling point of 145—165°C/3 Torr which was directly converted to the hydrochloride, m.p. 147—150°C (acetone). For $C_{18}H_{23}Cl_2NO$ (340·3) calculated: 63·53% C, 6·81% H, 4·12% N, 20·84% Cl; found: 63·64% C, 6·98% H, 4·14% N, 20·57% Cl.

1-Phenyl-1-(2-methylthiophenyl)-1-(2-dimethylaminoethoxy)ethane (*VI*)

Similarly to the preceding cases, reaction of 12·2 g alcohol *XI* with 5·4 g 2-dimethylaminoethyl chloride yielded 10·4 g of an oily base boiling at 155—165°C/1·5 Torr. *Hydrochloride*, m.p. 153—155°C (acetone–ether). For $C_{19}H_{26}ClNOS$ (351·9) calculated: 3·98% N, 9·11% S, 10·07% Cl; found: 4·02% N, 9·24% S, 10·18% Cl.

Molecular Complex of Base *I* and Alcohol *VIII*

A. *From preparation of ether* I: During preparation of ether *I* by a reaction of 1,1-diphenylethanol (*VIII*) with 2-dimethylaminoethyl chloride hydrochloride in benzene in the presence of sodium hydroxide (procedure according to[9]), concentration of the benzene solution resulted in a crystalline substance which was twice recrystallized from light petroleum, m.p. 51°C. IR spectrum (Nujol): 703, 762, 777 (monosubstituted benzene), 918, 932, 947, 1031, 1042, 1059, 1070, 1088 (C—O—C), 1498, 1570 and 1605 cm^{-1} (Ar). For $C_{32}H_{37}NO_2$ (467·6) calculated: 82·19% C, 7·98% H, 3·00% N; found: 82·67% C, 8·11% H, 3·25% N. Upon treatment with hydrogen chloride the molecular complex is dissociated, giving rise to hydrochloride of base *I*, m.p. 163—165°C (for analytically pure hydrochloride ref.[8] gives 168°C).

B. *From the components*: A mixture of 1·98 g alcohol *VIII* and 2·69 g base *I* was heated at 100°C to achieve complete homogenization. Upon cooling, a glassy substance was formed which was recrystallized from 5 ml light petroleum to yield 4·0 g substance melting at 50—52°C (without depression in admixture with the product from procedure *A*). The complex dissociates during crystallization from a larger volume of light petroleum giving rise to alcohol *VIII* with m.p. 81°C (see ref.[8]).

1-Phenyl-1-(4-bromophenyl)-1-(2-dimethylaminoethoxy)ethane (*II*)

Picrate, m.p. 100°C (ethanol). For $C_{24}H_{25}BrN_4O_7$ (561·4) calculated: 51·34% C, 4·49% H, 9·98% N; found: 51·70% C, 4·79% H, 10·15% N.

The molecular compound with 8-chlorotheophylline was obtained by five-hour refluxing of a solution of 51g base *II* (ref.[1]) in 300 ml ethanol with 30 g 8-chlorotheophylline; cooling resulted in 60 g (74%) crystalline product melting at 158—160°C (ethanol). Treatment of the mother liquor yielded a further fraction. For $C_{25}H_{29}BrClN_5O_3$ (562·9) calculated: 53·35% C, 5·19% H, 12·45% N; found: 53·61% C, 5·45% H, 12·30% N,

1-Phenyl-1-(4-fluorophenyl)-1-(2-dimethylaminoethoxy)ethane (*III*)

Hydrogen succinate, m.p. 105—106°C (acetone–ether). For $C_{22}H_{28}FNO_5$ (405·4) calculated: 65·17% C, 6·96% H, 3·45% N; found: 65·11% C, 7·10% H, 3·79% N.

Decomposition of the pure hydrogen succinate with aqueous ammonia and extraction with ether resulted in the base, b.p. 123°C/0·5 Torr. For $C_{18}H_{22}FNO$ (287·4) calculated: 75·24% C, 7·71% H, 4·87% N, 6·61% F; found: 75·18% C, 7·79% H, 5·12% N, 6·91% F.

The analytical estimations were done at the analytical department of this Institute (headed by Dr J. Körbl) by Mrs J. Komancová, V. Šmídová, E. Vaníčková, E. Dvořáková, M. Aixnerová, J. Schmidtová. The IR spectra were recorded and interpreted by Dr E. Svátek of the physico-chemical department of this Institute. The authors are indebted for technical assistance to Mrs M. Hrubantová.

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REDUCTION OF SECONDARY *p*-TOLUENESULPHONYLOXY GROUPS WITH LITHIUM ALUMINIUM HYDRIDE IN SUGAR SERIES. II.* **

REDUCTION OF α- AND β-METHYL-4,6-O-BENZYLIDENE-2,3-DI-O-*p*-TOLUENESULPHONYL-D-GALACTOPYRANOSIDE

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In our previous work[1] we studied reduction of secondary toluenesulphonyloxy groups with lithium aluminium hydride. We have found that the secondary toluenesulphonyl group may be reduced to the deoxy stage provided there is a suitably located group which can form an alkoxyaluminium hydride and thus enable an intramolecular reduction. Such a group may be a neighbouring ester or hydroxy group, *trans* to the tosyloxy group which is reduced: this we demonstrated by several successful reductions of 2- and 3-tosyloxy groups in sugar derivatives of the *gluco* series. It was of interest to know to what extent this reduction is influenced by steric arrangement of the whole molecule and we decided therefore to study the reduction of stereoisomeric *galacto* compounds. In the *gluco* series[1] it was the 2,3-ditosyl derivative *Ia* which afforded the appropriate deoxy compound in highest yield and for this reason we chose for the reduction study the analogous ditosyl galactoside *IIa* which differs only in the configuration on $C_{(4)}$ and which might give either 3-deoxy or 2-deoxy derivative. We performed reduction of the tosyl derivative *IIa* under the same conditions as in the case of the glucoside *Ia* but from the reaction mixture we isolated, in addition to the starting ditosyl derivative *IIa*, only the 2-O-tosylgalactoside *IIb* and the benzal derivative *IIc*. As shown by thin-layer chromatography, in several chromato-

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** Dedicated to the memory of Professor R. Lukeš (deceased 1960).