THE PRINCIPAL CONFORMATIONS OF SOME ORTHO-SUBSTITUTED DIPHENYL ETHERS[1]

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ABSTRACT

A study of the nuclear magnetic resonance, infrared, and ultraviolet spectra showed that some doubly and triply ortho-substituted diphenyl ethers adopt, principally but not exclusively, the "H-inside" conformation, while the quadruply ortho-substituted 7-(4′-carbomethoxy-2′,6′-dinitrophenoxy)metameconine (V) adopts the "methoxy-inside" conformation. Interconversion of conformational isomers is extremely fast. Reduction of methyl 4-methoxy-3-nitrobenzoate with tin and hydrochloric acid gave methyl 3-amino-2-chloro-4-methoxybenzoate.

It has been well established[2] that the principal conformations of diphenyl ethers, in solution or in the gas phase, are asymmetric (Fig. 1),[3] one ring being in the C—O—C plane and able to accommodate the ethereal oxygen's p-electrons, the other ring lying in a plane approximately perpendicular to the first so that resonance with the ethereal oxygen is small or negligible.

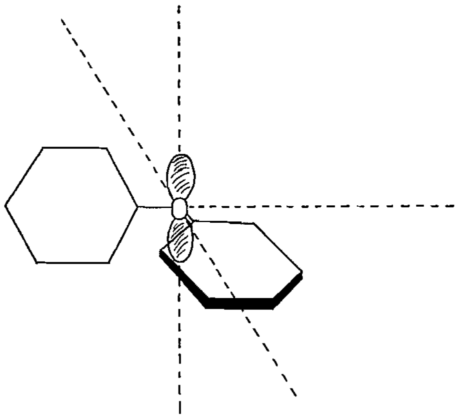

FIG. 1. Asymmetric diphenyl ether conformation.

Allen and Moir (17) pointed out that eight such conformations exist for a diphenyl ether bearing four different ortho-substituents, and that these conformations can be divided into two classes of four each. The members of each class are interconvertible by synchronous rotations which do not require ortho-groups to be forced past each other,

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[1] *Most of the material of this paper was presented at the national meeting of the Chemical Institute of Canada, Toronto, June 8, 1963.*

[2] *The asymmetry of ethers of low steric hindrance has been shown by ultraviolet spectroscopy (1–3), dipole moments (4–7), electron and X-ray diffraction (8–10), microwave absorption, and relaxation times (11–14), and from theoretical calculations of ultraviolet spectra (15). For highly hindered diphenyl ethers, the fact has been assumed from a study of models (2, 16–18).*

[3] *For convenience and clarity, an unshared pair is represented as essentially in a p-orbital, the planes of the rings at right angles, and the* C—O—C *valence angle as near 90°. It will be understood that these are intended only as rough approximations suitable to the present qualitative discussion. Because the figure does not display the easy increase in the oxygen valence angle, some of the conclusions of the paper seem more obvious, a priori, than is justified.*

but a member of one class can be converted to a member of the other only by surmounting this barrier. (The same idea of synchronous rotation had been developed in considerable detail for diphenyl ether itself by Calderwood and Smyth (11), who used it to explain the abnormally low relaxation time of diphenyl ether in the absorption of microwaves.) It is the object of this paper to show which of the eight conformations are occupied preferentially. Since the eight conformations are divided into pairs of mirror images, and since in a symmetrical environment mirror-image conformations will be equally occupied (18), it is enough to distinguish among the four conformations[4] of a single class.

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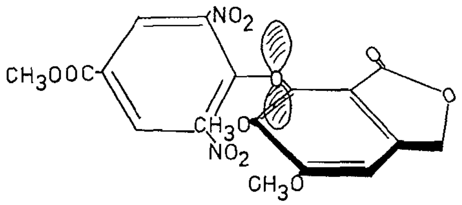

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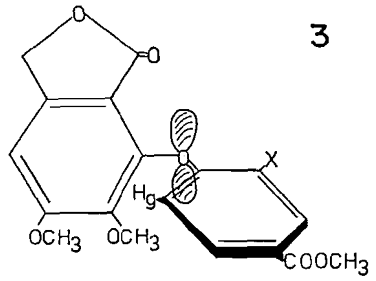

FIG. 2. "Methoxy-inside" conformation (V as example).
FIG. 3. "Hydrogen-inside" conformation (typical of I–IV).

The problem could be broken into two parts: to show (*i*) which ring lies in the C—O—C plane, and (*ii*) which ortho-substituent of this ring occupies the "inside" position (Figs. 1, 2, 3). Mangini and Passerini (1) were able to solve the first problem for some diphenyl sulphides by ultraviolet spectroscopy; the substances gave spectra typical of two almost independent chromophores, and the ring which included the sulphur in its chromophore must have been in the C—S—C plane. It will be shown later that this method can lead to erroneous conclusions if not carefully handled. The second problem does not seem to have been attempted previously. Our method is the straightforward one of comparing the proton magnetic resonance (n.m.r.), infrared, and ultraviolet spectra of a series of highly hindered diphenyl ethers with each other and with the spectra of the corresponding anisoles formed by replacing one or other of the phenyl groups with a methyl group.

Evidence from the N.M.R. Spectra

Although several factors determine the chemical shifts of aromatic protons, the relative shifts of H_a in a series such as I–VII depend mainly on inductive and resonance effects. Thus the electron-donating methoxy group would be expected to cause H_a to be more shielded in VI than in VII. The replacement of the 7-methoxy group in VI by aryloxy groups could have two opposite effects. (1) There would be a deshielding of H_a (relative to its environment in VI) by an increased inductive withdrawal of electrons which would become greater as the groups X and Y (in I–V) became more electronegative. The effect would be especially large if the lower ring were approximately in the plane of the C—O—C bonds. (2) A mesomeric electron donation, which would tend to offset the deshielding noted in (1), would occur if the upper ring were in the plane of the C—O—C bonds. The observed effects are noted in the second column of Table I. The shielding induced by the presence of methoxy at position-7 (VI), the lesser shielding by aryloxy groups in that

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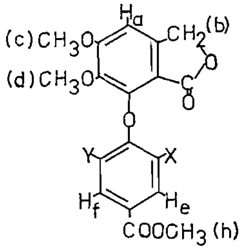
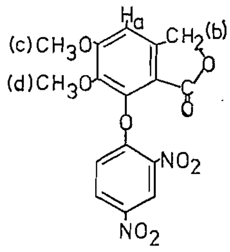
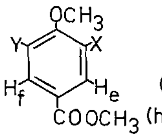
[4] *Each conformation is conveniently named by the ortho-group which occupies the "inside" position in that conformation (e.g. methoxy in Fig. 2, hydrogen in Fig. 3).*

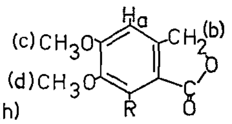


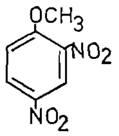


I : X = NH$_2$; Y = H$_g$
II : X = H$_k$; Y = H$_k$
III : X = I ; Y = H$_g$
IV : X = NO$_2$; Y = H$_g$
V : X = NO$_2$; Y = NO$_2$

VIII







Ia : X = NH$_2$; Y = H$_g$
IIa : X = H$_k$; Y = H$_k$
IIIa : X = I ; Y = H$_g$
IVa : X = NO$_2$; Y = H$_g$
V a : X = NO$_2$; Y = NO$_2$

VI : R = OCH$_3$
VII R = H

VIIIa

TABLE I

Chemical shifts* of hydrogens on the metameconine portion

	Tau values			
Compound	H_a	H_b†	H_c[5]	H_d[5]
VII	3.02	4.78	6.02	6.07
VI	3.25	4.82	6.03	6.12
I	3.13	4.82	6.02	6.23
II	3.10	4.80	6.03	6.23
III	3.07	4.82	6.03	6.20
IV	3.05	4.80	6.00	6.17
VIII	3.00	4.77	5.97	6.13
V	3.22	4.82	6.05	6.33

*In solution in chloroform or deuterochloroform, expressed as p.p.m. relative to an internal standard of tetramethylsilane set at τ = 10.

†Split by about 0.5 c.p.s.[6] The values given are for band centers.

position (I–IV), and the uniformly declining shielding of H_a as the electronegativity of the groups X and Y increases, all are exactly as expected in the sequences I–IV and VI–VIII. However, there is a sharply increased shielding of H_a in going from IV to V, in

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[5] *The assignment of the methoxy peaks was based on (a) their expected relative positions, and (b) the expected effects of changes in the group at position-7 and position-4, an ortho-methoxy being affected much more than a meta-methoxy. To some extent the conclusions have been checked with ethoxy analogues of substituted metameconines (7-ethoxymetameconine, 7-chloro-6-ethoxy-5-methoxyphthalide).*

[6] *These splittings of the phthalide hydrogens by a hydrogen ortho to them formed part of the evidence for the assignment of the configuration to the phthalide–isoquinoline alkaloids (19).*

spite of the much greater electron withdrawal of the groups in the latter. This can only mean that in V the two conformations corresponding to Fig. 2 are much more important than they are in I–IV or in VIII. In all these others, the two conformations corresponding to Fig. 3 must be more important than in V. It is most striking that the (inductively) electron-withdrawing aryloxy group produces almost the same shielding of H_a as does the methoxy group of VI.[7]

This argument cannot decide between the "methoxy-inside" conformation of Fig. 2 and the "carbonyl-inside" conformation for compound V. That the conformation of Fig. 2 is at least very important, and probably dominant,[7] is shown by an examination of the last column of Table I, where it is seen that the methoxy hydrogens H_d are much more shielded in V than in the other compounds, even though V possesses the most electron-withdrawing groups. Such shielding can only be due to the incursion of the methoxy into the shielding region of the other benzene ring (19–21). Since the effect is large,[7] the occupancy of the conformation of Fig. 2 must also be large in compound V, relative to that for the other compounds.[7]

A consideration of the chemical shifts of the hydrogens on the lower ring confirms and extends the previous conclusions. Examination of Figs. 4–9[8] shows that, except for compound I*a*, assignment of lines can be made by inspection, the ortho-coupling constants being much larger than the meta-coupling constants, and the para-coupling constants being unresolved. It will be seen that the signal for H_g in the triply ortho-substituted diphenyl ethers I, III, IV, and VIII lies at higher field by 16–23 c.p.s. than in the corresponding anisoles (I*a*, III*a*, IV*a*, and VIII*a*, respectively), the signal for H_f at higher field by 8–11 c.p.s., and the signal for H_e at lower field by 4–12 c.p.s. This variation for H_g and H_f is in a direction opposite to that actually observed for H_e (or for H_a in a similar situation in the upper ring). The increase in shielding of H_g and H_f can only be due to shielding by the other ring and the conformation of Fig. 3 must be important for these compounds.

The climax of our argument comes with the examination of the spectra of II and II*a* (Fig. 8). In the first place, the simple A_2B_2 pattern from II shows that the two "H-inside" conformations are exchanged at such a rate as to give each an average lifetime much shorter than the average lifetime of the proton spin states. In the second place, H_k is slightly less shielded in II than in the corresponding anisole II*a*; shielding by the other ring is not quite sufficient to compensate for inductive withdrawal, even though this is less than in III, IV, and VIII. Since the two "H-inside" states must be equally populated in II, the extra shielding of H_g in I, III, IV, and VIII shows that the "H_g-inside" conformation must be occupied much more than the "nitro-inside" conformation, and must be the dominant conformation.

The equivalence of the hydrogens H_e and H_f in V is less illuminating, since it could be due either to a predominantly "methoxy-inside" conformation (Fig. 2) or to a rapid averaging of the two "nitro-inside" conformations.

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[7] *The fact that compounds I–IV, and VIII, have* H_a *either more shielded than, or about as shielded as, in metameconine (VII), and the fact that* H_d *is more shielded in them than in methoxymetameconine (VI), in spite of the electrical character of the lower rings, presumably mean that in them the conformation corresponding to Fig. 2 also must be occupied an appreciable part of the time, though much less than in V. In principle, the relative occupancies are calculable from both effects. This is now being attempted with more favorable examples.*

[8] *In all the spectra, except that for Ia, the lines reproduce the center and the approximate amplitude of the observed peaks. The spectrum for Ia is the result of an ABX calculation which agreed very closely indeed with the observed spectrum. ABX calculations were done for a few other compounds as well, but except for Ia, the changes incurred in band positions with respect to simple inspection were negligible.*

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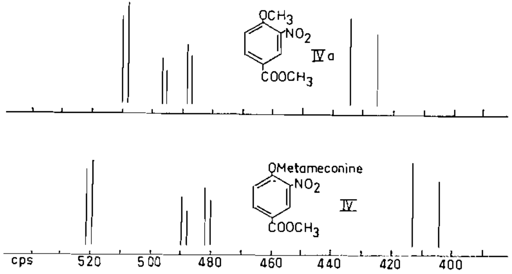

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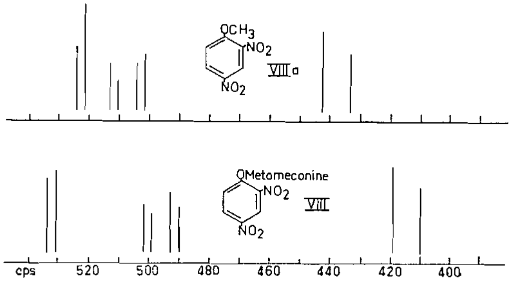

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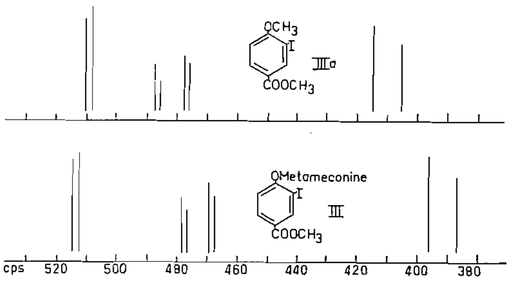

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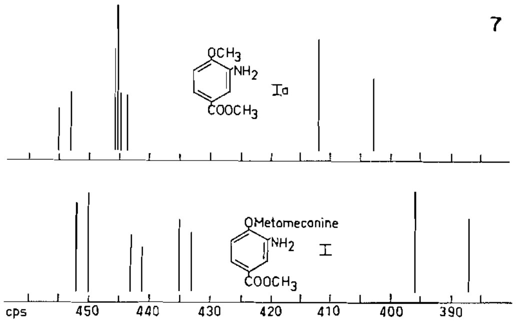

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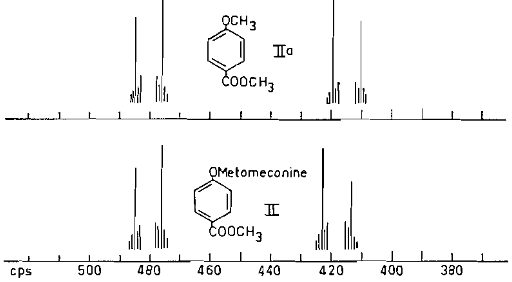

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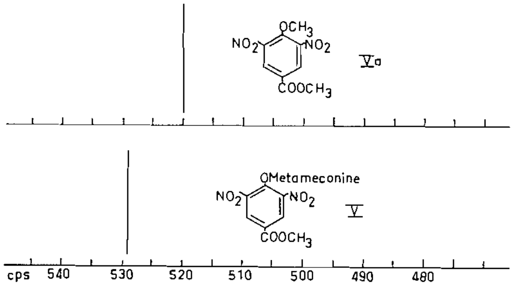

FIGS. 4–9. Schematic n.m.r. spectra of aromatic protons. C.p.s. down field from TMS in $CHCl_3$ or $CDCl_3$ solution, at 60 Mc.p.s.

General agreement with the geometry already proposed for the various ethers (and anisoles) can be deduced from Table II, in the manner already used for other groups.

TABLE II

Chemical shift of the carbomethoxy[9] protons H_h

Compound	Tau values	Compound	Tau values
I	6.15	IV	6.07
I*a*	6.15	IV*a*	6.07
II	6.13	V	5.98
II*a*	6.17	V*a*	5.98
III	6.13		
III*a*	6.13		

[9] *The signal was assigned on the basis of the expected chemical shift. It has been checked to some extent by comparing the spectrum of methyl 4-methoxy-3-nitrobenzoate (IVa) with that of the corresponding ethyl ester, and by comparing the spectrum of ester IV with that of the corresponding acid (in acetone).*

Evidence from Infrared Spectra

A plot of the stretching frequency of the phthalide carbonyl vs. the sum of the Hammett parameters σ_m for the ortho-groups of the lower ring of I, II, III, IV, and V (Fig. 10) shows a linear[10] variation for the first four ethers, but a sharp variation from the line for the fifth. The latter has a frequency lower than IV although it contains an extra nitro group. This evidence strongly indicates that the principal conformation of V must be that of Fig. 2, where the inductive effect is strongly opposed by electron donation from the ether oxygen to the carbonyl. Similarly, the high value of the asymmetric nitro stretching frequency (Table III), both for the quadruply ortho-substituted diphenyl ether V and the corresponding anisole V*a*, shows that in neither compound is the (lower) benzene ring coplanar with the C—O—C bond under study (Fig. 2). The lower values for IV and IV*a* are in agreement with the greater opportunities for resonance in the conformation similar to that of Fig. 3. The values for VIII and VIII*a*, though presumably they refer to the para-nitro group, also correspond to considerable resonance between the lower ring and the oxygen under study (Fig. 3).

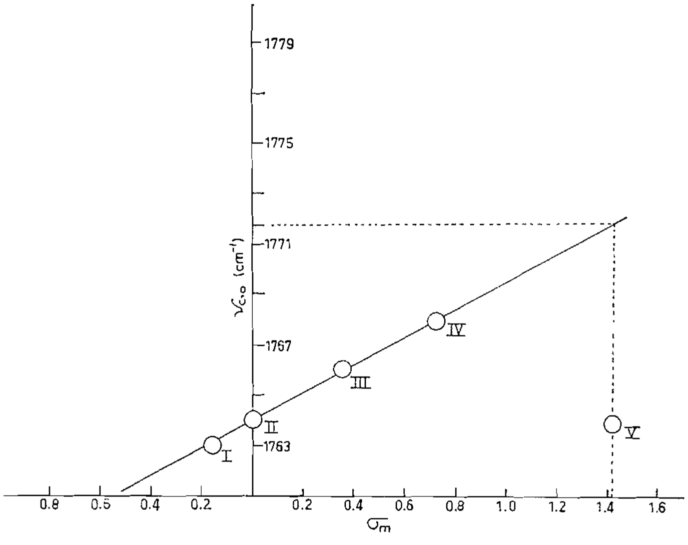

FIG. 10. Lactone carbonyl absorption vs. σ_m of ortho-substituent on other ring.

TABLE III

Asymmetric nitro absorption frequencies

Compound*	Frequency (cm^{-1})
V	1551
V*a*	1550
IV	1541
IV*a*	1539
VIII	1540†
VIII*a*	1531†

*In chloroform solution.
†With shoulder on the high-frequency side.

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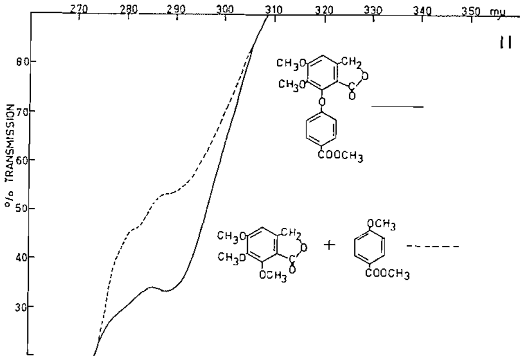
[10] *The linear variation is good evidence that the steric effects are the same in the four ethers concerned. The conformation of Fig. 3 also is strongly suggested, since otherwise the varying sizes of the ortho-groups would have a noticeable effect. However, it can be shown that the choice of* σ_m, *rather than some other, is not significant.*

The single sharp peak for the asymmetric nitro stretching vibration of V is noteworthy inasmuch as it is to be expected for the "methoxy-inside" conformation (Fig. 2), but would be surprising in the "nitro-inside" conformation because of the extremely short average lifetimes of vibration states. Conclusions from the ester carbonyl stretching frequency merely confirmed those made from the n.m.r. frequencies of the ester methyl.

Relation to the Ultraviolet Spectra

According to the method used by Mangini and Passerini (1) for diphenyl sulphides, the configuration of Fig. 2 (V) might be expected to show ultraviolet absorption approximately the same as the sum of the absorptions of methoxymetameconine (VI) and methyl 3,5-dinitrobenzoate, whereas the configuration of Fig. 3 should absorb the same as the sum of the absorptions of metameconine (VII) and the anisole corresponding to the other ring. In Figs. 11–16 are shown the absorption of several diphenyl ethers, together with the



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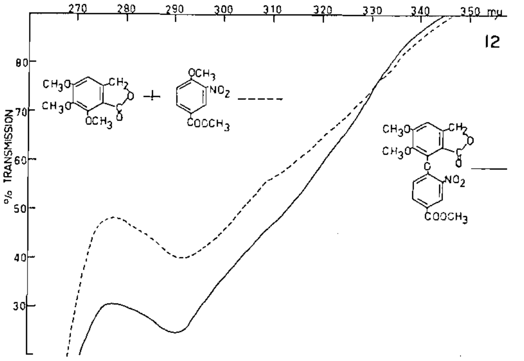

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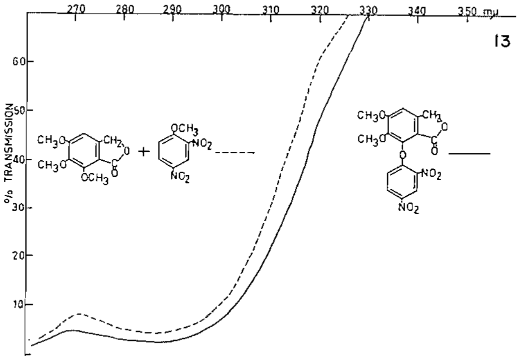

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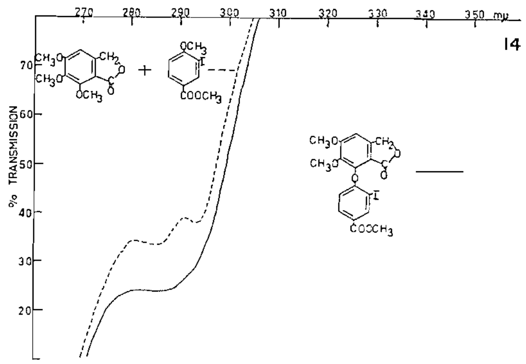

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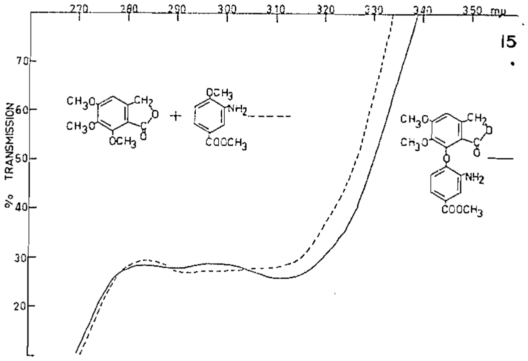

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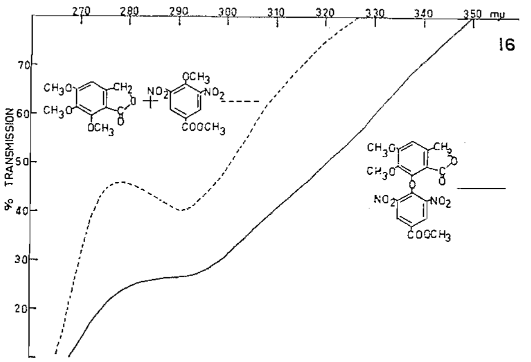

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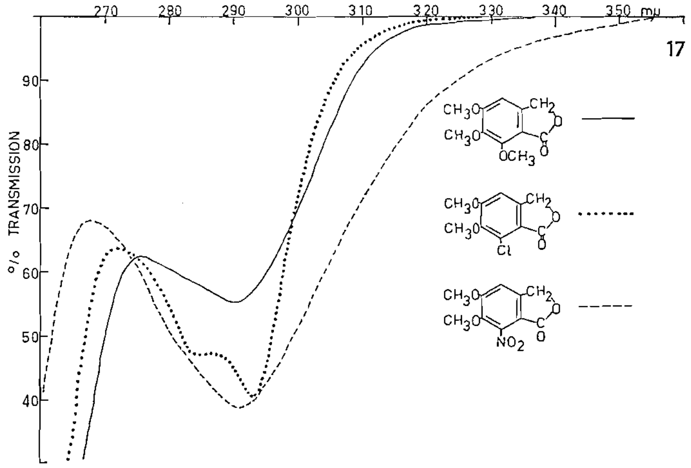

FIGS. 11–17. Ultraviolet spectra of diphenyl ethers and of corresponding anisoles. Concentrations are 1.00×10^{-4} *M* in CCl_4.

spectrum of a solution of a mixture of the two anisoles corresponding to the parts of the diphenyl ethers; each anisole is at the same molarity as its related diphenyl ether. It is at once evident that caution must be used in interpreting the curves. The absorption of each diphenyl ether is similar to, but greater than, the sum of the absorption of its two related anisoles, and therefore much greater than the absorption of the related anisole plus phenyl derivative considered by Mangini and Passerini. A first (naive) conclusion would be that the central ethereal oxygen is capable of resonance with both rings at once. The corrective to this conclusion is supplied by Fig. 17, where it is seen that an increasingly electron-withdrawing group at position-7 of metameconine results in an increasingly intense absorption. Therefore, the diphenyl ethers I–IV, and VIII, probably are acting simply as the summation spectra of the corresponding anisoles (I*a*–IV*a*, and VIII*a*, respectively) plus a metameconine substituted at position-7 with a group rather more electron-withdrawing than the methoxy group. In fact, the summation curve of IV*a* and either 7-nitrometameconine or 7-acetaminometameconine was found to be very close to that of the diphenyl ether IV. These results are therefore in agreement with the conformation of Fig. 3. We have not managed to obtain suitable monomers for comparison with V (expected to have the other configuration of Fig. 2), but at least it does differ empirically from all the other diphenyl ethers studied in the enormous difference in the long-wave absorption between the diphenyl ether (V) and its two related anisoles (VI and V*a*).

The practical utility of the determination of the principal conformations of diphenyl ethers was made apparent almost immediately by its use in the discovery of a new rearrangement reaction in the diphenyl ether series, and by the application of the method, based on the present work, to the determination of conformation and configuration in the phthalide–isoquinoline alkaloids (19). The present work is continuing in attempts to relate quantitatively the temperature, solvent, and the size and nature of the substituents to the principal variables of the system: the magnitude and area of the shielding current loops, the magnitude of the oxygen valence angle, and the percentage occupancy of each major conformation.

EXPERIMENTAL

Melting points below 215° were determined in a precision capillary apparatus; higher melting points were determined on a Kofler micro hot stage, and are uncorrected.

Solvents of spectral or analytical grade were used for ultraviolet and infrared spectroscopy. Ultraviolet spectra were determined on a Beckman model DK-1 recording spectrophotometer; calibration of the instrument with benzene (A.C.S. grade, 0.00788 M in heptane) showed that the corrections required were negligible (22). All spectra were obtained on solutions 1.00×10^{-4} M in carbon tetrachloride.

Infrared spectra were determined on a Perkin–Elmer model 21 spectrophotometer repeatedly calibrated with a polystyrene standard (23). With care, results were reproducible within 1 cm^{-1}. Spectra were determined on solutions in chloroform containing 6% of the substance investigated (w/v).

The n.m.r. spectra were determined on the Varian A-60 spectrometer at 60 Mc.p.s. At the end of the work, the same sweep width used to determine the reported frequencies was calibrated by a sideband method; the largest error was about 2 c.p.s. and was exceptional. The reproducibility of spectra taken several weeks apart ensured the stability of the calibration. Spectra for I*a*–VIII*a*, VI, and VII were determined on 75 mg of sample in 0.5 ml of chloroform or deuterochloroform. Minor variations in concentration were unimportant, as shown; IV*a* gave identical spectra in concentrations of 75 mg/0.5 ml and 30 mg/0.5 ml. The spectra of compounds II–V and VIII were determined using a concentration of 50 mg/0.5 ml chloroform or deuterochloroform. However, I, because of its low solubility, would dissolve only at a concentration of 20 mg/0.5 ml.

A few substances, mentioned in the introduction but not in the sections below, were available as analytical samples from previous work (16–18, 24).

The following substances were made by treatment of the appropriate phenol with ethereal diazomethane (the melting point after purification is also given): methyl 4-methoxybenzoate (II*a*) (25), 47.7–48.5°; methyl 4-methoxy-3-nitrobenzoate (IV*a*) (26), 109.1–109.4°; methyl 3,5-dinitro-4-methoxybenzoate (V*a*) (27, 28), 53.6–54.2°; 2,4-dinitroanisole (VIII*a*) (29), 87.2–88.1°.

Methyl 3-Amino-4-methoxybenzoate (Ia)

Methyl 4-methoxy-3-nitrobenzoate (IV*a*) (3.0 g, m.p. 107.5–108.5°) was covered with ethanol (95%, 150 ml) and water (100 ml) and stirred while amalgamated aluminium foil (10 pieces, 2 × 1 in.) was added. After 5–6 h, the heavy sludge was removed, the filtrate concentrated by evaporation, and then diluted with water to give needles, m.p. 69.3–69.6°, in a yield of 1.29 g. The needles were purified by solution in dilute hydrochloric acid and by reprecipitation with ammonia, and then by four recrystallizations from ligroin, to give the analytical sample, m.p. 70.1–70.8°, slightly yellow needles. The infrared spectrum showed the presence of N—H stretching bands and the absence of nitro-group stretching bands. The melting point differed considerably from the literature value of 85–86° (26).

Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.71, 59.77; H, 6.06, 6.05; N, 7.66, 7.67.

Attempts to reduce the nitro ester with iron and acetic acid failed, though this reduction system worked well for the corresponding diphenyl ether (IV). Reduction of 4-hydroxy-3-nitrobenzoic acid with aluminium amalgam also failed. The course of reduction of IV*a* with tin and hydrochloric acid was unusual, as shown in the next section.

Methyl 3-Amino-2-chloro-4-methoxybenzoate

Methyl 4-methoxy-3-nitrobenzoate (IV*a*) (2.0 g, m.p. 107.5–108.5°) was stirred with concentrated hydrochloric acid (25 ml) and aqueous ethanol (5 ml) while mossy tin (six pieces the size of a pea) was added. Heat was applied until a green solution resulted. The solution was cooled, neutralized with aqueous sodium hydroxide (30%), and the heavy white precipitate (0.66 g) was collected. Two crystallizations from ligroin (the material insoluble in hot ligroin being discarded) gave the analytical sample, obtained as white plates, m.p. 91.7–92.2°. (Recrystallization from dilute ethanol gave needles.) The infrared spectrum showed two bands of medium intensity in the N—H stretching region, and the orientation of the compound followed from the n.m.r. spectrum, which showed an aromatic AB pattern with a coupling constant (8.4 c.p.s.) characteristic of ortho-protons.

Calcd. for $C_9H_{10}O_3NCl$: C, 50.13; H, 4.67; N, 6.50. Found: C, 50.30, 50.38; H, 4.84, 4.74; N, 6.32, 6.26.

Methyl 3-Iodo-4-methoxybenzoate (IIIa)

This compound was difficult to obtain. The iodination of methyl 4-hydroxybenzoate in aqueous potassium hydroxide and potassium iodide gave only the free acid corresponding to the starting material. Iodination of 4-hydroxybenzoic acid in ethanol with mercuric oxide and iodine by the method of Brenans and Prost (30) failed to give a recognizable product. Reduction of 3,5-diiodo-4-hydroxybenzoic acid with triphenylphosphine in boiling xylene (31), or with iron and acetic acid, gave only starting material. Small yields of 4-hydroxy-3-iodobenzoic acid were obtained by the reduction of the 3,5-diiodo-acid with zinc and aqueous sodium hydroxide.

Moderate yields of the desired acid were obtained by the method of Sanromá (32). Methyl 4-hydroxybenzoate (6.0 g) was dissolved in aqueous sodium hydroxide (2.85 g in 25 ml of water). Iodine (10.0 g) and sodium peroxide (1.8 g) were added in alternate portions over the course of 4 h, and the mixture kept a further 18 h. The product was then fractionally precipitated with hydrochloric acid, seven fractions being obtained. The first six were united and recrystallized from a dilute aqueous solution of sodium bisulphite. The material insoluble in the hot solution was mainly the diido acid, while the cooled filtrate deposited crude 4-hydroxy-3-iodobenzoic acid, m.p. 160–175° (uncorrected), which gave a typical aromatic ABC pattern in the n.m.r. spectrum. (The seventh fraction seemed to be mainly 4-hydroxybenzoic acid.) The crude monoiodo acid was methylated with ethereal diazomethane and the product recrystallized once from ligroin, once from methanol, and once from absolute ethanol to give a fluffy white product, m.p. 94.6–95.2°. The lit. value (33) is 94–95°. Its aromatic spectrum showed a typical aromatic ABC pattern and two methoxy resonances; the infrared spectrum showed no bands due to hydroxyl or carboxyl.

7-(4′-Carbomethoxy-2′-nitrophenoxy)metameconine (IV) (16, 17), m.p. 155.6–156.6°, 7-(2′-amino-4′-carbomethoxyphenoxy)metameconine (I) (18), m.p. 197.1–197.8° (with slight softening at 195°), and 7-(4′-carbomethoxy-2′-iodophenoxy)metameconine (III) (18), m.p. 204.2–205.0°, were made as previously described.

4-Carbomethoxy-2-nitrophenyl Toluene-p-sulphonate

This compound, needed in the above syntheses, was made by a method giving a much purer product in better yield than obtained previously (16, 17). Methyl 4-hydroxy-3-nitrobenzoate (15 g) and *p*-toluenesulphonyl chloride (15 g tech.) were shaken with dry pyridine (25 ml) until the mass became almost solid (10–15 min). The solid was washed with water into a beaker containing dilute hydrochloric acid (500 ml) and ice, and the resulting lumps were thoroughly crushed under the acid solution. White crystals were recovered, washed, and dried, and without further purification had a m.p. of 93.4–94.2°, yield 26.65 g (100%).

7-(4′-Carbomethoxyphenoxy)-metameconine (II)

Sodium nitrite (0.124 g) was dissolved with slight heating in concentrated sulphuric acid (2.5 ml); the solution was cooled to 0° and treated with glacial acetic acid (2.5 ml). A second solution was prepared from 7-(2′-amino-4′-carbomethoxyphenoxy)-metameconine (I) (18) (0.5 g) in concentrated sulphuric acid (1.0 ml) and glacial acetic acid (2.5 ml). The second solution was slowly added to the first over a period of 0.5 h, the reaction temperature being kept slightly below 0°. A few milliliters of concentrated sulphuric acid were then added to make the mixture more fluid, and after a further 1.75 h, the mixture was poured onto ice (100 g) to which had been added a small amount of cupric sulphate. Hypophosphorous acid (12 ml, 50%) was added dropwise with stirring. The mixture was kept 42 h in the refrigerator, and the granular precipitate (0.45 g) recovered. Two recrystallizations from dilute ethanol gave yellowish-white crystals, m.p. 195.2–196.1°, more easily purified than those obtained by the previous method (18). The n.m.r. spectrum of the present sample was identical with that of the sample made in the previous work (18).

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