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The Conformations of Aromatic Ethers as Determined from their Ultraviolet Absorption Spectra

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A number of heterocyclic analogues of choline phenyl ether have been synthesised in order to investigate the relationship between conformation and biological activity in choline aryl ethers. The intensity of the Ph–O $\pi \longrightarrow \pi^*$ transition has been used to determine the angle (θ) between the plane of the benzene ring and the plane containing the oxygen bonds. The calculated angles increase in the order 2,3-dihydrobenzofuran < 2,3-dihydro-7-methylbenzofuran < chroman < homochroman; but the value of θ obtained for the 2,3-dihydro-7-methyl benzofuran is anomalously high and is explained on the basis of steric inhibition to sp^2 hybridisation of oxygen. Two β-methylated derivatives of choline phenyl ether bromide have also been investigated and the time-averaged values for θ calculated. It is deduced that unlike choline phenyl ether bromide these molecules are unable to adopt a conformation in which $\theta = 0°$.

THE pharmacological effects of choline phenyl ether bromide (VIIc) and choline 2,6-xylyl ether bromide (VIc) are strikingly different,[1] probably owing to the steric effect of the methyl groups in the latter, and it was of interest therefore to synthesise and examine a series of analogous compounds in which the conformation about the oxygen atom varies in a stepwise fashion. Baddeley *et al.*[2] examined the ultraviolet spectra, rates of bromination, and rates of solvolysis of the chloromethyl derivatives of 2,3-dihydrobenzofuran, chroman, homochroman, and 2,6-dimethylanisole, and concluded that increased buckling of the heterocyclic ring occurs through this series. The compounds (I)—(VI) [series a, b, and c, but excepting (Vb) and (Vc)] were therefore prepared and investigated. The quaternary ammonium compounds (I)—(IV)c were obtained from the corresponding carboxylic acids (I)—(IV)b by conversion into the *NN*-dimethyl-amides, reduction with lithium aluminium hydride, and quaternisation with methyl bromide. 8-Methylchroman-2-carboxylic acid (Vb) has not been reported, and it cannot be synthesised by a method analogous to that used [2a] for chroman-2-carboxylic acid owing to the non-availability of 8-methyl-1-tetralone. Other routes to the 8-methylchromans (Vb) and (Vc) have been tried, including catalytic hydrogenation of chromones over platinum black; this produced mixtures containing the required chromans but they could not be isolated sufficiently pure for ultraviolet spectroscopy. An intermediate reduction product, 2-dimethylaminomethyl-8-methylchroman-4-ol, was obtained pure and its spectrum recorded.

Of the compounds (I)—(VI) only those in which X = $CH_2{\cdot}NMe_3^+$ Br^- (series c) are of pharmacological interest, but the other two series are convenient model compounds in which the conformations about the ether link would be expected to parallel the quaternary salt series. The ring-methylated compounds (IVc) and (Vc) were of interest since superficially they resemble the known biologically active molecule choline 2,6-xylyl ether bromide (VIc) more closely than do the non-methylated structures (I)—(III)c, but the presence of the methyl

[1] (*a*) P. Hey, *Brit. J. Pharmacol.*, 1952, **7**, 117; (*b*) P. Hey and G. L. Willey, *ibid.*, 1954, **9**, 471.

[2] (*a*) G. Baddeley and J. R. Cooke, *J. Chem. Soc.*, 1958, 2797; (*b*) G. Baddeley, N. H. R. Smith, and M. A. Vickars, *ibid.*, 1956, 2455.

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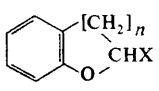
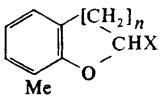
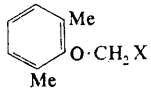
substituents in (IVc) and (Vc) was not expected to influence the conformation of the ether link.



(I)a—c; $n = 1$
(II)a—c; $n = 2$
(III)a—c; $n = 3$



(IV)a—c; $n = 1$
(V)a—c; $n = 2$



(VI)a—c

Series a, X = H; b, X = CO_2H; c, X = $CH_2{\cdot}NMe_3^+Br^-$

The absorption (ε) of a conjugated chromophore can be related [3] to the angular distortion (θ) from the conformation in which absorption is a maximum (ε_0) by equation (1), which was used by Braude and Sondheimer [3] to analyse the conformations of a series of methyl substituted acetophenones. However, some of their results are difficult to explain on stereochemical grounds alone. For example, 2-methyl- and 2,4-dimethyl-acetophenone, in which one would expect the same steric hindrance to planarity of the chromophore, were given values of θ of 40 and 24°, respectively, and for 2,6-dimethyl- and 2,4,6-trimethyl-acetophenone, 55 and 63°. It is difficult to believe that inductive and hyperconjugative effects of the *p*-methyl substituents can produce these differences in conformation, especially as the effect operates in the opposite sense for the two pairs of molecules. Further doubt has been cast on these results by Le Fèvre *et al.* who calculated from the observed molar Kerr constant that for 2,4,6-trimethylacetophenone θ = 90°.[4] However, a recent study [5] of the natural abundance ^{13}C n.m.r. frequencies of the carbonyl carbon in a series of methyl substituted acetophenones has led to values of θ which fall into a pattern similar to that obtained by Braude and Sondheimer. The values of θ obtained from these n.m.r. studies for 2-methyl- and 2,6-dimethyl-acetophenone are, however, less dependent on the presence of further methyl substituents in the ring, except for the buttressing effect noted in 2,3,5,6-tetramethylacetophenone (θ = 57°); cf. 2,6-dimethylacetophenone (θ = 50°). It appears, therefore, that the anomalies in the results of Braude and Sondheimer are due to the inductive and hyperconjugative effects of the methyl substituents directly affecting the intensity of the *K*-band rather than indirectly affecting the intensity through a conformational change.

$$\varepsilon/\varepsilon_0 = \cos^2\theta \qquad (1)$$

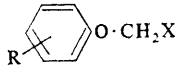
It has been shown for a series of anisoles that the intensity of the absorption near 2600 Å is due to a $\pi \longrightarrow \pi^*$ transition and is similarly dependent on the conformation about the phenyl–O bond.[6] An examination of these bands should in principle, therefore, permit the conformation of any such chromophore to be determined by use of equation (1). An assumption implicit in this equation, however, is that when the two parts of the chromophore are orthogonal (θ = 90°) the absorption will be zero. This is not necessarily so. Furthermore, by analogy with the methyl substituted acetophenones we may expect substituents to have "non-steric" effects which will introduce discrepancies into the calculated values of θ. It is therefore proposed that the equation

$$(\varepsilon_{corr.} - \varepsilon_{min.})/(\varepsilon_0 - \varepsilon_{min.}) = \cos^2\theta \qquad (2)$$

should be used for such conformational analysis, where $\varepsilon_{corr.}$ is the extinction coefficient for the chromophore corrected for the "non-steric" effects of each substituent, $\varepsilon_{min.}$ is the residual absorption in the relevant spectral region when the components of the chromophore are orthogonal (θ = 90°), and ε_0 is the maximum extinction coefficient for the chromophore (θ = 0°). The use of $\varepsilon_{max.}$, instead of band area as an indication of the relative oscillator strength of the transitions is considered to be a justifiable approximation, since the band widths at half maximum height were constant for the compounds investigated. Equation (2) may therefore be used for the conformational analysis of compounds (I)—(VI) provided that (*a*) the "non-steric" effects of any substituents are either very small or can be estimated and an appropriate correction applied to the observed extinction coefficients, (*b*) the absorption intensity ($\varepsilon_{min.}$) when θ = 90° is known, and (*c*) the absorption intensity (ε_0) when θ = 0° is known.

It is believed that this method for the determination of θ in aromatic ethers is likely to be more accurate than the use of either dipole moment or ^{13}C n.m.r. data since the Ph–O resonance is small compared with Ph–C=O resonance and we might expect, therefore, that changes in the angle θ will have only small effects on the dipole moment of the molecule and on the shielding of the non-aromatic ^{13}C nucleus bonded to the oxygen atom.

In order to determine the likely magnitude of the "non-steric" effects of substituents in compounds (I)—(VI) the analogous compounds (VII)—(XIV) were



(VII)a—d; R = H
(VIII)a—c; R = 4-Me
(IX)a—c; R = 3-Me
(X)a—c; R = 3,5-Me_2

(XI)a—d; R = 2-Me
(XII)a—c; R = 2,4-Me_2
(XIII)a—c; R = 2,5-Me_2
(XIV)a—c; R = 2,4,6-Me_3

a, X = H; b, X = CO_2H; c, X = $CH_2{\cdot}NMe_3^+$ Br^-;

d, X = $CHMe{\cdot}CH_2{\cdot}NMe_3^+$ Br^-

prepared and examined. These compounds, together with compounds (VI)a—c represent all the possible non-cyclic methyl substituted aromatic ethers belonging to the series a, b, and c, in which buttressing effects between methyls is absent. Their ultraviolet spectra are in Table 2.

[3] E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 1955, 3754.
[4] M. J. Aroney, M. G. Corfield, and R. J. W. Le Fèvre, *J. Chem. Soc.*, 1964, 648.
[5] K. S. Dhami and J. B. Stothers, *Tetrahedron Letters*, 1964, 631.
[6] L. J. Frolen and L. Goodman, *J. Amer. Chem. Soc.*, 1961, **83**, 3405.

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TABLE 1

Ultraviolet spectra of heterocyclic compounds

		$\lambda_{max.}$ (Å)	ε
(Ia)	2,3-Dihydrobenzofuran [2b]	2740, 2830, 2890	2250, 3095, 3055
(IVa)	2,3-Dihydro-7-methylbenzofuran	2715, 2775	2340, 2140
(IIa)	Chroman [2b]	2700, 2760, 2840	1500, 2125, 2520
(Va)	8-Methylchroman	2745, 2780, 2830	1885, 1820, 2175
(IIIa)	2,3,4,5-Tetrahydro-1-benzoxepin [2b]	2600, 2670, 2720	450, 678, 694
(VIa)	2,6-Dimethylanisole	2650, 2680, 2725	310, 334, 300
(Ib)	2,3-Dihydrobenzofuran-2-carboxylic acid [2a]	2790, 2850	2670, 2375
(IVb)	2,3-Dihydro-7-methylbenzofuran-2-carboxylic acid	2780, 2830, 2855sh	2265, 2235, 2135sh
(IIb)	Chroman-2-carboxylic acid [2a]	2735, 2810	1800, 1860
(IIIb)	2,3,4,5-Tetrahydro-1-benzoxepin-2-carboxylic acid [2a]	2650, 2700	570, 555
(VIb)	2,6-Dimethylphenoxyacetic acid	2645, 2685, 2730sh	130, 124, 96sh
(Ic)	(2,3-Dihydrobenzofuran-2-ylmethyl)trimethylammonium bromide	2775, 2825sh	2680, 2350sh
(IVc)	(2,3-Dihydro-7-methylbenzofuran-2-ylmethyl)trimethylammonium bromide	2760, 2815	2210, 2180
(IIc)	(Chroman-2-ylmethyl)trimethylammonium bromide	2735, 2790	1850, 1720
(IIIc)	(2,3,4,5-Tetrahydro-1-benzoxepin-2-ylmethyl)trimethylammonium bromide	2645, 2700	528, 520
(VIc)	Choline 2,6-dimethylphenyl ether bromide	2620, 2665	246, 222

The spectra of the quaternary compounds were recorded in distilled water and all the other spectra were recorded in n-hexane.

TABLE 2

Ultraviolet spectra of R-phenyl alkyl ethers, $ArO{\cdot}CH_2X$

R	Series a X = H $\lambda_{max.}$ (Å) (ε)	Series b X = CO_2H $\lambda_{max.}$ (Å) (ε)	Series c X = $CH_2{\cdot}NMe_3^+Br^-$ $\lambda_{max.}$ (Å) (ε)
H	2775 (1475)	2760 (1140)	2755 (1145)
	*2710 (1579)	*2700 (1275)	*2690 (1410)
	2650 (1125)		2640sh (1045)
4-Me	2860 (2120)	2845 (1290)	2825 (1235)
	2810 (2195)	*2780 (1500)	*2760 (1515)
	*2765 (1825)	2760 (1415)	
	2740 (1575)	2565 (1085)	
	2705 (1405)		
3-Me	2810 (1975)	2780 (1310)	2770 (1130)
	*2730 (1815)	*2720 (1310)	*2705 (1245)
3,5-Me_2	2820 (1735)	2800 (1060)	2795 (985)
	2775 (1295)	*2725 (975)	*2715 (985)
	*2735 (1495)		
	2630 (1255)		
2-Me	2780 (1768)	2775 (1275)	2835 (1305)
	*2720 (1812)	*2715 (1340)	*2770 (1450)
	2650sh (1245)		
2,4-Me_2	2860 (2040)	2830 (1465)	2800sh (1390)
	*2800 (2085)	*2770 (1635)	*2755 (1555)
	2760 (1990)		
2,5-Me_2	2820 (2110)	2810 (1530)	2785 (1620)
	*2765 (2075)	*2750 (1560)	*2735 (1695)
	2735 (1870)		
2,6-Me_2	2725 (300)	2730sh (96)	2665 (222)
	*2680 (334)	2685 (124)	*2620 (246)
	2650 (310)	*2645 (130)	
2,4,6-Me_3	2795 (690)	2780 (234)	2760 (428)
	*2745 (615)	2735 (223)	2715sh (440)
	2715 (620)	*2700 (230)	*2680 (454)

* Indicates the peak taken as a measure of absorption intensity.

The spectra of the quaternary compounds were recorded in distilled water and all the other spectra were recorded in n-hexane.

Tables 1 and 2 show that all these aromatic ethers exhibit at least two peaks in the 2600—2900 Å region. In general the shorter wavelength peak is broader and more intense than the other, and the extinction coefficient at this shorter wavelength was taken as a measure of the relative oscillator strengths of the $\pi \longrightarrow \pi^*$ transition. Several of the anisoles exhibited more than two peaks, but in each case it was apparent that a shorter wavelength peak, by virtue of its position and breadth, was the principal peak. Fine-structure bands of greater intensity were ignored (see Figure 2).

Table 3 records the average change of the absorption intensity per methyl group when methyl groups are

TABLE 3

Change in molecular extinction coefficient per additional methyl substituent in R-phenyl alkyl ethers, $ArO{\cdot}CH_2X$

	Δε per additional Me		
R	X = H	X = CO_2H	X = $CH_2{\cdot}NMe_3^+Br^-$
H	—	—	—
2-Me	233	65	40
3-Me	236	35	−165
4-Me	246	225	105
3,5-Me_2	−42	−150	−212
2-Me	—	—	—
2,4-Me_2	273	295	105
2,5-Me_2	263	220	245
2,6-Me_2	—	—	—
2,4,6-Me_3	281	100	208

introduced into any of nine reference compounds (VI), (VII), and (XI), series a—c. The introduction of a *p*-methyl group into either the unsubstituted or the mono-*ortho*-substituted compounds enhances the absorption intensity, the enhancement being similar within each series, *e.g.*, 246 and 273 (average = 260) when X = H, 225 and 295 (average = 260) when X = CO_2H, and 105 and 105 (average = 105) when X = $CH_2{\cdot}NMe_3^+Br^-$. The effects of single *o*-methyl substituents are very similar, but the change in intensity produced by *m*-methyl substituents is more varied and may vary in sign. If scale drawings of *o*-methylanisoles are constructed using interference radii equal to twice the covalent radii,[3] very little interaction is seen between the ether oxygen and the *o*-methyl group, and there need be no interaction between the *o*-methyl and the function $-CH_2X$ (Figure 1). It is unlikely therefore that the conformation about the ether link is altered on introducing the single *o*-methyl group, and since the spectra of series a and b in hexane parallel those of series c in water, the effect of the *o*-methyl group on solvation of the chromophore must be small. It is suggested therefore that the steric effect of a single *o*-methyl group is

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minimal, and since the enhancements of absorption caused by introducing single *o*- or *p*-methyl groups are small and of similar magnitude (Table 3), it seems

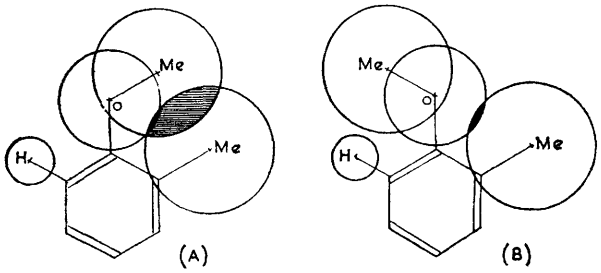

FIGURE 1 The two " in-plane " conformations of (XI)

(A) Bond lengths * ..... C–H 1·07 Å
C–C 1·54 Å
C–O 1·43 Å
C=C 1·39 Å

(B) Interaction radii [3] ..... Me 1·70 Å
O 1·32 Å
H 0·62 Å

(shaded portion represents Me ◀—▶ Me interaction, and black portions represent Me ◀—▶ O interactions)

* Pauling, " The Nature of the Chemical Bond," 2nd edn., Cornell University Press, London, 1948, p. 164.

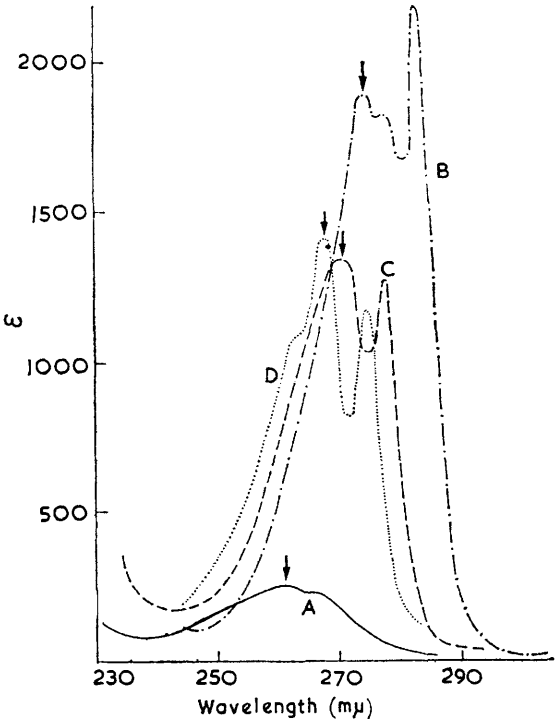

FIGURE 2 Examples of the spectra of the aryl ethers

A, Choline 2,6-xylyl ether bromide; B, 8-methylchroman; C, 2-methylphenoxyacetic acid; D, choline phenyl ether bromide.

Arrows denote the absorption peaks which were taken as a relative measure of the oscillator strength of the $\pi \longrightarrow \pi^*$ transition

reasonable to use the average effect of the latter in each series as a correction for the " non-steric " effect of either. It is not possible to suggest a correction for the presence of *m*-methyl groups.

The effects of the *p*-methyl group on the 2,6-dimethyl substituted compounds have not been considered in deriving this correction for *o*- and *p*-methyl since their very low extinction coefficients indicate that an extreme steric situation exists, and corrected values would be meaningless since they would be very sensitive to the corrections chosen. However, the calculated distance between the centres of the *o*-methyl group and the non-aromatic carbon attached to the oxygen atom is 3·39 Å when $\theta = 90°$ using the bond lengths in Figure 1 and assuming a Ph–O–C angle of 108° (sp^3 hybridisation of the O-atom). This distance is very close to 3·40 Å which is twice the chosen interference radius for a methyl (or methylene) group. This implies that in the 2,6-dimethyl substituted ethers the interference spheres of the methyl or methylene groups are in contact even when $\theta = 90°$. Such a situation gives rise to compressional energies [3] of less than *ca.* 3 kcal./mole, and at room temperature we may expect these molecules to adopt a fairly rigid conformation in which θ is close to 90°. A similar conclusion was drawn from molar Kerr constant data for 2,4,6-trimethylanisole [7] and is consistent with the very low extinction coefficient for the $\pi \longrightarrow \pi^*$ transition in such molecules. The effect of a *p*-methyl substituent in these sterically hindered molecules suggests that a considerable part of the observed absorption may be due to " non-steric " effects of the methyl substituents. We may conclude, therefore, that when the oxygen–benzene π-bond system is orthogonal, the absorption of such molecules in the 2600—2900 Å region will be very small and we may set $\varepsilon_{min.}$ [equation (2)] equal to zero.

The " non-steric " effects of the *o*- or *p*-methyl substituents (Table 3) are small compared with the extinction coefficients of the heterocyclic compounds (Table 1), and if they result from the inductive and conjugative properties of the methyl substituent then they are likely to be very much less for a n-alkyl substituent. It seems reasonable, therefore, to neglect the effects of ring fusion in the heterocyclic compounds and, since it is widely accepted that the two rings of dihydrobenzofuran are coplanar, set the extinction coefficient for the 2,3-dihydrobenzofuran derivative in each series equal to ε_0. Any error introduced by this approximation will be present for each of the cyclic structures and will therefore tend to cancel out. Equation (2) may now be used to analyse the conformations of the compounds.

Table 4 records the values of θ for each series of compounds calculated by means of equation (2). The results for the three series are closely parallel, and as expected the values of θ increase in the order 2,3-dihydrobenzofuran < chroman < homochroman owing to increased buckling of the heterocyclic rings. Dreiding stereo-models of the chroman and homochroman skeletons show this effect plainly. For the homochroman model, the conformation in which the heterocyclic ring is a pseudo-chair such that the oxygen, C-2, C-4, and

[7] M. J. Aroney, M. G. Corfield, and R. J. W. Le Fèvre, *J. Chem. Soc.*, 1964, 2954.

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C-5 are almost in a plane, with C-3 and the benzene ring above and below it, has the smallest amount of H–H interaction. These models were photographed from a point in the plane of the benzene ring on the axis of the phenyl–O bond, and the angle θ was measured directly from these photographs. The measured angles were 37° for chroman and 73° for homochroman, to be compared with a spectroscopically determined angle averaged over the three analogous compounds of each type of 34 and 63°, respectively (see Table 4).

TABLE 4

Values of $\varepsilon_{corr.}$ and θ for heterocycles and phenyl and *o*-tolyl ethers

	Series a, X = H			Series b, X = CO_2H			Series c, X = $CH_2{\cdot}NMe_3^+Br^-$		
	ε	$\varepsilon_{corr.}$ [a]	θ [b]	ε	$\varepsilon_{corr.}$ [a]	θ [b]	ε	$\varepsilon_{corr.}$ [a]	θ [b]
(I)	3095	3095	0	2670	2670	0	2680	2680	0
(IV)	2385	2125	34 [c]	2265	2005	30	210	2105	27·5 [c]
(II)	2125	2125	34	1800	1800	35	1850	1850	34
(V)	1885	1625	43·5 [c]	—	—	—	—	—	—
(VII)	1579	1579	44·5	1275	1275	46·5	1410	1410	43·5
(XI)	1812	1552	45	1340	1080	50·5	1450	1345	45
(III)	678	678	62	570	570	62·5	528	528	63·5
	$\varepsilon_{corr.} = \varepsilon - 260$ per Me substituent						$\varepsilon_{corr.} = \varepsilon - 105$/Me		
	$\varepsilon_0 = 3095$			$\varepsilon_0 = 2670$			$\varepsilon_0 = 2680$		
	$\varepsilon_{min.} = 0$			$\varepsilon_{min.} = 0$			$\varepsilon_{min.} = 0$		

[a] No correction for ring fusion. [b] θ calculated by equation (2). [c] See text.

It is likely that the values of θ deduced from the spectroscopic observations are influenced by vibrations in which θ oscillates about the minimum energy conformation, the spectroscopic value of θ being a time-averaged value. Furthermore, the skew effect produced by the $\cos^2\theta$ function will tend to decrease the "spectroscopic" estimate of θ. The similarity of the "model" and "spectroscopic" estimates of θ for the chroman skeleton suggests therefore that this skeleton is comparatively rigid whereas the discrepancy in the estimate of θ for the homochroman skeleton suggests a greater flexibility. We may also deduce that in neither skelton does the C-2 atom regularly pass through the plane of the benzene ring, since in these circumstances the spectroscopic values of θ would be considerably less than those estimated from the models. This does not mean, of course, that no inversion of the heterocyclic rings occurs,[8] although this has been postulated for the extreme case of 5,5-dimethylhomochroman.[9]

For the non-cyclic ethers (VII)a—c it is seen that the observed values of θ all lie close to 45° (Table 4). This implies that the small Ph–O conjugation, unlike the Ph–C=O conjugation in acetophenones, is insufficient to produce a large potential energy well for the conformation in which θ is close to 0°. This experimental result strongly suggests that in such ethers there is free rotation about the phenyl–oxygen bond at room temperature.

The three analogous *o*-methyl substituted ethers (XI)a—c also have calculated values of θ very close to 45° (Table 4). Since the interference sphere of an *o*-methyl substituent and that of a methyl or methylene group attached to the oxygen atom just touch when θ = 90°, steric compression forces will increase rapidly as θ approaches 90° and any torsional vibration about the Ph–O bond of such molecules will have limits close to ±90°. If such a vibration occurs with a constant angular velocity and the accelerating forces are only effective near to each limit, and over a range of θ which is small enough to be neglected, then the vibration is equivalent to free rotation and again the "spectroscopic angle" would be expected to be close to 45°. This prediction agrees closely with experiment.

Finally, we must consider the cyclic ethers listed in Table 4 in which there is a methyl substituent on the benzene ring *ortho* to the ether oxygen, (IV)a—c and (Va). Their extinction coefficients are less than for the corresponding unsubstituted compounds (I)a—c and (IIa), whereas the usual effect of a single *o*-methyl group in non-rigid molecules is to cause a small enhancement of the absorption intensity (Table 3). It is suggested that this anomalous inhibition of resonance may arise from steric effects of the oxygen lone pairs.

Evidence has been presented[10] that lone pairs are sufficiently large to produce observable steric effects. In the ground state the lone pairs of the oxygen atom of 2,3-dihydro-7-methylbenzofuran derivatives (IV)a—c will straddle the 7-methyl group and interact minimally with it. During a $\pi \longrightarrow \pi^*$ transition, however, when the hybridisation of the oxygen atom essentially changes from sp^3 to sp^2, the newly created lone pair will be in the plane of the benzene ring and will interact maximally with the 7-methyl group. This interaction will be absent in the unsubstituted compounds (I)a—c, and if the difference

(Gain of mesomeric stabilisation energy) — (Energy for $sp^3 \longrightarrow sp^2$ rehybridisation)

is small and of the same order as the esteric compression between the 7-methyl and the sp^2 lone pair, then this latter factor might cause a substantial drop in mesomerism and account for the different absorption intensities of the two groups of compounds.

In the case of 8-methylchroman (Va) the same arguments apply, but in this case the lone pair of the sp^2 hybrid state will be twisted some 34° out of plane and the interaction with the methyl group will be less. The spectral data indicates that after correcting for the non-steric effect of the substituent the introduction of a 7-methyl group into the 2,3-dihydrobenzofuran compounds causes an average loss of 26% of the Ph–O resonance exhibited by the parent 2,3-dihydrobenzofuran whereas the introduction of the 8-methyl group into chroman causes a loss attributable to steric effects of only 16% of the resonance of 2,3-dihydrobenzofuran, in agreement with the above hypothesis. The two analogous compounds (V)b and c are not available for

[8] E. M. Philbin and T. S. Wheeler, *Proc. Chem. Soc.*, 1958, 167.

[9] H. Hart and C. R. Wagner, *Proc. Chem. Soc.*, 1958, 284.

[10] K. Brown, A. R. Katritzky, and A. J. Waring, *Proc. Chem. Soc.*, 1964, 257.

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comparison, but we may conclude that the values of θ calculated for the 2,3-dihydro-7-methylbenzofurans (IV)a—c from spectroscopic data are anomalously high. The true angles are probably zero.

The introduction of a β-methyl substituent into either choline phenyl ether bromide or its *o*-tolyl homologue completely destroys the powerful nicotine-like ganglion stimulant activity of the parent compounds. It appeared likely that this change in biological activity might also be due to conformational changes. The spectroscopic evidence cited above indicates that choline phenyl ether can adopt a conformation in which $\theta = 0°$ and the hydrogen atoms of the β-methylene group are equidistant from either *ortho* hydrogen atom. Replacement of one of these methylene hydrogen atoms by a methyl group will destroy this symmetry, and in order to minimise the compression between the substituent and the *ortho* hydrogen the molecule must rotate about the Ph–O bond so that $\theta > 0$. Since the extinction coefficients for these compounds are less than for choline phenyl ether bromide (Table 5) we may assume that the β-carbon atom does not pass regularly through the plane of the benzene ring and that at room temperature there is a certain minimum angle possible for θ denoted by θ′. If we assume that when $\theta > \theta'$ steric interactions are negligible then β-methylcholine phenyl ether may oscillate freely about its Ph–O bond within the limits $\theta' < \theta < (\pi - \theta')$. In the presence of a single *o*-methyl substituent this oscillation will be limited to $\theta' < \theta < \pi/2$ because of interaction between the *o*-methyl and methine groups. The extinction coefficients observed for these compounds will therefore be an averaged value for the period of the oscillation, and using equation (2) and setting $\varepsilon_{min.} = 0$, we may write,

$$\varepsilon_{corr.}/\varepsilon_0 = \left(\int_{\theta}^{\pi/2} \cos^2\theta \, d\theta\right) \Big/ (\pi/2 - \theta')$$

which may be evaluated as

$$\varepsilon_{corr.}/\varepsilon_0 = \tfrac{1}{2}[1 - (\sin 2\theta')/(\pi - 2\theta')] \qquad (3)$$

If suitable values of $\varepsilon_{corr.}/\varepsilon_0$ can be inserted, equation (3) can be solved graphically for θ′. The results of Baddeley *et al.*,[2b] who examined the spectra of the ethers Ph–O–R (R = Me, Et, Pr^i, and Bu^t), suggest that the increased electron-donating properties of the function R along the series tends to increase the Ph–O resonance, except that when R = Pr^i the expected increase is offset by steric effects analogous to those considered above and when R = Bu^t steric effects predominate (Table 5). In anisole and phenetole, however, steric effects are absent, and it is reasonable therefore to take the difference of 360 between the absorption coefficients of these two compounds as a measure of the non-steric effects of β-methyl substituents in choline phenyl ethers. The values of $\varepsilon_{corr.}$ for (VIId) and (XId) are therefore ($\varepsilon_{obs.}$ — 360) and ($\varepsilon_{obs.}$ — 360 —105), respectively. Using the same value of ε_0 as before, the calculated values of θ′ [equation (3)] are 24 and 23°, and the calculated values of θ [equation (2)] are 54·5 and 54°, respectively. If the assumption that the angular velocity is constant about the Ph–O bond when $\theta > \theta'$ is incorrect, and, instead, a potential energy well exists near to the limit of the oscillation when θ is small, then, since the value of $\cos^2\theta$ decreases continuously between 0 and π/2, the actual value of θ′ will be greater than the value calculated by equation (3). It is concluded therefore that in both of these molecules the minimum value of θ is considerably greater than zero and is probably comparable to the values found for the chroman compounds. The importance of these studies in understanding the pharmacological properties of aryl choline ethers will be discussed elsewhere.

TABLE 5

Ultraviolet spectra of straight- and branched-chain aryl alkyl ethers

	$\lambda_{max.}$ (Å)	ε
Anisole [2b] *	2275, 2710, 2650	1475, 1579, 1125
Phenetole [2b] *	2780, 2710, 2650	1815, 1938, 1340
Isopropyl phenyl ether [2b] *	2800, 2730, 2670	1700, 1920, 1360
t-Butyl phenyl ether [2b] *	2800, 2700, 2640	125, 454, 460
Choline phenyl ether bromide †	2755, 2690, 2640sh	1145, 1410, 1045sh
β-Methylcholine phenyl ether bromide †	2760, 2695, 2645sh	1000, 1260, 958sh
β-Methylcholine *o*-methylphenyl ether bromide †	2760, 2705	1244, 1388

* Recorded in n-hexane. † Recorded in distilled water.

EXPERIMENTAL

Spectra.—Infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer model 137 and were consistent with the assigned structures.

Ultraviolet spectra were recorded on a Unicam SP 700 recording spectrophotometer using solutions (see Tables) with a maximum optical density between 0·1 and 1·0. Band widths at half peak height for a representative sample of fifteen spectra recorded in different solvents were in the range 2500—2961 cm.$^{-1}$ with a standard deviation of 135 cm.$^{-1}$ about a mean of 2743 cm.$^{-1}$. The band widths, at half peak height, of all the 2,6-dimethylphenoxy-derivatives were greater than 3090 cm.$^{-1}$

Chromatography.—The α-aryloxycarboxylic acids described below were purified by a method due to Bhargava and Heidelberger [11] as modified by Baddeley and Cooke.[12] Silica gel (27 g.) was wetted with 16·2 ml. of equilibrated stationary phase (methanol–0·5N-sulphuric acid, 9 : 1 v/v), slurried with the equilibrated mobile phase (light petroleum, b. p. 100—120°) and packed into a column 1·8 cm. in diameter by 14 cm. high. A 30 cm. head of mobile phase gave a flow rate of approximately 2 ml./min. The methods employed by Bhargava and Heidelberger were used to add up to 200 mg. of acid to the column and to analyse the fractions. The fractions containing the acidic material were combined and the acid was extracted through aqueous alkali into ether and recovered as a white solid which was recrystallised from light petroleum.

[11] P. M. Bhargava and C. Heidelberger, *J. Amer. Chem. Soc.*, 1955, **77**, 166.
[12] G. Baddeley and J. R. Cooke, personal communication.

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Analytical vapour phase chromatography was conducted on a Pye series 104 chromatograph model 24 using 5 ft. columns.

1,2-Dihydro-7-methylbenzofuran (IVa).—Attempts to cyclise 2-methylphenoxyethanol with an excess of phosphorus pentoxide in boiling benzene always gave an involatile material. Heating the alcohol with phosphorus pentoxide under reflux for 2 hr. in the absence of solvent (b. p. drops from 235 to 216°) and fractionation of the reaction mixture gave the required ether, b. p. 115°/61 mm. (Found: C, 80·45; H, 7·65. Calc. for $C_9H_{10}O$: C, 80·55; H, 7·5%).

8-Methylchroman (Va).—This was prepared in good yield by cyclisation of 3-(2-methylphenoxy)propan-1-ol with phosphorus pentoxide in boiling benzene,[13] b. p. 100°/10 mm. (Found: C, 80·8; H, 8·05. Calc. for $C_{10}H_{12}O$: C, 81·05; H, 8·15%).

2,3-Dihydro-7-methylbenzofuran-2-carboxylic Acid (IVb).—2-Hydroxy-3-methylbenzaldehyde [14] (112 g.) was heated with diethyl malonate (145 g.) in absolute ethanol (350 ml.) for 3 hr. in the presence of piperidine (8·25 ml.) and acetic acid (0·85 ml.); a yellow precipitate from the cooled mixture gave *ethyl 8-methyl-2-oxochromen-3-carboxylate* (169 g.), m. p. 83—85° (from aq. ethanol), $\nu_{max.}$ 1750vs, 1710s, and 798vs cm.$^{-1}$ (Found: C, 67·4; H, 5·1. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). Alkaline hydrolysis in aqueous ethanol gave the 3-carboxylic acid, m. p. 161—164° (lit.,[15] 142—143°), which was decarboxylated [16] to give the 2-ketone, m. p. 110—111° (lit.,[15] 109—110°), $\nu_{max.}$ (Nujol) 1724s, and 750m cm.$^{-1}$ (Found: C, 74·65; H, 5·0. Calc. for $C_{10}H_8O_2$: C, 75·0; H, 5·0%). This material reacted slowly with bromine in cold chloroform to give the dibromide (m. p. 86—91°) which was converted, by a method analogous to that described for the preparation of benzofuran-2-carboxylic acid, into *7-methylbenzofuran-2-carboxylic acid*, m. p. 222—224·5°, $\nu_{max.}$ (Nujol) 1686 cm.$^{-1}$ (Found: C, 68·2; H, 4·5. $C_{10}H_8O_3$ requires C, 68·2; H, 4·6%). A solution of this acid (10·8 g.) in butan-1-ol (100 ml.) was hydrogenated over 5% palladium–charcoal (2 g.) for 24 hr. at 100°/3 atm., and the resulting oil [$\nu_{max.}$ (film) 1750 cm.$^{-1}$] on alkaline hydrolysis yielded the *product* (IVb), m. p. 151—153° (7·2 g.) [from light petroleum (b. p. 100—120°)], $\nu_{max.}$ (Nujol) 1733s cm.$^{-1}$ (Found: C, 67·4; H, 5·45. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·65%).

(2,3-Dihydrobenzofuran-2-ylmethyl)trimethylammonium Bromide (Ic).—2,3-Dihydrobenzofuran-2-carboxylic acid [17] (4·2 g.) in benzene was heated under reflux with a 3 molar excess of oxalyl chloride [18] for 2 hr. Removal of the excess of oxalyl chloride and solvent and distillation of the residue gave a clear oil (3·55 g.), b. p. 115—116°/10 mm., which was dissolved in ether (60 ml.) and slowly added to a solution of dimethylamine (25 ml.) in ether (90 ml.) maintained at −15°. The precipitate was filtered off and the solution evaporated, yielding NN-*dimethyl-2,3-dihydrobenzofuran-2-carboxyamide* (3·73 g.), m. p. 79·5° (from water), $\nu_{max.}$ (Nujol) 1642vs cm.$^{-1}$ (Found: C, 68·7; H, 6·7; N, 6·9. $C_{11}H_{13}NO_2$ requires C, 69·1; H, 6·85; N, 7·3%). A solution of this amide (2·2 g.) in ether (150 ml.) was slowly added to a suspension of a 4 molar excess of lithium aluminium hydride in boiling ether. The resulting mixture was stirred and heated for 20 hr. and the basic product isolated in the usual way, to give *N-(2,3-dihydrobenzofuran-2-ylmethyl)dimethylamine* (0·94 g.), b. p. 116°/10 mm. (Found: C, 74·5; H, 8·45; N, 7·75. Calc. for $C_{11}H_{15}NO$: C, 74·55; H, 8·55; N, 7·9%). Quaternisation of this amine with an excess of methyl bromide in ether yielded the required *quaternary salt*, m. p. 189·5—191° (Found: C, 52·65; H, 6·45; Br, 29·25; N, 5·0. $C_{12}H_{18}BrNO$ requires C, 52·95; H, 6·65; Br, 29·5; N, 5·15%).

(2,3-Dihydro-7-methylbenzofuran-2-ylmethyl)trimethylammonium Bromide (IVc).—This was prepared from 2,3-dihydro-7-methylbenzofuran-2-carboxylic acid by a route analogous to that described above. Oxalyl chloride readily formed the acid chloride (b. p. 124—126°/15 mm.) which, on reaction with dimethylamine, gave NN-*dimethyl-2,3-dihydro-7-methylbenzofuran-2-carboxyamide*, b. p. 90—110° (bath)/0·1 mm., $\nu_{max.}$ (film) 1655vs cm.$^{-1}$ (Found: C, 70·1; H, 7·4; N, 6·95. $C_{12}H_{15}NO_2$ requires C, 70·2; H, 7·35; N, 6·8%). Lithium aluminium hydride reduction yielded N-*(2,3-dihydro-7-methylbenzofuran-2-ylmethyl)dimethylamine*, b. p. 78—80°/0·2 mm. (Found: C, 75·25; H, 8·9; N, 7·55. $C_{12}H_{17}NO$ requires C, 75·35; H, 8·95; N, 7·3%), which with methyl bromide yielded the required *quaternary salt*, m. p. 150—151·5° (Found: C, 54·4; H, 7·0; Br, 27·85; N, 5·1. $C_{13}H_{20}BrNO$ requires C, 54·55; H, 7·05; Br, 27·9; N, 4·9%).

(Chroman-2-ylmethyl)trimethylammonium Bromide (IIc).—This was similarly obtained from chroman-2-carboxylic acid, which was prepared from 2-bromo-1-tetralone by the method of Baddeley and Cooke.[2a] A small quantity of the crude chroman-2-carboxylic acid was purified by liquid–liquid partition chromatography, yielding crystals, m. p. 99—101° (Found: C, 67·05; H, 5·5. Calc. for $C_{10}H_{10}O_3$: C, 67·4; H, 5·65%). Reaction of the unpurified acid (m. p. 85—94°) with oxalyl chloride gave an oil, b. p. 140—141°/mm., $\nu_{max.}$ (film) 1795s cm.$^{-1}$, which was hydrolysed with moist ether to a solid identical with that obtained from the chromatogram. Reaction of the derived acid chloride with dimethylamine gave a further oil, $\nu_{max.}$ (film) 1660s cm.$^{-1}$, which was reduced with lithium aluminium hydride to N-*(chroman-2-ylmethyl)dimethylamine*, b. p. 140°/13 mm. (Found: C, 75·1; H, 8·85; N, 7·2. $C_{12}H_{17}NO$ requires C, 75·35; H, 8·95; N, 7·3%), which with methyl bromide gave the required *quaternary salt*, m. p. 199—202° (Found: C, 54·2; H, 6·9; Br, 27·7; N, 4·6. $C_{13}H_{20}BrNO$ requires C, 54·55; H, 7·05; Br, 27·9; N, 4·9%).

N-(4-Hydroxy-8-methylchroman-2-ylmethyl)dimethylamine.—Fries rearrangement [19] of *o*-cresol acetate gave 2-hydroxy-3-methylacetophenone, b. p. 98—101°/9 mm. (Found: C, 71·85; H, 6·7. Calc. for $C_9H_{10}O_2$: C, 72·0; H, 6·7%); oxime, m. p. 132—135° (lit.,[20] 132—133°). The ketone was treated with ethyl dimethylaminoacetate by the method of Schmutz *et al.*,[21] to yield N-*(8-methyl-4-oxochromen-2-ylmethyl)dimethylamine hydrochloride*, m. p. 221—222° (from ethanol), $\nu_{max.}$ (Nujol) 2595m, 2538m, 2494m, 1655vs, and 768s cm.$^{-1}$, $\lambda_{max.}$ (water) 3055 Å (ε 5990) (Found:

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[21] J. Schmutz, R. Hirt, F. Künzle, E. Eichenberger, and H. Lauener, *Helv. Chim. Acta*, 1953, **36**, 620.

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C, 61·25; H, 6·3; Cl, 13·8; N, 5·65. $C_{13}H_{16}ClNO_2$ requires C, 61·55; H, 6·35; Cl, 14·0; N, 5·5%). This material (2·5 g.) in 50% aqueous ethanol (300 ml.) was hydrogenated (room temperature, 3 atm.) over platinum black (1·5 g.). The reduction was followed by observing the disappearance of the absorption at 3055 Å. After 16 hr. a further quantity of platinum black (0·5 g.) was added and the reduction continued for 6 hr. The catalyst was removed and the basic material extracted from the solution. A white solid was obtained and crystallised from 1 : 4 benzene–light petroleum (b. p. 60—80°), to give the required *product* 1·33 g.), m. p. 102·5—104°, $\nu_{max.}$ (Nujol) 3120s, 2778m, 1215vs, and 788s cm.$^{-1}$, $\lambda_{max.}$ (n-hexane) 2730 and 2800 Å (ε 1750 and 1784) (Found: C, 70·6; H, 8·45; N, 6·4. $C_{13}H_{19}NO_2$ requires C, 70·55; H, 8·65; N, 6·35%).

(*2,3,4,5-Tetrahydro-1-benzoxepin-2-ylmethyl*)*trimethylammonium Bromide* (IIIc).—2,3-Benzocyclohept-2-en-1-one,[22] b. p. 133—134°/11 mm. (Found: C, 81·7; H, 7·4. Calc. for $C_{11}H_{12}O$: C, 82·45; H, 7·55), was converted first into 2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylic acid by the method of Baddeley and Cooke [2a] and then into the required quaternary salt by a route analogous to that described above for the benzofuran derivative. Reaction of the unpurified acid (m. p. 88—92°) with oxalyl chloride gave the acid chloride, b. p. 149°/13 mm., hydrolysis of which gave a product of m. p. 102—105° (Found: C, 69·3; H, 6·8. Calc. for $C_{11}H_{12}O_3$: C, 68·75; H, 6·3), identical with that obtained by chromatography of the acid. The acid chloride with dimethylamine gave NN-*dimethyl-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxyamide*, m. p. 71—72°, $\nu_{max.}$ (Nujol) 1650s cm.$^{-1}$ (Found: C, 71·05; H, 7·75; N, 6·25. $C_{13}H_{17}NO_2$ requires C, 71·2; H, 7·8; N, 6·4%), which was reduced with lithium aluminium hydride to N-(*2,3,4,5-tetrahydro-1-benzoxepin-2-ylmethyl*)*dimethylamine*, b. p. 135°/10 mm. (Found: C, 76·2: H, 9·4; N, 6·7. $C_{13}H_{19}NO$ requires C, 76·05; H, 9·35; N, 6·8%), which with methyl bromide yielded the required *quaternary salt*, m. p. 256° (Found: C, 55·9; H, 7·45; Br, 26·8; N, 4·45. $C_{14}H_{22}BrNO$ requires C, 56·0; H, 7·4; Br, 26·6; N, 4·65%).

Methyl-substituted Anisoles.—Commercial samples of the various methyl substituted phenols which are precursors of the required anisoles (Table 2) were distilled, and in all cases their melting points were in close agreement with literature values. Gas chromatography of the phenols on Celite–5% xylenyl phosphate at 110° showed that they all contained less than 1% of impurity, and their relative retention times were in agreement with published results. The phenols were methylated with dimethyl sulphate. In no case was there a detectable (infrared) amount of the parent phenol present in these ethers, and several of them gave single peaks in gas phase chromatography on Celite–10% Carbowax (1500) at 120°.

Methyl-substituted Phenoxyacetic Acids.—The phenols purified as above were converted into the aryloxyacetic acids and recrystallised several times from water. The melting points of the products were in good agreement with literature values.

Methyl-substituted Choline Phenyl Ether Bromides.—All the required compounds (Table 6), except the β-methylcholine derivatives, were available in the laboratory having been prepared by Hey.[1a] Their purity was checked by infrared and elemental analysis, and if necessary they were recrystallised from a mixture of acetone, ethanol, and light petroleum.

2-(*2-Methylphenoxy*)*propyltrimethylammonium Bromide* (XId).—*NN*-Dimethyl-α-bromopropionamide (9 g.) was condensed with *o*-cresol (5·4 g.) in ethanolic solution in the presence of an equivalent amount of sodium ethoxide. After heating on a steam-bath for 4 hr. the alcohol was distilled off, water added to the residue, and the oily product extracted with ether. Distillation yielded NN-*dimethyl-2-(2-methylphenoxy)propionamide*, b. p. 116—118/0·8 mm., $\nu_{max.}$ (Nujol) 1642vs, 1235vs, and 756vs cm.$^{-1}$ (Found: C, 69·55; H, 8·25; N, 6·95. $C_{12}H_{17}NO$ requires C, 69·55; H, 8·25; N, 6·75%). Reduction with lithium aluminium hydride as described above yielded NN-*dimethyl*-2-(2-*methylphenoxy*)*propylamine*, b. p. 68—70°/0·8 mm., $\nu_{max.}$ (film) 1600m, 1587m, 1490s, 1238vs, and 748s cm.$^{-1}$ (Found: C, 72·95; H, 9·4; N, 7·5. $C_{12}H_{19}NO$ requires C, 74·55; H, 9·9; N, 7·25%), which with methyl bromide yielded the required *quaternary salt*, m. p. 168—169°, $\nu_{max.}$ (Nujol) 1590m, 1580m. 1490s, 1236vs, and 775vs cm.$^{-1}$ (Found: C, 54·45; H, 7·65; Br, 28·15; N, 5·05. $C_{13}H_{22}BrNO$ requires C, 54·15; H, 7·7; Br, 27·7; N, 4·85%).

2-*Phenoxypropyltrimethylammonium Bromide* (VIId).—This was prepared by a process analogous to that described for the *o*-tolyl derivative, m. p. 161—163° (lit.,[1a] 166°), $\nu_{max.}$ (Nujol) 1637w, 1592s, 1486vs, 1232vs, 758s, and 695m cm.$^{-1}$ (Found: C, 52·3; H, 7·5; Br, 28·8; N, 4·8. Calc. for $C_{12}H_{20}BrNO$: C, 52·55; H, 7·35; Br, 29·1; N, 5·1%).

TABLE 6

Analysis of R-phenyl choline ether bromides, $ArO{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_3^+Br^-$

			Found (%)					Required (%)			
	R	M. p.	C	H	Br	N	Formula	C	H	Br	N
(VIIc)	H	165—166°	50·5	6·7	30·95	5·5	$C_{11}H_{18}BrNO$	50·8	6·95	30·7	5·4
(VIIIc)	4-Me	129—131	52·3	7·1	29·1	5·15	$C_{12}H_{20}BrNO$	52·55	7·35	29·15	5·1
(IXc)	3-Me	158	52·25	7·2	29·0	5·1	$C_{12}H_{20}BrNO$	52·55	7·35	29·15	5·1
(Xc)	3,5-Me_2	215—217	53·9	7·5	28·1	5·05	$C_{13}H_{22}BrNO$	54·15	7·7	27·7	4·85
(XIc)	2-Me	162·5—163·5	52·3	7·2	29·6	5·4	$C_{12}H_{20}BrNO$	52·55	7·35	29·15	5·1
(XIIc)	2,4-Me_2	191—193	54·3	7·7	27·3	4·85	$C_{13}H_{22}BrNO$	54·15	7·7	27·7	4·85
(XIIIc)	2,5-Me_2	182—183·5	54·2	7·5	27·4	4·8	$C_{13}H_{22}BrNO$	54·15	7·7	27·7	4·85
(VIc)	2,6-Me_2	208—209	54·2	7·6	27·5	4·75	$C_{13}H_{22}BrNO$	54·15	7·7	27·7	4·85
(XIVc)	2,4.6-Me_3	183·5—184·5	55·8	7·6	26·2	4·6	$C_{14}H_{24}BrNO$	55·6	8·0	26·45	4·65

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