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The Effects of Alkyl Substitution in Drugs— I. Substituted Dimethylaminoethyl Benzhydryl Ethers

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The relation between chemical structure and biological activity is still the central problem of drug research. Formerly, the solution of this problem was sought in the classification of various atoms and atom groups in a system of therapogenic groups, each making a specific contribution to the therapeutic effect of the drug in the molecule in which these groups were present.

This view distracted attention from the fact that compounds which differ considerably in chemical constitution often show very similar activities; it was also at variance with the observation that introduction of a so-called 'neutral' group, e.g. a methyl group, often was by no means ineffectual, but on the contrary induced profound alterations in the activity sphere of the compound in question, although not always in a negative sense, as Fraenkel[1] was led to believe: 'die Methylgruppe wirkt im allgemeinen dystherapeutisch'.

On the other hand, the marked influence of small alterations in chemical structure on biological activity emphasized the strong specificity of certain structures. For a long time, therefore, pharmacological knowledge has been extended by the occasional emergence from the almost countless new chemicals synthesized and pharmacologically tested, of a compound with remarkable properties and active in one or more fields, which was then immediately made to serve as a model for large numbers of new derivatives.

Experience with these large numbers of compounds, grouped in longer or shorter series, gradually led to the formulation of

* The main part of this work was made the subject of an academical thesis, Vrije Universiteit, Amsterdam, 1956.

requirements to be met by a compound if certain biological activities were to be present. These requirements, however, frequently proved to be only approximately correct; convulsants, for example, being produced when sedatives were expected and vice versa. Gradually, however, efforts to define more specifically the structures required for activity became more successful, especially owing to the mutual comparison of data from different groups of compounds.

A good example is found in the developments in the field of the plant growth regulators.[2] Here a large variety of analytical methods (tensiometry, ultraviolet spectrophotometry, dipole moment measurements, etc.) have eventually yielded enough data about the shape of the active molecules and about other limiting factors, e.g. the balance between lipophilic and hydrophilic parts of the molecule, to make possible the more than merely descriptive formulation of requirements. The synthesis of a number of active compounds, such as 1,2,3,4-tetrahydro-1-naphthoic acid and 2-chloro-1-naphthoic acid, was motivated by basic information so acquired, although the deplorable situation remains that much of the nature of the action proper still eludes us. In the field of the synthetic analgesics, also, a more definite picture was obtained of the shape, not only of the active compound, but also of the receptor site (Beckett[3]), while the first steps have already been taken towards an understanding of the mechanisms of the action,[3–5] a result which could only be reached by considering the joint aspects of compounds from differing groups.

Although the examination of series of substituted derivatives of a parent compound is made in these investigations, this certainly does not mean that we want to put the clock back and to search for 'active substituents'; rather we hope to shed some more light on the fundamental relations between drug and living cell by modifying the shape of, and the charge distribution in, a parent compound by carefully controlled molecular variations.

Although the literature abounds with investigations of series of compounds which are substituted derivatives of a parent compound, it would seem that systematic investigations into the effect of alkyl substitution in phenyl groups are rather infrequent. A collection of data on the effect of such substitution, from investigations of the last decade or so, is recorded in Table I.

From the table it is clear that introduction of one of more alkyl groups into the phenyl group(s) may or may not influence the activity significantly. In local anaesthetics, for example, Büchi[18] has indicated that physico-chemical properties such as solubility, membrane and phase boundary potentials, surface activity, etc., which determine to a large degree the absorption and distribution of the drug, predominate over all other aspects of the effect of alkyl substitution upon the efficacy of the drug.

On the other hand, activity often appears to be influenced to a much larger extent than would be expected on the basis of the 'neutral' character of these substituents. When this is the case with *ortho*-substitution, one is inclined to hold steric effects primarily responsible, although inductive effects may also play a role; the question of the relative importance of the effects appears to be as yet unsolved.

Stereospecificity, which sometimes implies large differences in activity even between optical antipodes (e.g. adrenaline), directs the attention to the final reaction between drug and receptor site as the determining factor. In such cases, the hope may be cherished that a closer definition will be attainable of the shape of the 'ideal drug', of the receptor site itself, or even of the processes taking place upon or immediately after the formation of the drug–receptor complex.

In view of the relative neglect which, as mentioned earlier, the systematic investigation of the influence of alkyl substitution seems to have suffered, we aimed to fill some gaps by synthesizing several series of alkyl substituted compounds and investigating their pharmacological properties, especially in those fields where stereospecificity might be expected.

An additional advantage of substitution of the type envisaged is that the variations are introduced into that part of the molecule (the phenyl group(s)), where in all probability they do not essentially affect the ability of the drug to reach the site of action. In this way the activity proper will not be greatly obscured by differences in absorption or transportation.

Diphenhydramine Derivatives

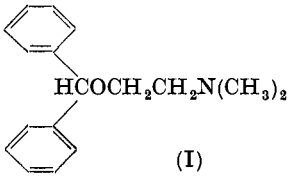
The compound used as a starting point for our first series was β-dimethylaminoethyl benzhydryl ether (I), a compound synthe-

Table. I. Some examples of the influence of alkyl substitution on biological activity

Parent compound	Mode of action	Substituent	Activity of substituted compound (parent = 1)	Author
Phenylacetylurea	anticonvulsant	2-methyl	none	M. A. Spielman[6]
		4-methyl	less	
		4-ethyl	very slight	
2-Chloroethyldibenzylamine	adrenergic blockade	2,2′-dimethyl	much less	M. Nickerson[7]
		4,4′-diethyl	none	
2-Chloroethylbenzylphenoxy-isopropylamine	adrenergic blockade	2-methyl	1·0	G. E. Ullyot[8]
		3-methyl	0·4–1·0	
(substituted in the phenoxy-group)		4-methyl	0·1–0·4	
		3,4-dimethyl	0·4–1·0	
		2-isopropyl-5-methyl	0·4–1·0	
		2-isopropyl	1·0	
Benzylsulphonamide	chemotherapeutic	2,3-dimethyl	none	P. Läuger[9]
		2,4-dimethyl	none	
		2,5-dimethyl	none	
		3,4-dimethyl	good	
		3,5-dimethyl	slight	
α,β-Di(diethylamino)propionanilide	local anaesthetic (surface anaesthesia)	2-methyl	2·0	H. Weidmann, P. V. Petersen[10]
		2,6-dimethyl	3·0	
		2-ethyl	0·16	
		2-isopropyl	0·23	

2-Amino-1-phenylpropane	stimulant	2-methyl	0·27	D. F. Marsh,
		3-methyl	0·40	D. A. Herring[11]
		4-methyl	0·13	
		2,5-dimethyl	0·06	
		3,4-dimethyl	0·20	
4-Acetoxy-4-phenyl-*N*-*n*-butyl-piperidine	analgesic	2-methyl	0·08	R. H. K. Foster,
		3-methyl	0·2	A. J. Carman[12]
		4-methyl	0·02	
3-Methyl-4-phenyl-4-propionoxy-*N*-methylpiperidine (*trans*)	analgesic	2-methyl	0·42	A. H. Beckett *et al.*[13]
		3-methyl	0·25	
		4-methyl	0·75	
3-Methyl-4-phenyl-4-acetoxy-*N*-(β-phenylethyl)piperidine (*trans*)	analgesic	2-methyl	3·44	A. H. Beckett *et al.*[5]
		3-methyl	0·46	
		4-methyl	0·23	
Diethylaminoacetanilide	local anaesthetic	2-methyl	1·25	N. Löfgren[14]
		3-methyl	1·33	
		4-methyl	0·80	
		2,3-dimethyl	0·90	
		2,4-dimethyl	1·00	
		2,5-dimethyl	1·06	
		2,6-dimethyl	1·80	
		3,4-dimethyl	1·14	
		3,5-dimethyl	1·55	
		2,4,6-trimethyl	1·77	
β-Phenylethyl-methylamine	vasopressor	2-methyl	0·5	A. M. Lands[15]
		3-methyl	1·0	
		4-methyl	1·0	
β-Diethylaminoethyl 4-amino-benzoate	local anaesthetic	2-methyl	8·0	J. Büchi[16]
		3-methyl	2·0	
β-Dimethylaminoethyl α-phenyl-α-pyridyl-2-ethyl ether	antihistaminic	2-methyl	0·01	C. H. Tilford *et al.*[17]
		3-methyl	0·1	
		4-methyl	1·0	
		3,4-dimethyl	0·05	

sized by Rieveschl[19] in 1944, introduced as an antihistaminic in 1945 and since known under the trade names Benadryl ® and Benodine ® and under the generic name diphenhydramine.



(I)

Diphenhydramine

The original authors (Rieveschl,[20] Loew[21]) tried to enhance activity by substitution, but their first reports on the influence of substitution into the phenyl groups were unfavourable. The present authors[22] concluded that introduction of a methyl group at the *para* position in one of the phenyl groups enhanced antihistaminic activity, a result which was corroborated in an independent and more extensive investigation by Chen *et al.*,[23] who in 1954[24] published a further report on the pharmacological properties of diphenhydramine and a number of its derivatives.

Büchi *et al.*[25] investigated a number of similar compounds, including the 4-ethyl derivative of diphenhydramine. They did not succeed in finding substances with an activity equal to that of diphenhydramine itself, but the 4-ethyl compound was only slightly less active as an antihistaminic, whilst its anticholinergic potency was also found to be almost equal to that of the parent compound. This result contrasts rather strongly with the results of Chen *et al.*[23,24]: that the anticholinergic activities of these compounds are in the ratio 1 : 20.

As asymmetrically substituted benzhydryl ethers show optical isomerism, it is of interest to note that the two stereoisomers of β-dimethylaminoethyl 4-methylbenzhydryl ether were found by Jarrousse and Régnier[26] to differ in antihistaminic activity, the (+)- isomer being three to four times as potent as the (−)-isomer. As diphenhydramine also possesses antiacetylcholine activity, an investigation into the influence of alkyl substitution on this property was clearly required, the more so as Swiss scientists[27] independently and simultaneously with Rieveschl developed

the closely related β-diethylaminoethyl benzhydryl ethers for use as spasmolytics. Although many compounds have been investigated for atropine-like activity, notably esters of carboxylic acids with aliphatic or cyclic aminoalcohols, it would seem that most authors have confined themselves to an examination of variations in the alcohol, even if the acid in question contained phenyl groups.

Authors who did investigate the influence of alkyl substitution, like Domenjoz[28] who examined the *ortho*, *meta* and *para* methyl substituted derivatives of diethylaminoethyl 1-phenylcyclopentane-1-carboxylate, in general obtained negative results, which, as Baltzly[29] remarks, led to the general belief that nuclear substitution is undesirable in a spasmolytic. From his own work on quaternary salts of benzhydryl piperazines, Baltzly concludes that *ortho* halogen substitution may, however, lead to very useful compounds.

The occurrence of strong stereospecificity in this field is indicated by the fact that the spasmolytic activity of 1-phenyl-1-cyclohexyl-3-piperidinopropanol-1 (Artane) and of several of its derivatives is reported by Duffin and Green [30] to be almost entirely due to the laevo-rotatory isomer. This was also the case with the spasmolytics studied by Fromherz[31] and by Sternbach and Kaiser.[32]

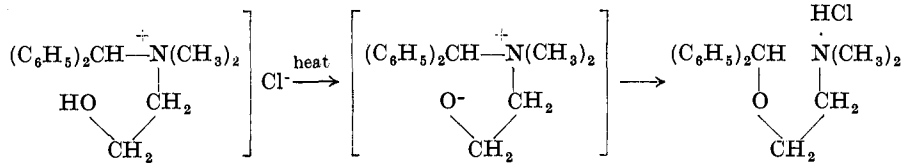
Materials and Methods

Chemical Section

In general, the β-dimethylaminoethyl benzhydryl ethers were prepared by the reaction of a benzhydryl halide with dimethylaminoethanol, the hydrogen halide formed being bound either (A) by excess aminoalcohol or (B) by the resulting aminoether itself when reactants were used in equimolecular amounts, preferably in an inert solvent of not too low polarity.

A further method[33] of preparation (C) consisted of heating the dimethyl-2-hydroxyethyl-benzhydrylammonium chlorides either alone or in an inert solvent, e.g. 1,2-dichlorobenzene; these quaternary ammonium compounds were prepared when an equimolecular mixture of a benzhydrylchloride and dimethylaminoethanol is left standing at room temperature. This type of

rearrangement seems to be related to those reactions which proceed, like the Stevens and the Sommelet rearrangement, by way of so called Ylide structures (Wittig[34]):



The substituted benzhydryl chlorides used were prepared according to Norris and Blake[35] from the corresponding benzhydrols, which in their turn were synthesized by a Grignard reaction between a substituted benzaldehyde and an arylmagnesium bromide or by reduction of the corresponding ketone.

Experimental

The substituted benzhydryl ethers prepared in this investigation are recorded in Table II. The details concerning the required intermediates are described below; the numbers correspond to those used for the final compounds in Table II.

Compound 1. Benzhydryldimethyl β-hydroxyethylammonium chloride was prepared by mixing benzhydryl chloride (50·5 g) and dimethylaminoethanol (22 g) and allowing to stand overnight. The resulting mass was crystallized from an ethanol–ether mixture as colourless crystals, m.p. 129–131°: yield 65 g (90 per cent). *Anal.* Calcd. for $C_{17}H_{22}ClNO$: Cl, 12·18. Found: Cl, 11·92.

When a solution of this compound (14 g) in anhydrous methanol (30 ml) was heated with potassium hydroxide (2·8 g), potassium chloride precipitated. After filtration, the solvent was evaporated in vacuo and the resulting syrupy residue was heated, ultimately to 180°. The mass boiled violently and when no more gases were evolved, the molten mass was cooled, and the resultant solid crystallized from alcohol to yield β-dimethylaminethyl benzhydryl ether m.p. and mixed m.p. with an authentic sample 68–69°.

Compound 2. In the same way 2-methylbenzhydryl dimethyl β-hydroxyethylammonium chloride was prepared: m.p. 116–120°.

Table II. Substituted β-dimethylaminoethyl benzhydryl ethers $(C_6H_5)_2CHOCH_2CH_2N(CH_3)_2.HX$

Compound	Substituents on the rings	HX	m.p. °C	b.p. (base) °C/mm	Calcd. C	Calcd. H	Found C	Found H	Method of synthesis
1	None	HCl	166–168						B, C
2	2-methyl	HCl	154–156	190/12	70·69	7·91	70·44	7·82	A, B, C
3	3-methyl	HCl	131–133		70·69	7·91	70·30	7·74	B, C
4	4-methyl	HCl	149–151	140/0·1	70·69	7·91	70·60	7·80	B, C
5	2,3-dimethyl	HCl	179–181		71·34	8·20	70·63	8·27	B
6	2,6-dimethyl	HCl	164–165	168–175/5	71·34	8·20	71·82	8·35	A, B
7	2,2′-dimethyl	HCl	200–201		71·34	8·20	71·15	8·17	A, B
8	2,4′-dimethyl	maleic acid	119–121		69·20	7·32	68·84	7·33	A
9	3,3′-dimethyl	maleic acid	120–121		69·20	7·32	69·06	7·24	B, C
10	3,5-dimethyl	HCl	138–140		71·34	8·20	71·44	8·17	A
11	4,4′-dimethyl	HCl	164–166		71·34	8·20	70·98	8·13	A, B
12	2-ethyl	maleic acid	86– 90		69·20	7·32	68·79	7·46	A, B
13	4-ethyl	HCl	103–107		71·34	8·20	71·26	8·20	B, C
14	2,6,2′-trimethyl	maleic acid	149–152		69·71	7·56	69·61	7·89	A
15	2,6,4′-trimethyl	HCl	176–177		71·95	8·45	71·71	8·28	A
16	2-*n*-propyl	oxalic acid	97– 99		68·19	7·54	67·33	7·67	A
17	2-isopropyl	HCl	132–134		71·95	8·45	71·71	8·41	A
18	4-isopropyl	maleic acid	130–132	145/0·1	69·71	7·56	69·40	7·35	A, B
19	2,3,5,6-tetramethyl	HCl	203–205		72·50	8·69	72·42	8·65	A
20	2,6,2′,6′-tetramethyl	HCl	185–186	190–195/3	72·50	8·69	72·89	8·90	A
21	3,5,3′,5′-tetramethyl	HCl	182–183		72·50	8·69	71·85	8·82	A
22	2-*n*-butyl	oxalic acid	95– 98		68·80	7·78	68·14	7·82	A
23	2-isobutyl	oxalic acid	100–102		68·80	7·78	67·94	7·59	A
24	2-*sec*-butyl	oxalic acid	94– 96		68·80	7·78	68·69	7·78	A
25	2-*tert*-butyl	HCl	179–180		72·50	8·69	72·48	8·70	A
26	4-*tert*-butyl	maleic acid	113–115	145/0·1	70·23	7·78	69·71	7·50	A, B
27	2-*n*-amyl	oxalic acid	112–114		69·37	8·00	69·46	8·16	A
28	2-*tert*-amyl	HCl	177–180		73·00	8·92	73·02	8·81	A
29	2,4,6,2′,4′,6′-hexamethyl	maleic acid	139–141		71·18	8·19	70·72	8·13	
30	2,3,5,6,2′,3′,5′,6′-octamethyl	oxalic acid	175–177		71·96	8·55	70·89	8·59	A

Anal. Calcd. for $C_{18}H_{24}ClNO$: Cl, 11·62. Found: Cl, 11·86. β-Dimethylaminoethyl 2-methylbenzhydryl ether hydrochloride was prepared by way of method A in the following manner.

A mixture of 2-methylbenzhydryl chloride (80 g) and dimethylaminoethanol (70 g) was heated to a temperature of 130–140° for 1 h. Two layers formed and the lower layer, consisting of dimethylaminoethanol hydrochloride, solidified on cooling. The upper layer was dissolved in ether (250 ml) and the ethereal solution was washed twice with 50 ml portions of water and dried over anhydrous potassium carbonate. After evaporation of the ether, the base was fractionated, b.p. 195°/12 mm: yield 85 g (75 per cent).

The distilled base was dissolved in ethanol (100 ml) and neutralized with an ethanolic solution of hydrochloric acid. The solution of the hydrochloride thus obtained was poured into about 1,200 ml of ether. The salt precipitated and was filtered off, m.p. 154–156°.

Compound 3. 3-Methylbenzhydryl dimethyl β-hydroxyethyl ammonium chloride melted at 155–158°. *Anal.* Calcd. for $C_{18}H_{24}ClNO$: Cl, 11·62. Found: Cl, 11·60.

Compound 4. 4-Methylbenzhydryl dimethyl β-hydroxyethyl ammonium chloride melted at 95–99°. *Anal.* Calcd. for $C_{18}H_{24}ClNO$: Cl, 11·62. Found: Cl, 11·40.

An illustration of method B is given in the following description of the preparation of β-dimethylaminoethyl 4-methylbenzhydryl ether hydrochloride. A mixture of 4-methylbenzhydryl chloride (110 g) and dimethylaminoethanol (45 g) was added dropwise to boiling 1,2-dichlorobenzene (250 ml). When all was added (45 min) the reaction mixture was refluxed for another 15 min. The crystals which separated on cooling were filtered off and washed three times with 50 ml portions of ether. Then the crude product was dissolved in a hot mixture of acetone (150 ml) and ethanol (50 ml). The solution was treated with activated charcoal and filtered. About 350 ml of ether was slowly added with stirring, following which the turbid solution was stored overnight in a refrigerator. The crystal mass was filtered off and was washed with ether (50 ml): m.p. 149–151°; yield 105 g (70 per cent). Rieveschl[19] reported: m.p. 143–144·5°.

Compound 6. 2,6-Dimethylbenzhydrol was obtained by

coupling benzaldehyde with 2,6-dimethylbromobenzene (from 2,6-dimethylaniline, diazotized in hydrobromic acid and treated with copper bronze (Coops *et al.*[35])); m.p. 64°. *Anal.* Calcd. for $C_{15}H_{16}O$: C, 84·87; H, 7·60. Found: C, 85·20; H, 7·67. 2,6-Dimethylbenzhydryl chloride; b.p. 175–177°/18 mm. *Anal.* Calcd. for $C_{15}H_{15}Cl$: Cl, 15·4. Found: Cl, 15·2.

Compound 8. 2,4′-Dimethylbenzhydryl chloride; b.p. 175–176°/14 mm. *Anal.* Calcd. for $C_{15}H_{15}Cl$: Cl, 15·4. Found: Cl, 15·2.

Compound 10. 3,5-Dimethylbenzhydrol was prepared from benzaldehyde and 3,5-dimethylbromobenzene; m.p. 49°, b.p. 138°/0·1 mm. *Anal.* Calcd. for $C_{15}H_{16}O$: C, 84·87; H, 7·60. Found: C, 84·73; H, 7·64. 3,5-Dimethylbenzhydryl chloride; b.p. 158–160°/5 mm.

Compound 12. 2-Ethylbenzhydryl chloride; b.p. 174–176°/12 mm. *Anal.* Calcd. for $C_{15}H_{15}Cl$: Cl, 15·4. Found: Cl, 15·6.

Compound 13. 4-Ethylbenzhydryl dimethyl β-hydroxyethyl ammonium chloride; m.p. 96 – 100°. *Anal.* Calcd. for $C_{19}H_{26}ClNO$: Cl, 11·11. Found: Cl, 10·93.

To synthesize β-dimethylaminoethyl 4-ethylbenzhydryl ether hydrochloride by way of method C, the above chloride (30 g) was heated to 180°. On cooling, the mass solidified and after two crystallizations from ethanol–ether had m.p. 103–107°; yield 25 g (80 per cent).

Büchi[25] reported b.p. 114°/0·001 mm for the corresponding base.

Compound 15. 2,6,4′-Trimethylbenzhydrol was prepared from 4-methylbenzaldehyde and 2,6-diinethylbromobenzene; b.p. 156°/1 mm. 2,6,4′-Trimethylbenzhydryl chloride: *Anal.* Calcd. for $C_{16}H_{17}Cl$: Cl, 14·5. Found: Cl, 14·9.

Compound 16. 2-Propylbenzhydrol (b.p. 145°/0·1 mm) was obtained from benzaldehyde and 2-bromopropylbenzene [prepared from 2-bromobenzyl bromide (Goerner and Nametz[37]) and diethyl sulphate, in a way analogous to the preparation of propylbenzene[38]]; b.p. 100°/18 mm; yield 20 per cent.

Anal. Calcd. for $C_{16}H_{18}O$: C, 84·91; H, 8·02. Found: C, 83·96; H, 8·27.

Compound 17. 2-Bromocumene was prepared according to Crawford and Stewart.[39] The Grignard compound with benzaldehyde yielded the benzhydrol, b.p. 140°/3 mm. *Anal.* Calcd. for $C_{16}H_{18}O$: C, 84·91; H, 8·02. Found: C, 84·41; H, 8·22.

2-isoPropylbenzhydryl chloride: *Anal.* Calcd. for $C_{16}H_{17}Cl$: Cl, 14·5. Found: Cl, 14·6.

Compound 22. 2-Bromo-*n*-butylbenzene was prepared from 2-bromobenzyl bromide and propyl *p*-toluene sulphonate (Hahn and Walter[40]), in a way analogous to the preparation of *n*-amylbenzene,[41] purified by steam distillation and by washing with concentrated sulphuric acid, and distilled to yield 30 per cent of a product with b.p. 114°/18 mm. The corresponding benzhydrol, m.p. 49°, was obtained by reaction of the Grignard compound with benzaldehyde. *Anal.* Calcd. for $C_{17}H_{20}O$: C, 84·95; H, 8·39. Found: C, 84·85; H, 8·46. 2-*n*-Butylbenzhydryl chloride. *Anal.* Calcd. for $C_{17}H_{19}Cl$: Cl, 13·7. Found: Cl, 13·3.

Compounds 23, 27. 2-isoButylbenzhydrol and 2-*n*-amylbenzhydrol were prepared in the same way as 2-*n*-butylbenzhydrol, starting from 2-bromobenzylmagnesium bromide and isopropyl *p*-toluene sulphonate, or *n*-butyl *p*-toluene sulphonate. 2-Bromoisobutylbenzene, b.p. 113°/19 mm; 2-isobutylbenzhydrol, b.p. 144°/0·5 mm. 2-Bromo-*n*-amylbenzene, b.p. 128°/19 mm; 2-*n*-amylbenzhydrol, b.p. 195–200°/17 mm.

Compounds 24, 25 and 28. 2-Bromo-*tert*-butylbenzene was prepared according to Crawford and Stewart[39] and this method was followed also for 2-bromo-*sec*-butyl- and 2-bromo-*tert*-amylbenzene. The b.p. of the intermediates were as follows: 4-nitro-*sec*-butylbenzene: b.p. 150–160°/18 mm, 4-nitro-*tert*-amylbenzene: b.p. 158°/7 mm, 2-bromo-4-nitro-*sec*-butylbenzene: b.p. 107°/0·1 mm, 2-bromo-4-nitro-*tert*-amylbenzene: b.p. 98°/0·05 mm, 3-bromo-4-*sec*-butylaniline: b.p. 150–160°/16 mm, 3-bromo-4-*tert*-amylaniline: b.p. 154°/18 mm, 2-bromo-*sec*-butylbenzene: b.p. 118–120°/20 mm, 2-bromo-*tert*-amylbenzene: b.p. 120°/18 mm, 2-*sec*-butylbenzhydrol: b.p. 128–132°/0·05 mm (Lamneck and Wise[42]; b.p. 142–148°/4 mm).

2-*tert*-butylbenzhydrol: m.p. 96°. *Anal.* Calcd. for $C_{17}H_{20}O$: C, 84·95; H, 8·39. Found: C, 84·42; H, 8·23.

2-*tert*-amylbenzhydrol: m.p. 92°. *Anal.* Calcd. for $C_{18}H_{22}O$: C, 84·99; H, 8·72. Found: C, 84·93; H, 8·89.

2-*tert*-butylbenzhydryl chloride: m.p. 87°. *Anal.* Calcd. for $C_{17}H_{19}Cl$: Cl, 13·7. Found: Cl, 13·8.

2-*tert*-amylbenzhydryl chloride: b.p. 130°/0·01 mm.

Compound 29. To prepare β-dimethylaminoethyl 2,4,6,2′,4′,6′-

hexamethylbenzhydryl ether maleate we had to resort to still another method as the hexamethylbenzhydryl chloride is prone to disproportionation when heated with dimethylaminoethanol. The ether was therefore prepared by way of the 2-chloroethyl ether in the following manner: 2,4,6,2′,4′,6′-hexamethylbenzhydrol (6·5 g) was dissolved in 2-chloroethanol (25 ml) and heated to boiling after addition of 2 ml of concentrated hydrochloric acid. After cooling the precipitate was filtered off and recrystallized from ethanol to give the 2-chloroethyl ether, m.p. 72–75°; yield 4·9 g (61 per cent). This material was heated in a sealed tube with liquid dimethylamine (20 ml) for 1½ h at 120°. After cooling, the tube was opened and the reaction mixture taken up in 100 ml of ether. Water was added to dissolve the dimethylammonium chloride formed. The ether layer was extracted with two portions of 25 ml of water and dried over anhydrous potassium carbonate. When an alcoholic solution of maleic acid was added to the dried ethereal solution, a precipitate was formed which was collected on a filter and crystallized from water, m.p. 139–141°; yield 2·5 g (50 per cent).

Compound 25 (*a*, *b*, *c*). To prepare the optical isomers of β-dimethylaminoethyl 2-*tert*-butylbenzhydryl ether, the base (m.p. 69–70·5°) was dissolved in ethanol and an equimolecular amount of D-tartaric acid added. Upon the addition of ether, an oil separated which afterwards solidified. Several crystallizations from ethanol–ether mixtures were necessary to obtain the laevo-rotatory component. The dextro-rotatory component could be isolated in the same manner from the combined mother liquors.

The difference in solubility between the diastereoisomers is apparently small, as it has several times been observed that the isomer present in the higher concentration separated first.

Racemic D-*tartrate*, m.p. 106–108°, $[\alpha]^{20}$ +6·25° (*c*, 4·0 in water).

Laevo-rotatory D-*tartrate*, m.p. 122–123°, $[\alpha]_D^{20}$ −23·6° (*c*, 2·5 in water).

Dextro-rotatory D-*tartrate* m.p. 131–132°, $[\alpha]_D^{20}$ +36·5° (*c*, 4·0 in water).

Pharmacological Section

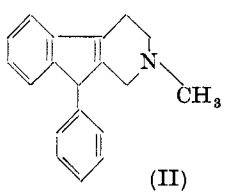
The compounds synthesized were screened for antihistaminic, anticholinergic, myotropic, spasmolytic and local anaesthetic

action in comparison with diphenhydramine and procaine respectively. The first three properties were assayed on the isolated guinea pig ileum, the concentrations being estimated which caused a 90–100 per cent reduction of the spasm produced by either histamine, acetylcholine or barium chloride. Local anaesthetic activity was determined by von Frey's method[43] on the rabbit cornea which was tested for the blink reflex at regular intervals with a series of hairs of increasing stiffness. The results are shown in Table III.

Discussion

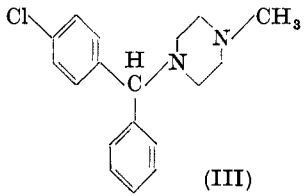
As may be seen from Table III, antihistaminic activity is generally decreased by alkyl substitution in benzhydryl ethers, with the exception of *para*-substitution in only one phenyl group. Compounds 4 and 13 have the greatest activity, whereas branching of the *para*-alkyl substituent (18 and 26) causes a decrease again. *Ortho* and *meta* substitution invariably decrease activity and, generally, more strongly so with increasing bulk or number of substituents (cf. 2 with 25 or 30, 3 with 21). The unfavourable influence of *ortho* substituents would seem to indicate that steric effects are at least partly responsible.

In view of the fact that several very active antihistaminics possess completely rigid or semi-rigid structures, the side chain either being fixed to one of the rings (II) (phenindamine), or able to rotate around one axis only (III) (chlorocyclizine), it would seem likely that *ortho* substituents weaken antihistaminic activity by



(II)

Phenindamine

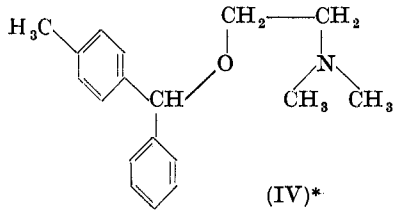


(III)

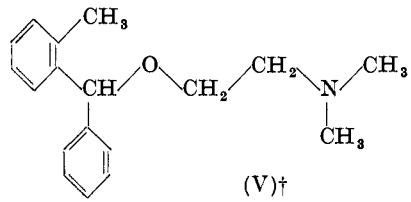
Chlorocyclizine

interfering with the possibility for the flexible side chain, as present in our series of ethers, to take the 'curled up' position, which in

the rigid structures mentioned is associated with high activity, c.f. (IV) and (V).



(IV)*



(V)†

* Neo-benodine, Toladryl

† Orphenadrine

As studies on Stuart Briegleb models indicate, the ability of a given molecule to imitate the spatial configuration of a molecule of the rigid type illustrated above appears to be inherent to practically all useful antihistaminics. The concept of a necessary close 'fit' at an antihistamine-receptor surface thus gains in strength, especially when we recall the earlier mentioned strong stereospecificity which was found by Jarrousse and Régnier[26] for the optical isomers of compound (IV).

The receptor site might be postulated to comprise an anionic site accommodating the basic centre, and a flat region at a more or less fixed distance, accommodating one of the aromatic rings which has to be approximately co-planar with the side chain. Just how the interaction between receptor and antihistaminic compound interferes with the mechanism of action of histamine remains, however, a problem which pharmacological screening methods are incapable of solving.

In our compounds, high antihistaminic activity appears to be incompatible with high anticholinergic activity. *Ortho* substitution has a favourable effect on the latter activity in nearly all cases, activity increasing with larger alkyl groups to reach a maximum with the 2-*tert*-butyl derivatives (compound 25). In view of the fact that the activity of this compound resides almost exclusively in the laevo-rotatory isomer, it must be assumed that this stereospecificity again is to be interpreted in terms of a 'fit' at a specific receptor surface. A bulky substituent like the *tert*-butyl group, while imparting high activity, sterically hinders 'curling up' of the side chain. The distance between the nitrogen

Table III. Pharmacological properties of alkyl substituted dimethylaminoethyl benzhydryl ethers

Compound	Substituents on the rings	HX	Spasmolytic action on guinea-pig ileum against			Local anaesthetic activity (Procaine=1)
			Histamine	Acetyl-choline	$BaCl_2$	
1	None	HCl	1	1	1	1
2	2-methyl	HCl	0·2	2·1	1·6	7
3	3-methyl	HCl	0·2	1·3	0·5	10
4	4-methyl	HCl	3·7	0·4	1·1	5
5	2,3-dimethyl	HCl	0·03	0·6	1·8	13
6	2,6-dimethyl	HCl	0·05	3·3	2·8	40
7	2,2′-dimethyl	HCl	0·09	1·3	0·9	35
8	2,4′dimethyl	maleic acid	0·4	0·7	0·4	10
9	3,3′-dimethyl	maleic acid	0·2	1·5	1·4	—
10	3,5-dimethyl	HCl	0·03	0·4	0·3	13
11	4,4′-dimethyl	HCl	0·5	0·7	1·1	5
12	2-ethyl	maleic acid	0·1	4·2	5·9	5
13	4-ethyl	HCl	2·4	0·4	1·4	4
14	2,6,2′-trimethyl	maleic acid	0·04	1·0	0·1	16
15	2,6,4′trimethyl	HCl	0·1	0·7	1·5	10

16	2-*n*-propyl	oxalic acid	0·1	4·9	0·7	4
17	2-isopropyl	HCl	0·1	6·5	1·3	4
18	4-isopropyl	maleic acid	1·4	0·4	2·3	—
19	2,3,5,6-tetramethyl	HCl	0·01	0·7	1·7	10
20	2,6,2′,6′-tetramethyl	HCl	0·06	1·8	3·6	200
21	3,5,3′,5′-tetramethyl	HCl	0·03	0·2	1·3	15
22	2-*n*-butyl	oxalic acid	0·07	5·5	0·6	50
23	2-isobutyl	oxalic acid	0·1	16·0	4·7	—
24	2-*sec*-butyl	oxalic acid	0·4	7·0	2·7	6
25	2-*tert*-butyl	HCl	0·05	33·0	2·4	30
26	4-*tert*-butyl	maleic acid	0·6	0·4	2·3	—
27	2-*n*-amyl	oxalic acid	0·1	1·7	0·7	14
28	2-*tert*-amyl	oxalic acid	0·07	18·0	3·1	5
29	2,4,6,2′,4′,6′-hexamethyl	maleic acid	0·02	0·8	0·5	50
30	2,3,5,6,2′,3′,5′,6′-octamethyl	oxalic acid	0·02	0·4	0·8	50
25a	2-*tert*-butyl (±)	D-tartaric acid	0·08	26·0	—	> 3[a]
b	2-*tert*-butyl (−)	D-tartaric acid	0·06	50·0	—	> 3[a]
c	2-*tert*-butyl (+)	D-tartaric acid	0·06	0·3	—	> 3[a]
	Atropine		—	±50	—	
	Papaverine		—	—	±6	

[a] The rabbits used differed from those used in the screening of compound 25 in requiring much greater doses of both procaine and the test substances. The racemic tartrate, its optical components and the hydrochloride were about equally active, but efforts to evaluate more exactly the local anaesthetic activity of 25 a, b and c were unsuccessful owing to the insensitivity of the animals.

atom and the central carbon atom thus approaches the maximum value of about 5 Å. This value corresponds with the dimensions given by Lands[44], who writes that in cholinolytic agents the distance between the nitrogen atom and the substituted terminal methane does not appear to be critical, but lies between 4 and 8 Å.

Although giving some indication about the myotropic spasmolytic activity of the compounds investigated, the antagonism against $BaCl_2$ does not lend itself very well to evaluating structure-activity relationships. In our series, papaverine-like activity certainly does not vary so widely as antihistaminic or anticholinergic activity, and no general conclusions can be reached as to the influence on papaverine-like activity of the introduction of substituents differing in location or dimension.

On all three aspects of spasmolytic activity, our results and conclusions generally agree with those of Chen and co-workers[23, 24] although differences in testing techniques may account for some discrepancies. However, their statement, 'as a series the alkyl substituted compounds produce less central effects',[24] although true as regards the prolongation of barbital-induced central depression in mice, appears to be too much of a generalization in view of the clinically established anti-Parkinson and other central effects of compound 2.[45]

A further property which many antihistaminics have in common is local anaesthetic potency. All compounds in our series show this activity to a greater or lesser degree. Diphenhydramine itself is least active, inhibiting the corneal blink reflex in the rabbit only in a concentration equal to that of procaine. *Ortho*-substituents however, impart a high activity, the 2,6,2′,6′-tetramethyl derivative (compound 20) being about 200 times as active as procaine in this test. No structure-activity relationships emerge however, which may indicate that, in accordance with current opinion,[18] no specific receptor surfaces are involved in local anaesthetic activity and that non-specific physico-chemical properties, such as lipoid solubility (Skou[46]) and distribution coefficients, play a predominant role.

Thus our investigation has shown that alkyl substitution in dimethylaminoalkyl benzhydryl ethers does influence the various pharmacological properties, and in different ways. All sorts of transitions from one type of activity to another occur. It is

shown that steric factors are of great significance both with regard to antihistamine and anticholinergic activity, the shape of the side chain ('curled up' or stretched) presumably playing an important role. The principal, though evidently not the only effect of the alkyl substituents in this series of compounds, is supposed to be their influencing the spatial configuration, especially with regard to the position of the side chain relative to the phenyl groups.

Summary. The possibility of obtaining more information about structure-activity relationships by studying extensive series of closely related substituted derivatives of a parent substance is discussed and exemplified by diphenhydramine and its alkyl substituted derivatives. The synthesis of thirty aminoethers of this type is described and the results of a pharmacological screening for antihistaminic, anticholinergic, myotropic, spasmolytic and local anaesthetic activity are given.

The 4-methyl derivative proved to be the most active antihistaminic of the series, anticholinergic activity being strongest in the laevo-rotatory isomer of the 2-*tert*-butyl compound. The 2-methyl derivative has found clinical application as an anti-Parkinson drug and in several other neurological and psychiatric disorders.

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