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THYROXINE ANALOGS—XIII[1]

NMR EVIDENCE FOR HINDERED ROTATION IN DIPHENYL ETHERS[2]

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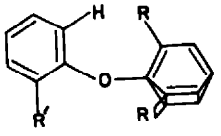
Abstract—The postulate[3] that *o,o*-disubstituted diphenyl ethers related to thyroxine may exist in a preferred skewed conformation was examined by NMR. Aromatic proton absorption at anomalously high fields (ca. $\delta = 6$), ascribable to a proton positioned above an aromatic ring, is found when rotation is hindered by a sufficiently bulky substituent (R′) at the third position flanking the ether linkage:

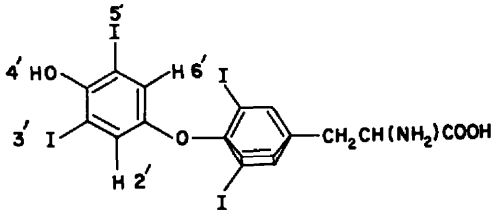


R = NO_2 or I; R′ = C_6H_{11}, $CH(CH_3)_2$, CH_2—CH=CH_2, CF_3, CH_3

The complete NMR spectra of some thyroxine analogs in the form of their N-acetyl ethyl esters have been analyzed, and previous work on the stereochemistry of diphenyl ethers is discussed in view of these results.

INTRODUCTION

AS THE basis for our work on the structure-activity relationships of thyroxine analogs, we postulated[3] that these *o,o*-disubstituted diphenyl ethers may exist in a preferred conformation due to hindered rotation about the ether linkage. The ring bearing the bulky *ortho* substituents positions the other ring in a plane perpendicular to and bisecting the plane which it occupies:

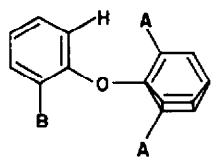


Thyroxine

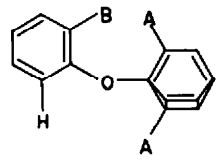
In this skewed conformation positions 2′ and 6′ (as also 3′ and 5′) are not equivalent.

[1] Previous paper in this series, E. C. Jorgensen and J. A. W. Reid, *J. Org. Chem.*, **29**, 3396 (1964).
[2] A preliminary account of this work was presented to the American Pharmaceutical Association in New York, August (1964).
[3] N. Zenker and E. C. Jorgensen, *J. Amer. Chem. Soc.* **81**, 4643 (1959).

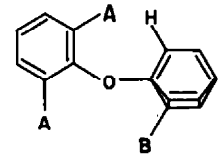
Examination of models of various 2′-substituted 2,6-dinitro- and 2,6-diiododiphenyl ethers showed that there are three possible skewed conformations (I–III):



I H-proximal



II H-distal



III

Conformer I, in which the 6′-proton is *proximal*[4] to the positioning ring is greatly preferred over II and III in which a bulky substituent is *proximal*.

Measurements on models and calculations for conformer I show that the 6′-proton is located about 1·6 Å from the normal to the center of the positioning ring (approximately over the carbon bearing the ether linkage) and about 2·3 Å above the plane of the ring. That is, well within the region in which the magnetic resonance of this proton would be affected by the π-cloud as estimated by Johnson and Bovey.[5] This observation, together with the availability of an extensive collection of such diphenyl ethers in the form of thyroxine analogs and synthetic intermediates provided a practical way of obtaining physical evidence for our postulated conformation.

EXPERIMENTAL

About 25–50 mg of the N-acetyl ethyl ester derivative of the thyroxine analog, chosen on account of solubility in aprotic solvents, was dissolved in about 1 ml. of $CDCl_3$ to which a trace of TMS had been added. The NMR spectra were obtained on a Varian Associates A-60 spectrometer at 35–37°. The assignments are accurate to $\pm$0·01 ppm and the coupling constants are estimated to $\pm$0·5 c/s. Chemical shifts are expressed in ppm (δ units) from TMS taken as 0·00.

RESULTS

Protons invariably present

Table 1 gives the average chemical shifts of protons present in all analogs other than those directly pertinent to the stereochemical argument. They are presented since no report has been found on the NMR spectra of compounds related to thyroxine or of amino acids in the form of their N-acetyl esters. Typical spectra are shown in Fig. 1.

β-Carbon protons. In the dinitro series these appear as an unresolved multiplet (four main peaks) due to coupling with the α-carbon proton and the presence of a neighbouring asymmetric center.[6] In the diiodo series this methylene group shows only a doublet ($J = 6{\cdot}5$) as a result of coupling with the α-carbon proton; the signals are broadened due to incomplete equivalence of these protons (e.g. Fig. 1b).

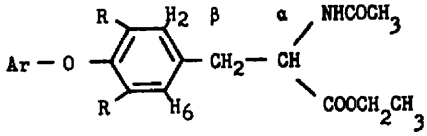
α-Carbon proton. In the dinitro series this proton appears as an unresolved multiplet due to splitting by the amido proton and the non-equivalent methylene protons. In the diiodo series a double triplet was expected due to coupling with the β-carbon protons and the amido proton. Four peaks of intensities 1:3:3:1 were observed in most cases, with a separation between the central peaks of 7·5 c/s and

[4] The terms *proximal* and *distal* are preferred to *cis* and *trans* on account of the three dimensional nature of the question.

[5] C. E. Johnson, Jr. and F. A. Bovey, *J. Chem. Phys.* **29**, 1012 (1958).

[6] L. M. Jackman, *Applications of NMR in Organic Chemistry* p. 99. Pergamon Press, London (1959).

TABLE 1. AVERAGE CHEMICAL SHIFTS OF PROTONS IN N-ACETYL ETHYL ESTER DERIVATIVES OF THYROXINE ANALOGS[a]



Proton	R	Mean δ, ppm	Range of δ, ppm	Number of compounds[b]	Multiplicity	J, c/s
Ethyl methyl	NO_2, I	1·29	1·25–1·32	65	Triplet	7·5
Ethyl methylene	NO_2, I	4·22	4·13–4·30	65	Quartet	7·5
Acetyl methyl	NO_2, I	2·02	1·97–2·06	65	Singlet	—
α-Carbon	NO_2, I	4·82	4·71–4·90	64	Four peaks[c]	—
β-Carbon	NO_2	3·24	3·11–3·32	34	Four peaks[c]	—
β-Carbon	I	3·05	3·02–3·10	29	Two peaks[c]	6·5
Amido	NO_2	6·42	6·22–6·68	28	Broad doublet[c]	7·0–8·0
Amido	I	6·26	6·12–6·70	21	Broad doublet[c]	7·0–8·0
2,6	NO_2	7·96	7·78–8·10	36	Singlet	—
2,6	I	7·64	7·57–7·70	29	Singlet	—

[a] Includes D-, L- and D,L-compounds.
[b] Only compounds where an unequivocal assignment was possible are included.
[c] See text.

of 6·0 c/s between the outer ones. This is the result of two triplets of relative intensities 1:2:1 being offset by 7·5 c/s and superimposed. In a few instances (e.g. No. 47, Fig. 2) the six peaks could be discerned.

Amido proton. The absorption of the amido proton was found to be concentration dependent. Since it was not possible to obtain all spectra at the same molar concentration, a large portion of the observed range for this proton may be due to this effect. This was proven for one particular compound (No. 19, Table 2) which on twofold dilution showed a shift from 6·41 to 6·28.

Aromatic methyl protons

These appeared at an average position of 2·27 (2·02 to 2·48 among 56 examples in 33 compounds) in both the dinitro and diiodo series (compounds in Tables 2–4). In analogs with more than one aromatic methyl group, no consistent relationship between point of substitution and chemical shift could be discerned.

Aromatic methoxy protons

Compounds in Tables 2–4. In the dinitro series the average position was 3·76 (3·58 to 3·93 among 13 examples in 12 compounds) and no apparent difference was noted between methoxy groups *ortho* and *para* to the ether linkage. (No *meta*-methoxy compounds were examined.) However in the diiodo series the average position for a *p*-methoxy proton was 3·80 (3·73 to 3·91 in 8 examples) and 3·98 (3·92 to 4·08 in 4 examples) for an *o*-methoxy proton.

Aromatic protons

Most of the compounds examined were found to fall into two categories: those in which there was no evidence for a positioning of one ring by the other (Table 2), and those in which it appeared that positioning was being observed (Table 3).

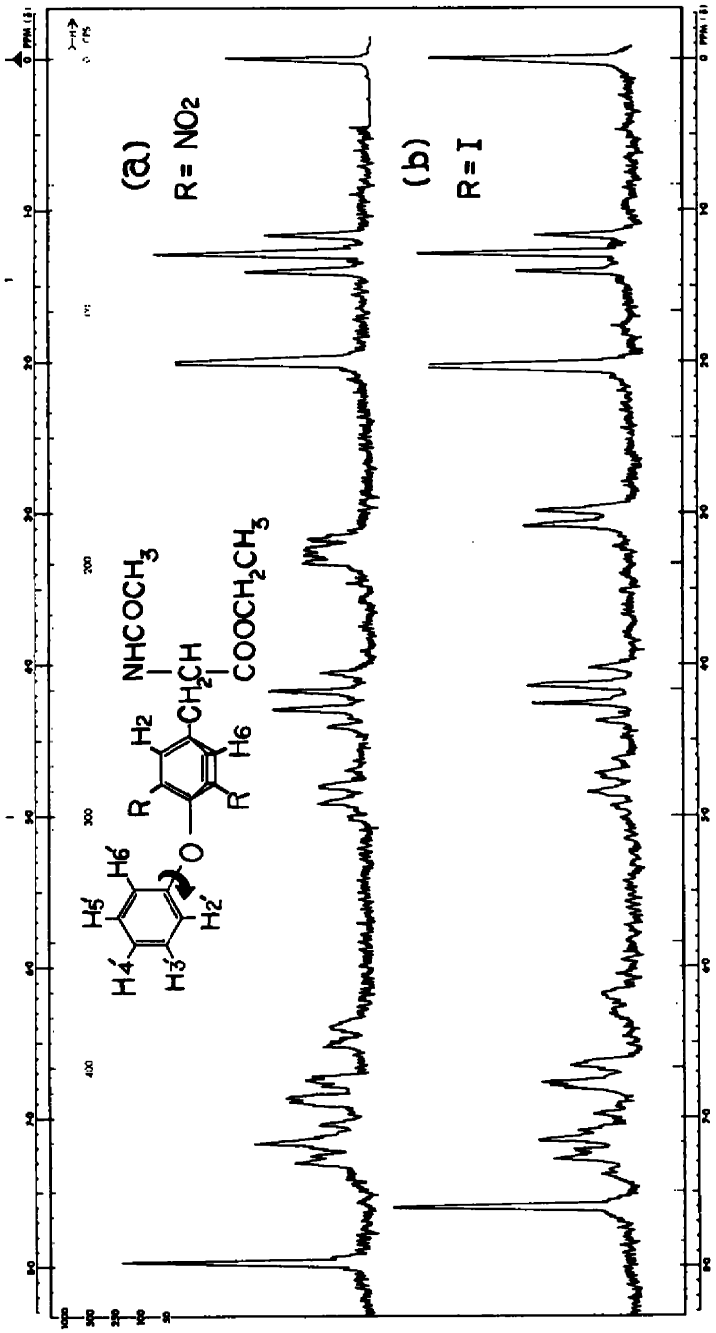


FIG. 1. NMR spectra of
(a) N-acetyl-4-phenoxy-3,5-dinitrophenylalanine ethyl ester (No. 1) and
(b) N-acetyl-4-phenoxy-3,5-diiodophenylalanine ethyl ester (No. 2).

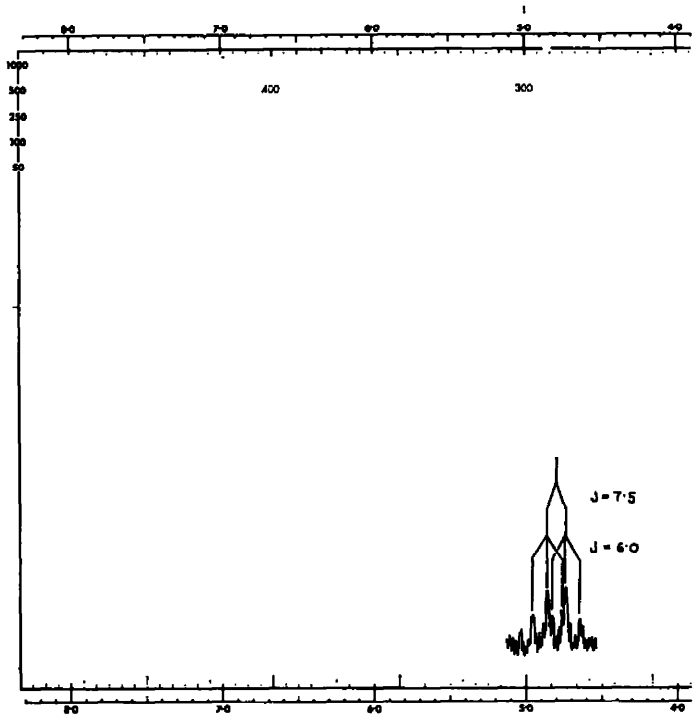


FIG. 2. α-Carbon proton NMR spectrum of N-acetyl-2′-cyclohexyl-4-phenoxy-3,5-diiodophenylalanine ethyl ester (No. 47).

In the non-positioned group the chemical shifts for the aromatic protons in the outer ring range from 6·36 to 8·2. In the unsubstituted analogs (No. 1 and 2, Fig. 1a and 1b) the phenoxy protons resonate between 6·6 and 7·5, which can be considered a normal range for protons of this type.

In Table 3 are listed those analogs whose spectrum could be interpreted in terms of the postulated skewed conformation, with the positioned *proximal* proton resonating at an unusually high field. The average chemical shift of these positioned protons was 6·22 (5·98 to 6·45 in 17 examples) in the dinitro series, and 6·07 (5·87 to 6·27 in 15 examples) in the diiodo series.

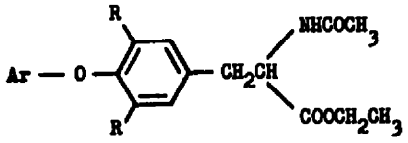
Table 4 lists those compounds in which it is not clear whether positioning is taking place or not.

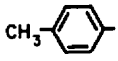
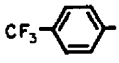
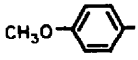
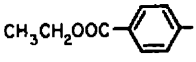
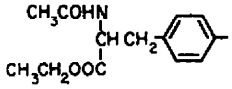
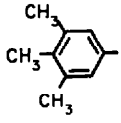
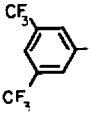
DISCUSSION OF THE RESULTS

Chemical shift of the positioned proton

The average resonance position of the positioned proton was 6·22 in the dinitro series and 6·07 in the diiodo series, representing respectively a shielding of 1·15 and 1·30 ppm relative to benzene protons (7·37). As Table 3 shows, the positioned proton resonates 0·4 to 1·2 ppm (except No. 54) upfield from any other proton on the same ring. This consistent difference is seen throughout the series examined which includes a great variety of substituents attached at different points to the positioned ring, excluding the possibility that the observed shifts are due to the substituents. Conversely,

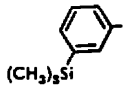
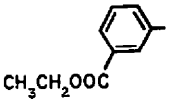
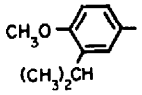
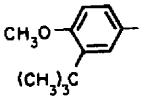
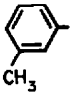
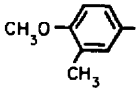
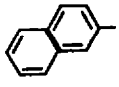
TABLE 2. CHEMICAL SHIFTS OF THE OUTER RING PROTONS IN NON-POSITIONED N-ACETYL ETHYL ESTER DERIVATIVES OF THYROXINE ANALOGS



No.	Ar	R	δ, ppm 2′,6′	4′	3′,5′	Ref.
1		NO_2	—	6·7–7·5[a]	—	7
2		I	—	6·6–7·5[a]	—	7
3		NO_2	—	6·6–7·2[a]	—	8
4		NO_2	7·02[b]	—	7·41[b]	8
5		I	6·81[b]	—	7·55[b]	8
6		NO_2	6·78	—	6·78	9
7		NO_2	6·97[b]	—	7·98[b]	8
8		I	6·77[b]	—	7·99[b]	8
9		I	6·70[b,c]	—	7·06[b,c]	10
10		NO_2	6·46	—	—	8
11		I	7·17	7·56	—	8

[7] E. C. Jorgensen, unpublished.
[8] S. J. Feinglass, Dissertation, University of California, San Francisco (1964).
[9] E. C. Jorgensen and R. W. Wiley, *J. Med. Chem.* **6**, 459 (1963)
[10] E. C. Jorgensen and R. Cavestri, *J. Pharm. Sci.* **52**, 481 (1963).

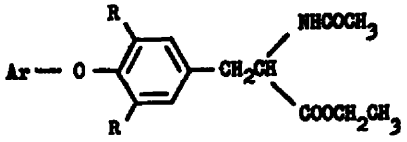
TABLE 2 (*Contd.*)

No.	Ar	R	δ, ppm 2′,6′	4′	3′,5′	Ref.
12		NO_2	—	6·5–7·8[a]	—	11
13		NO_2	—	6·9–7·9[a]	—	8
14		I	—	6·7–7·9[a]	—	8
15		I	2′ = 6·78[c]	5′ = 6·73[b]	6′ = 6·36[b,c]	3
16		I	2′ = 6·87[c]	5′ = 6·72[b]	6′ = 6·37[b,c]	12
17		NO_2	—	6·4–7·2[a]	—	8
18		I	—	6·5–7·4[a]	—	8
19		NO_2	—	6·5–6·8[a]	—	9
20		NO_2	—	7·0–8·0[a]	—	13
21		I	—	6·7–8·2[a]	—	13

[a] Spectrum was not interpreted; total absorption span.
[b] Doublet, J = 7–9 c/s.
[c] Doublet or further splitting, J = 3 c/s.

[11] E. C. Jorgensen and P. Slade, unpublished.
[12] B. Blank, F. R. Pfeiffer, C. M. Greenberg and J. F. Kerwin, *J. Med. Chem.* **6**, 554 (1963). We are grateful to Dr. J. A. W. Reid of our laboratories for a sample of this compound as the L-isomer.
[13] E. C. Jorgensen and P. A. Lehman, *J. Org. Chem.* **26**, 897 (1961).

TABLE 3. CHEMICAL SHIFTS OF THE OUTER RING PROTONS IN POSITIONED N-ACETYL ETHYL ESTER DERIVATIVES OF THYROXINE ANALOGS



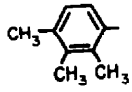
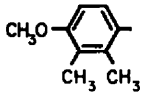
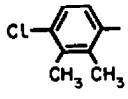
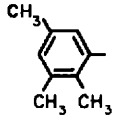
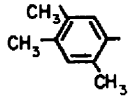
No.	Ar	R	δ, ppm 6′	5′	4′	3′	Ref.
22		NO_2	6·12[b]	6·78[b]	—	—	8
23		I	5·93[b]	6·75[b]	—	—	8
24		NO_2	6·12[b]	6·46[b]	—	—	7
25		I	5·96[b]	6·47[b]	—	—	7
26		NO_2	6·18[b]	7·00[b]	—	—	3
27		I	5·97[b]	6·98[b]	—	—	3
28		NO_2	5·98	—	6·65	—	8
29		I	5·87	—	6·68	—	8
30		I	6·25[b,c]	6·77[b]	7·48[b,c]	—	8
31		NO_2	6·14	—	—	6·94	8

TABLE 3 (*Contd.*)

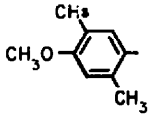
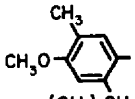
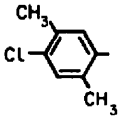
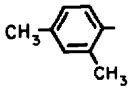
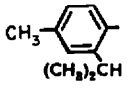
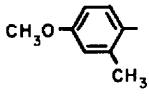
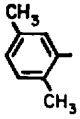
No.	Ar	R	δ, ppm 6′	5′	4′	3′	Ref.
32		NO_2	6·18	—	—	6·64	3
33		I	5·94	—	—	6·71	3
34		NO_2	6·27	—	—	6·69	3
35		I	6·05	—	—	6·74	3
36		NO_2	6·22	—	—	7·16	3
37		I	6·02	—	—	7·22	3
38		I	6·20[b]	6·74[b]	—	6·99	3
39		NO_2	6·20[b]	6·77[b]	—	7·10	3
40		NO_2	6·29[b]	6·69[b]	—	6·74	3
41		I	6·09[b]	6·54[b,c]	—	6·83[c]	3
42		NO_2	6·15	—	6·77[b,d]	7·10[b,d]	3
43		I	6·00	—	6·75[b,d]	7·13[b,d]	3

TABLE 3 (*Contd.*)

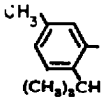
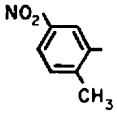
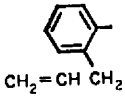
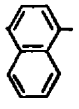
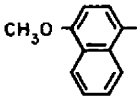
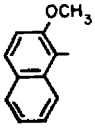
No.	Ar	R	δ, ppm 6′	5′	4′	3′	Ref.
44		NO_2	6·13	—	6·82[b,d]	7·19[b,d]	3
45		NO_2	7·20[c,e,f]	—	7·89[b,e]	7·38[b]	8
46		NO_2	6·32[b]	—	6·9–7·4[e]	—	8
47		I	6·14[b]	—	6·8–7·4[e]	—	8
48		NO_2	6·32[b]	—	6·9–7·3[a]	—	3
49		I	6·2[b]	—	6·8–7·3[a]	—	3
50		NO_2	6·61[b,e,f]	—	7·0–8·2[a]	—	8
51		NO_2	6·33[b]	—	6·8–7·3[a]	—	8
52		NO_2	6·45[b,g]	—	7·1–8·2[a]	—	13
53		I	6·27[b,c,g]	—	7·1–8·4[a]	—	13
54		NO_2	6·36[b,g]	6·53[b,h]	—	7·4–8·4[a]	—	13
55		I	6·12[b,g]	6·53[b,h]	—	7·4–8·4[a]	—	13

TABLE 3 (*Contd.*)

No.	Ar	R	δ, ppm 6′	5′	4′	3′	Ref.
56		NO_2	—	—	7·0–8·3[a]	—	11

[a] Spectrum was not interpreted; total absorption span.
[b] Doublet, J = 7–9 c/s.
[c] Doublet or further splitting, J = 3 c/s.
[d] Unequivocal assignment not possible.
[e] Not included in calculation of average shift of positioned protons.
[f] Considered positioned on the basis of this shift relative to that of the other protons on the same ring.
[g] 2′-Proton; see text.
[h] 3′-Proton; see text.

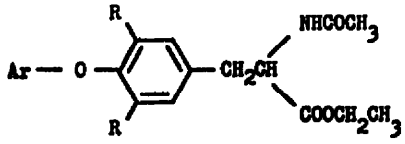
comparison of isomeric compounds such as No. 10 and 31 (Fig. 3) confirms the fact that the shielding observed is due to the positioning of the proton over the opposite ring; in these compounds no difference of the magnitude observed would be expected from the difference in points of substitution of the methyl groups.

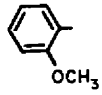
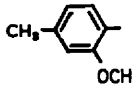
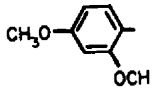
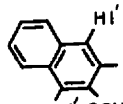
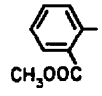
The positioned proton in the diiodo series is found consistently upfield (average 6·07) from that in the dinitro series (average 6·22). This is probably a result of higher π-electron density in the diiodo ethers. However differences in long-range shielding effects by the magnetically anisotropic nitro group and the iodine-carbon bond, as well as differences in inductive effects from one ring to the other may also be involved.

Johnson and Bovey[5] have calculated the theoretical chemical shift of protons in the neighbourhood of a benzene ring. Using these calculations and accepted bond lengths (C—C = 1·39 Å; C—H = 1·08 Å; C—O = 1·42 Å) together with values of the oxygen valency angle of 116° and 125°, which are reasonable values bracketing the "best" value of 120°,[16] the calculated shielding is approximately 2·5 to 3·0 ppm. The observed shieldings were about one half to one third as great. However the *direction* of the change towards greater shielding is in agreement with theory. This discrepancy may have several explanations. The density of the π-cloud over the point in question is certainly smaller in a dinitrobenzene than in benzene itself, and probably smaller in a diiodobenzene as well. The long-range anisotropic effects of a nitro group and of an iodine-carbon bond may partially neutralize the effects of the π-cloud. It is also possible that inversion of the oxygen valency angle can take place forming the conformer in which the 2′-substituent is *proximal* and the 6′-proton is *distal*, i.e. removed from the π-cloud (see below). Finally, the positioned ring may oscillate a few degrees around the position of least steric hinderance.

[16] C. P. Smyth, *Dielectric Behavior and Structure* p. 326. McGraw-Hill, New York (1955); L. E. Sutton, *Determination of Organic Structures by Physical Methods* (Edited by E. A. Braude and F. C. Nachod) p. 400. Academic Press, New York (1955).

TABLE 4. CHEMICAL SHIFTS OF THE OUTER RING PROTONS IN N-ACETYL ETHYL ESTER DERIVATIVES OF THYROXINE ANALOGS WITH QUESTIONABLE POSITIONING



No.	Ar	R		δ, ppm		Ref.
57		NO_2	—	6·5–7·1[a]	—	14, 15
58		I	—	6·3–7·1[a]	—	14, 15
59		NO_2	6·57 (two H)		6·63 (one H)	14
60		I	6′ = 6·15[b]	5′ = 6·57[b,c]	3′ = 6·83[c]	14
61		NO_2	6′ = 6·73[b]	3′ = 6·48[c]	5′ = 6·29[b,c]	14
62		I	6·22 (two H)		6·60 (one H)	14
63		NO_2	4′ = 6·92	1′ = 7·19	others 7·2–7·8	11
64		I	4′ = 6·58	1′ = 7·38	others 7·2–7·9	11
65		NO_2	6′ = 6·56[b,c]	—	6·9–8·2[a] —	8

[a] Spectrum was not interpreted: total absorption span.
[b] Doublet, J = 7–9 c/s.
[c] Doublet or further splitting, J = 3 c/s.

[14] P. Berteau, Dissertation, University of California, San Francisco (1964).
[15] E. C. Jorgensen and P. Berteau, *Ind. Chim. Belge.* **27**, 559 (1962).

Positioning groups

Among the 2,6-dinitro and diiodo ethers examined, the following 2′-substituents hinder rotation to the point where the skewed conformation is preferred: cyclohexyl, i-propyl, allyl, trifluoromethyl and methyl (Table 3). In addition an α-naphthyl ring is positioned (see below).

When only hydrogen is present in the 2′ and 6′ positions, no positioning takes place (Table 2). This is true even in the presence of a very bulky 3′-substituent e.g. trimethylsilyl (No. 12) and t-butyl (No. 16, Fig. 6b).

Our evidence for positioning by a 2′-methoxy group is ambiguous. Of eight compounds examined (Table 4), four (No. 57, 59, 63 and 64) show no aromatic resonance upfield from 6·5. One compound, No. 62, shows two protons at 6·22 where only one would be expected, indicating that the inductive effect of two methoxy groups is sufficient to shift the resonance of at least one proton this far upfield. Another analog (No. 58) had a spectrum which could not be interpreted, but showed

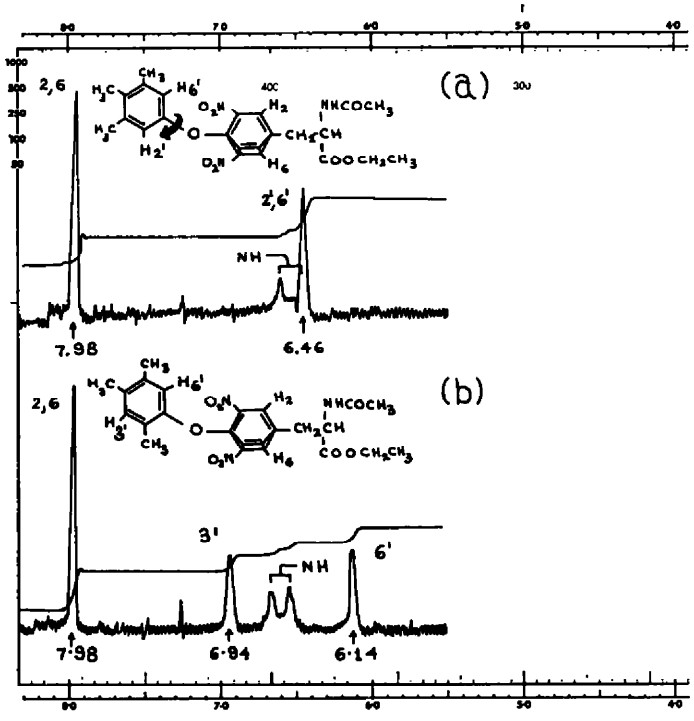


FIG. 3. Partial NMR spectra of

(a) N-acetyl-3′,4′,5′-trimethyl-4-phenoxy-3,5-dinitrophenylalanine ethyl ester (No. 10) and

(b) N-acetyl-2′,4′,5′-trimethyl-4-phenoxy-3,5-dinitrophenylalanine ethyl ester (No. 31).

some absorption as high as 6·3. No. 61 showed one proton at 6·29, but the magnitude and direction of the coupling constants showed that this could only be ascribed to proton 5′. Finally, one compound (No. 60) showed one peak at 6·15 which on the basis of coupling constants has been assigned to the 6′-proton. Further evidence is given below for the ability of methoxy to shift the resonance position of protons *ortho* to it into the region in question. Thus it would seem that a 2′-methoxy does not position but further evidence is necessary to establish this point.

It also was not possible to decide whether a 2′-carboxymethyl group positions since the resonance of the upfield aromatic proton in compound No. 65 (Table 4) at 6·56 may be due to a non-positioned proton, or to a positioned proton shifted to lower field by the inductive effect of the carboxymethyl group.

Naphthyl analogs

Fig. 4 and 5 show the pertinent portions of the NMR spectra of several naphthyl compounds. Beginning with No. 54 (Fig. 4a) we have assigned the doublet at 6·36 to the positioned 2′-proton and the doublet at 6·53 to the neighbouring 3′-proton, the upfield position of the latter being ascribed to the influence of the 4′-methoxy *ortho* to it. As Fig. 4b shows, on going from the dinitro to the diiodo analog (No. 55), there is no change in the shift of the 3′-proton (6·53), but the peak assigned to the

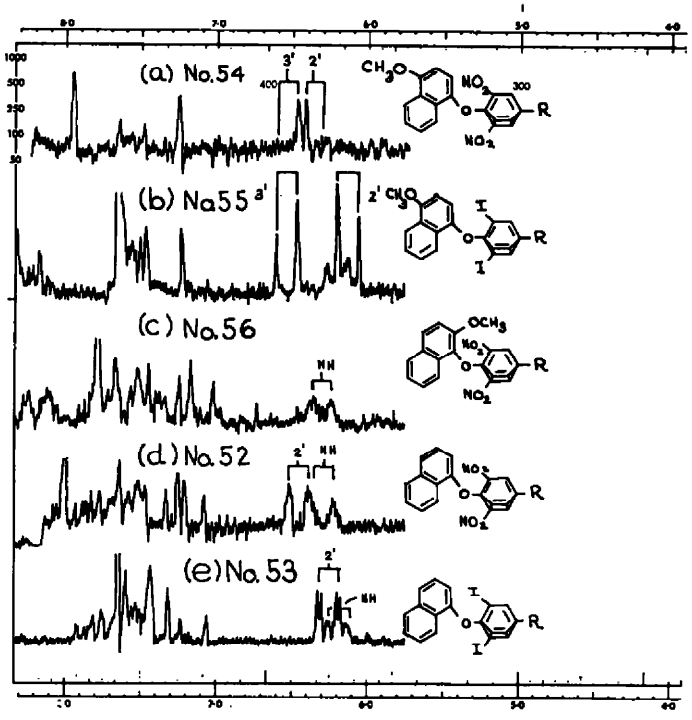


FIG. 4. Partial NMR spectra of

(a) N-acetyl-4-(4′-methoxy-α-naphthoxy)-3,5-dinitrophenylalanine ethyl ester (No. 54)
(b) N-acetyl-4-(4′-methoxy-α-naphthoxy)-3,5-diiodophenylalanine ethyl ester (No. 55)
(c) N-acetyl-4-(2′-methoxy-α-naphthoxy)-3,5-dinitrophenylalanine ethyl ester (No. 56)
(d) N-acetyl-4-(α-naphthoxy)-3,5-dinitrophenylalanine ethyl ester (No. 52) and
(e) N-acetyl-4-(α-naphthoxy)-3,5-diiodophenylalanine ethyl ester (No. 53).

2′-proton in shifted upfield to 6·12, in agreement with the observed trend (Table 3). Fig. 4c (No. 56) shows the disappearance of both these peaks from this region upon moving the 4′-methoxy group to the 2′-position. The disappearance of the peak ascribed to the 2′-proton confirms its assignment in the previous compounds and the disappearance of the 3′-proton signal may be a reflection of a smaller chemical shift due to methoxy *ortho* to phenoxy as compared to *para*. The unsubstituted α-naphthyl analogs No. 52 (Fig. 4d) and 53 (Fig. 4e) show doublets at 6·45 and 6·27 respectively, assigned to the positioned 2′-proton. Their coupling constants of 8·5 c/s (and a further splitting of 1·3 c/s in the diiodo compound) would indicate α-β coupling (Pople, Schneider and Bernstein[17] found J = 8·5 c/s for α-β, 6·0 for β-β

[17] J. A. Pople, W. G. Schneider and H. G. Bernstein, *Canad. J. Chem.* **35**, 1060 (1957).

and 1·3 for *meta* α-β coupling in naphthalene). However this must be β-β coupling to the *ortho* 3′-proton since the 8′-proton can be excluded from positioning on steric grounds and because no peak was found for this proton in this region in compound No. 56 (Fig. 4c).

As Fig. 5a and b show, the absence of aromatic absorption upfield from 7·0 (No. 20) and 6·7 (No. 21) means that there is no positioning in β-naphthyl compounds of this type. The appearance of a peak at 6·82 (No. 63, Fig. 5c) and at 6·58 (No. 64, Fig. 5d) on introducing a methoxy *ortho* to the ether linkage in the β-naphthyl

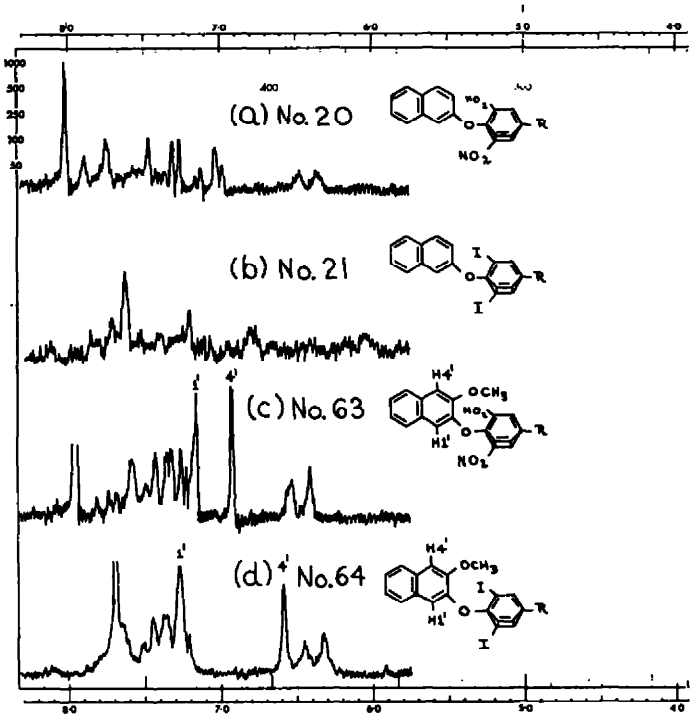


FIG. 5. Partial NMR spectra of

(a) N-acetyl-4-(β-naphthoxy)-3,5-dinitrophenylalanine ethyl ester (No. 20)
(b) N-acetyl-4-(β-naphthoxy)-3,5-diiodophenylalanine ethyl ester (No. 21)
(c) N-acetyl-4-(3′-methoxy-β-naphthoxy)-3,5-dinitrophenylalanine ethyl ester (No. 63) and
(d) N-acetyl-4-(3′-methoxy-β-naphthoxy)-3,5-diiodophenylalanine ethyl ester (No. 64).

analogs, might indicate positioning. However it is more likely that this is due to the proton *ortho* to methoxy (4′-H) because as was shown above and as comparison with Fig. 4a and b shows, methoxy is capable of shifting the peak of a proton *ortho* to it into this range. This leaves the peaks at 7·19 (No. 63, Fig. 5c) and at 7·38 (No. 64, Fig. 5d) assignable to proton 1′, which is then not positioned.

3′-i-Propyl-4′-methoxy analog

Among the thyroxine analogs synthesized in our program,[3] one considered to be 2′-i-propyl-3,5-diiodothyronine showed a very high level of thyromimetic activity. This was surprising in view of the fact that the highest activities in this series have

been associated with occupancy of the 3′-position (*viz.* triiodothyronine). IR comparison of this compound with an authentic sample[18] of 3′-i-propyl-3,5-diiodothyronine in our laboratories[19] showed their identity. Confirmation is provided by the NMR spectrum (Fig. 6a) of the precursor N-acetyl-4′-methoxy ethyl ester (No. 15).[3] This compound shows no positioned proton and a spectrum completely analogous to that of the 3′-t-butyl analog (No. 16, Fig. 6b) and different from that of a positioned 2′-i-propyl analog (No. 35, Fig. 6c).

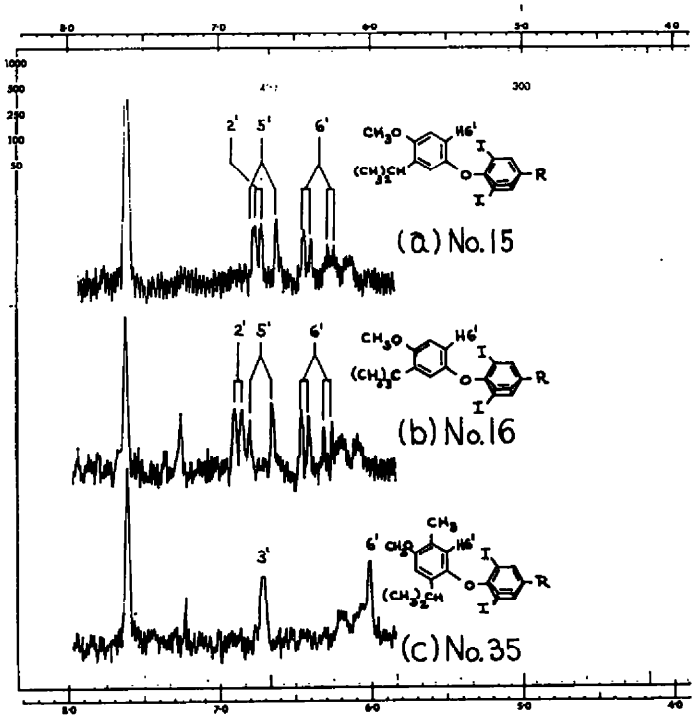
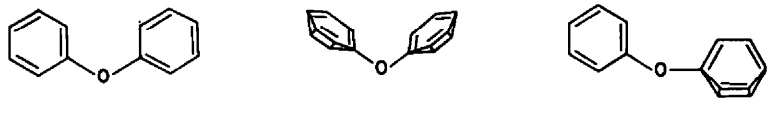


FIG. 6. Partial NMR spectra of

(a) N-acetyl-3′-i-propyl-4′-methoxy-4-phenoxy-3,5-diiodophenylalanine ethyl ester (No. 15)
(b) N-acetyl-3′-t-butyl-4′-methoxy-4-phenoxy-3,5-diiodophenylalanine ethyl ester (No. 16) and
(c) N-acetyl-2′-i-propyl-4′-methoxy-5′-methyl-4-phenoxy-3,5-diiodophenylalanine ethyl ester (No. 35).

Stereochemistry of diphenyl ethers

Three conformations have been considered for diphenyl ethers:



Planar "Butterfly" Skewed

[18] Kindly provided by Dr. B. Blank, Smith, Kline and French Laboratories; see Ref. 12.
[19] We thank Dr. S. J. Feinglass for this information.

Smyth and Walls[20] pointed out that a "butterfly" conformation is more likely than the planar conformation[16] since steric overlap of the *ortho* protons would be avoided. Evidence for lack of coplanarity was presented by Cerniani *et al.*[21] (UV) and by Dahlgard and Brewster[22] (UV and IR) who showed that conjugation between the ether oxygen and the rings is reduced upon increasing the bulk of *ortho* substituents.

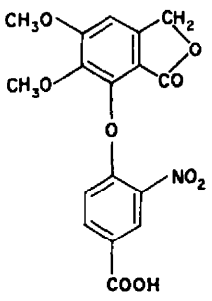
The skewed conformation was first proposed by Higasi and Uyeo[23] on the basis of dipole moment measurements on 2,2′-disubstituted diphenyl ethers, and later confirmed by them with electron diffraction studies on 2,2′-dihalodiphenyl ethers.[24] Further evidence was given by Smyth *et al.*[25,26] from dielectric relaxation times. Recently Shimizu *et al.*[27] presented NMR evidence for the existence of 2,2′-dimethyldiphenyl ether in this conformation, but it was challenged on experimental grounds[28] and was retracted by its authors.[29] Most recently Katon *et al.*[30] in a detailed examination of the IR and Raman spectra of liquid diphenyl ether find the skewed conformation the only one compatible with the data. They further state that although the dihedral angle between the skewed rings is unknown, it is probably not 90° and note that the two rings are electrically and chemically non-equivalent.

Under the conditions of our present work the skewed conformation is preferred *only* when there are present three bulky substituents around the ether linkage.[31] Further studies will be carried out at other temperatures in order to provide estimates of barrier heights to rotation in these substituted diphenyl ethers.

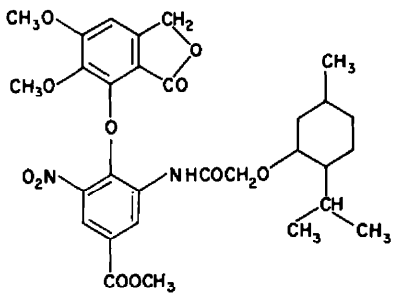
In 1958 Dahlgard and Brewster[22] suggested the possibility of isolating optical antipodes resulting from hindered rotation in an appropriately substituted diphenyl ether. Their unsuccessful attempt on an unspecified diphenyl ether was explained by suggesting that this type of isomerism may be theoretically impossible due to inversion at the oxygen atom in the same way that it occurs with nitrogen in ammonia and substituted amines. However Roberti *et al.*[25] do not consider inversion to take place as judged by evidence from dielectric relaxation times. In 1959 Allen and Moir[32] pointed out that *even if* inversion occurs, concerted allowed rotation converts a given antipode into itself, and that rotation *past* the flanking groups is necessary to racemize it. They attempted[32] to resolve two hindered ethers related to

[20] C. P. Smyth and W. S. Walls, *J. Amer. Chem. Soc.* **54**, 3230 (1932).
[21] A. Cerniani, R. Rasserini and G. Richi, *Bull. Sci. fac. chim. ind. Bologna* **12**, 7 (1954).
[22] M. Dahlgard and R. Q. Brewster, *J. Amer. Chem. Soc.* **80**, 5861 (1958).
[23] K. Higasi and S. Uyeo, *J. Chem. Soc. Japan* **60**, 199, 204 (1939).
[24] K. Higasi, S. Uyeo and N. Yamaguchi, *Bull. Inst. Phys. Chem. Res., Tokyo, Chem. Ed.* **23**, 788 (1944).
[25] D. M. Roberti, O. F. Kalman and C. P. Smyth, *J. Amer. Chem. Soc.* **82**, 3523 (1960).
[26] K. Higasi and C. P. Smyth, *J. Amer. Chem. Soc.* **82**, 4759 (1960).
[27] H. Shimizu, S. Fujiwara and Y. Morino, *J. Chem. Phys.* **34**, 1467 (1961).
[28] G. V. D. Tiers and F. A. Bovey, *J. Chem. Phys.* **37**, 1564 (1962).
[29] H. Shimizu, S. J. Fujiwara and Y. Morino, *J. Chem. Phys.* **37**, 1565 (1962).
[30] J. E. Katon, W. R. Feairheller, Jr. and E. R. Lippincott, *J. Molec. Spectroscopy* **13**, 72 (1964).
[31] In this connection it is interesting to note that H. E. Zimmerman and D. H. Paskovich [*J.Amer. Chem. Soc.* **86**, 2149 (1964)] have proposed the same skewed conformation for dimesityl carbene.
[32] M. Allen and R. Y. Moir, *Canad. J. Chem.* **37**, 1799 (1959).

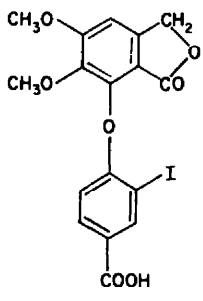
metameconine (IV and V):



IV



V



VI

Recently[33] an attempt to resolve VI also failed. The lack of success was attributed to insufficient hindrance to rotation, an observation which receives support from the present work which shows that *o*-methoxy probably does not hinder rotation sufficiently. Since the fourth *ortho* substituent (IV–VI) is the *o*-carbomethoxy group, it may be concluded that this group also has insufficient bulk to prevent rotation, in accord with our finding that an *ortho* carboxymethyl group may not position.

Note added in proof: Moir and his co-workers[34] have reported similar conclusions regarding the principal conformations of *o*-substituted diphenyl ethers from NMR, UV and IR studies.

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[34] W. D. Chandler, W. MacFarlane Smith and R. Y. Moir, *Canad. J. Chem.* **42**, 2549 (1964).