Intramolecular Aryl-Iodine π Complex Formation and Its Relation to Thyromimetic Activity†,[1]

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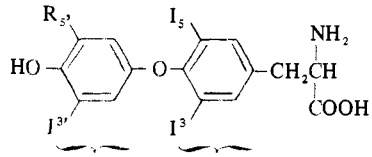
Dipole moment determinations and nmr studies of 2,6-dihalodiphenyl ethers have established that these exist preferentially in a twisted conformation which results from the opposing tendencies toward coplanarity demanded by resonance stabilization, and toward a skew conformation demanded by minimum steric interference. In 2,6-diiododiphenyl ethers this conformation places one iodine directly opposite the other ring so that its outer orbitals overlap extensively with the densest part of the π-electron cloud on the other ring. The ensuing π complex (intramolecular donor-acceptor charge transfer complex) extends to the π electrons the heavy-atom effect of the iodine through spin-orbital coupling. This confers on these ethers special properties such as enhanced singlet-triplet transitions, long-lived triplet states, facilitated one-electron interactions, etc. It is proposed that the existence of this π complex is essential to thyromimetic activity since it is possible on this basis to rationalize all known structure-activity relationships, including the indispensable requirement for iodine. Possible submolecular mechanisms, such as the intermediacy of low energy biradicals, are advanced to explain the mode of action of the thyroid hormones. The pmr and dipole moment of 2,6-diiodo-4-methylphenyl 2′,4′-dinitrophenyl ether are described.

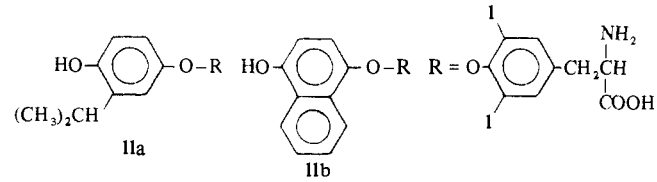
As the only biologically active molecules in nature which contain iodine, the thyroid hormones (L-thyroxine, Ia, and 3,5,3′-triiodo-L-thyronine, Ib) have long been subject to



Ia, R = I
Ib, R = H

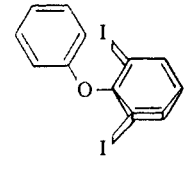
study.‡ On the one hand, extensive structure-activity relationships have been established§ for these relatively simple molecules, and on the other, several interesting proposals have been made[4,5] to explain their biological activity in terms of atomic properties peculiar to iodine. It is the purpose of this paper to show that these, taken together with conformational considerations allow further insight into the mode of action of the thyroid hormones.

Structure-Activity Relationships. The minimal structural requirements for thyromimetic activity# are:[3] (a) *two aromatic rings* joined by an oxygen or sulfur *bridge*;[6] (b) two *bulky substituents* at the 3 and 5 positions of which *at least one must be iodine or bromine*;[7] and (c) a hydrophilic carbon side chain at position 1. To these must be added for maximal activity (d) a phenolic hydroxyl group at 4′, or another group convertible to it *in vivo*; (e) a substituent of appropriate electron-donating ability, bulk, and lipophilicity at one position ortho to the hydroxyl (3′); and (f) no substituent at the other position ortho to the hydroxyl (5′).[8] These optimal requirements are best exemplified by 3,5,3′-triiodo-L-thyronine (Ib),[9,10] 3,5-diiodo-3′-isopropyl-L-thyronine (IIa),[11] and the "benzo" analog 4-(4′-hydroxynaphthoxy)-3,5-diiodo-DL-phenylalanine (IIb),[12] which are all more potent than L-thyroxine itself.



Role of Iodine. Although the presence of iodine in the thyroid has been known since 1895,[2] it was only in 1957 that Szent-Györgyi advanced[4] a possible reason for this. He suggested that it may stabilize the triplet state of certain molecules by the heavy-atom effect[13] and that this is related in some way to the role of the thyroid hormones in the regulation of energy metabolism. Independently Cilento and Berenholc suggested[5] a similar idea and obtained experimental evidence linking the presence of iodine to the perturbation of spin-forbidden processes in iodophenols. They also indicated that thyroxine and similar molecules might interact with Mulliken-type acceptors due to the presence of iodine atoms, and noted that in thyroxine good conditions exist for stationary perturbation.[14] These suggestions cannot, however, explain the known structure-activity relationships and would imply that much simpler iodine-containing molecules should exhibit thyromimetic properties. Thus 3,5-diiodo-L-tyrosine, which shows a strong perturbing effect,[14] is completely inactive.

Conformation of Diphenyl Ethers. Zenker and Jorgensen[15] first called attention to the fact that conformational considerations should be of importance in the thyroid hormones, and suggested that they adopt a skew conformation (III). The hypothesis that adoption of this conformation (III) results in enhanced activity was extensively tested but



III

†Constitutes Part 10 of the series on Conformations of Highly Hindered Aryl Ethers; presented in part to the Medicinal Chemistry Section at the XXIII International Congress of Pure and Applied Chemistry, Boston, Mass., July 27, 1971 (Abstract 170); dedicated to my father Federico A. Lehmann, M.D., Ph.D., on his 74th birthday.

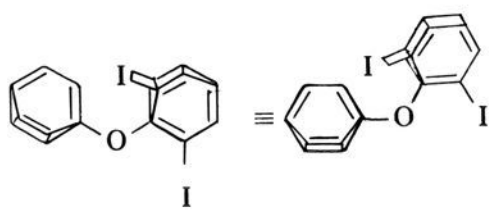
‡See the detailed account given by Pitt-Rivers and Tata.[2]

§A survey is given by Jorgensen.[3]

#The principal activity of the thyroid hormone is its calorigenic action; however since comparative data are scarce for it and since in general it runs parallel to antigoitrogenic action, the term thyromimetic activity will be taken here to mean essentially antigoitrogenic activity.

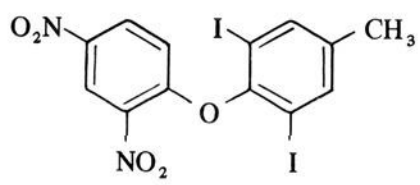
not confirmed. Thus 3′-methyl-3,5-diiodo-L-thyronine whose activity is 77–100% of L-thyroxine,[6,11] upon introduction of a methyl group at 2′ to stabilize the skew conformation, should result in a much more potent analog. In fact the 2′,3′-dimethyl analog is less active (50% of L-thyroxine).[6]

Nevertheless, other results indicated that conformational effects are certainly important and extensive studies were undertaken on model ethers by various instrumental methods.[16-21] It was established that not only steric, but also resonance and electrostatic factors are important, and that in general a twisted conformation (IV) is preferred.



IV

In order to establish whether this conformation is also preferred by 2,6-diiododiphenyl ethers, the easily accessible ether V was prepared by an improved procedure.[21] The



V

large group moments of the substituents in this ether could be expected to result in a large overall dipole moment, reducing the relative error of the determination and permitting small differences to be detected among various possible conformations.

Results and Discussion

Pmr and Dipole Moment of 2,4-Dinitrophenyl 2′,6′-Diiodo-4′-methylphenyl Ether. The pmr spectrum of the ether V is as expected except that it shows the same upfield shift (δ 6.71) for the proton at position 6 as other 2,4-dinitrophenyl aryl ethers,[20] indicating that it is located close enough to the other aromatic ring so as to be influenced by its magnetic anisotropy. The observed shielding is lower than that calculated with Johnson and Bovey's model** for the molecule in the skew conformation, and approximately that predicted for it in the twisted conformation. The measured dipole moment of V is presented in Table I together with the values calculated for various probable conformations. For comparison the closely related 2′,4′,6′-tribromophenyl ether (VI, already reported[18]) is included. It can be seen that for both ethers the twisted conformation is clearly indicated by the fact that the values calculated for both possible skew conformations fall well outside the error limits. Agreement for the twisted conformation of VI improves upon including a mesomeric moment into the tribromophenyl ring which may well be present.

Intramolecular Aryl-Iodine Interaction. In this conformation (IV) the halogen atom closer to the other ring lies directly over the C_1 carbon atom of that ring, about 3.5 Å from it, placing its outer orbitals in the densest part

**Johnson and Bovey[22] assume a model in which the π-cloud *torii* are 0.64 Å from the ring plane.

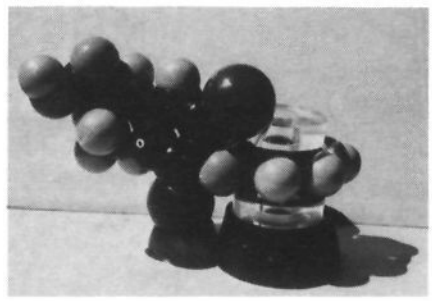
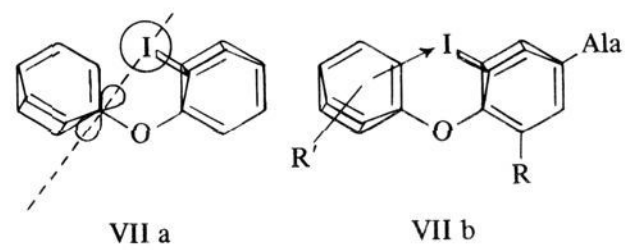


Figure 1. Molecular model (Fisher-Taylor-Hirschfelder) of the twisted conformation ($\theta = 37°$, $\theta = 217°$) of 3,5,3′-triiodo-L-thyronine showing the interaction of one ortho iodine on the inner ring with the π cloud of the outer ring.

of the π-electron cloud.** The internuclear separation, which is close to the sum of the van der Waals' radii, is such that an interaction between the aromatic π cloud and the halogen atom is to be expected. In analogy to the well-documented[23] intermolecular interaction between aromatic compounds and halogens (*viz.* benzene and iodine and the visualization of spots in tlc), this interaction should be of an intramolecular electron donor-acceptor (EDA) charge-transfer (CT) complex type. Or briefly, it can be said that they form an intramolecular π complex (VII and Figure 1).††



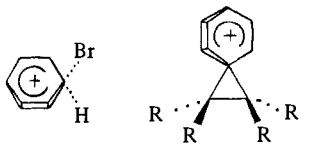
VII a VII b

Complexes of this type have been described previously[25] but none are known involving iodine.

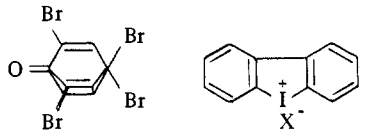
The formation of this π complex is strongly implied by the following considerations. (1) An appropriate donor moiety is present in the outer ring as demonstrated experimentally by its intermolecular association with other acceptors.[5,26] (2) An appropriate acceptor is present in the iodine atom.‡‡ (3) Spatial proximity is achieved by the conformational preference and van der Waals-London forces (see for example ref 27) may even stabilize it further. (4) The oblique approach of the iodine to the edge of the aromatic ring is favorable to complex formation since calculations by Mulliken[28] have shown that this is one of the favored geometries for the benzene-iodine complex (O_X). (5) The well-established intermediacy of bromonium (VIII) and phenonium (IX) ions in different reactions, as well as the existence and stability of "tetrabromophenol" (2,4,4,6-tetrabromocyclohexadienone, X)[29] and diphenylene iodonium salts (XI)[30] further show that the geometry of such interactions is feasible. (6) In analogy to similar intermolecular complexes, the highest filled orbital of the donor is energetically close to the lowest empty orbital of the acceptor, thus fulfilling one further requirement for these complexes.[23,31] (7) Finally, entropy considerations con-

††The terms *electron donor-acceptor, charge transfer* and *π-complex* have been used in the past with mutually overlapping meanings that do not necessarily correspond to physical reality, and precise delineations are currently being drawn.[24] Until these terms are properly defined it seems preferable to use the descriptive term π complex.

‡‡No complexes have been described in which simple aryl iodides function as acceptors; however no great difference is expexted in this regard on going from the iodine molecule to an aryl iodide. Many examples are known in which halogen atoms enhance the acceptor properties of an accepting moiety, *e.g.*, hexafluorobenzene, bromanil, and iodanil.



VIII IX

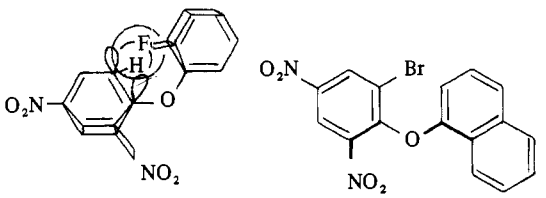


X XI

siderably favor intramolecular complex formation over its intermolecular counterpart.

Extended Hückel theory molecular orbital calculations have been carried out on several halothyronines by Kier and Hoyland,[32] but the approximations which were necessary in the treatment of bromine and iodine (ignoring the outer orbitals) would obscure any indication of the existence of the π complex.

Direct evidence has been obtained from three sources. (1) The pmr spectrum of an *o*-fluoro ether (XII) investi-



XII XIII

gated earlier[20] showed a fine splitting for H_6 which was tentatively assigned to coupling with the fluorine at $C_{2'}$ on the other ring. A careful study of this and related ethers by ^{19}F nmr confirmed the existence of this interannular coupling between H_6 and fluorines at $C_{2'}$ and/or $C_{6'}$.[33] In view of the large number of bonds and their geometry, it is likely that the coupling between the nuclei is effected by π electrons.

(2) The dipole moment determinations[1] of four 2,4-dinitro-6-bromophenyl ethers showed that in one of them (XIII) the measured moment could only be explained by invoking a charge-transfer moment from the inner portion of the naphthyl ring to one of the ortho substituents on the other ring (Br or NO_2).

(3) X-Ray crystallographic structure determination[34] of ether V showed that its conformation in the solid state is a twisted one ($\theta = 26°$, $\theta' = 84°$), similar to that deduced in this paper. One iodine is definitely closer than the other one to the face of the opposite ring, and the distance from it to the closest aromatic bond ($C_{1'}$-$C_{6'}$) is 3.7 Å, close to the separation (3.2-3.4 Å) encountered in most intermolecular π complexes (ref 23, p. 234).

So far no direct spectroscopic evidence has been obtained, possibly because detection of the characteristic CT band is often difficult or impossible in complex systems.

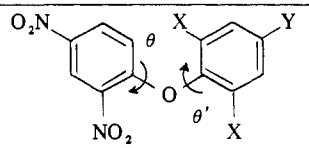
Rationalization of Structure-Activity Relationships. If the presence of such a π complex is essential to thyromimetic activity, then it is possible to explain most of the known structure-activity relationships.

The *aromatic character* requirement of the outer ring is explained since aliphatic chains do not form such bonds. On the other hand, enlarging the aromatic system and intensifying its aromatic character results in reduced ionization potentials and enhanced donor ability.[35] This is strikingly confirmed by the high activity in the 1-naphthyl analog (IIb) which is 20 times as potent as its lower benzolog.[36] (The inactivity of the 2-naphthyl analog has been explained on the basis of a blocked 4′ position.)

Only *iodine and bromine* are highly effective in the 3 and 5 positions[36] because only they are sufficiently large to overlap extensively with the π cloud and are sufficiently "heavy" heavy atoms; chlorine and fluorine are deficient in these characteristics and do not confer activity. Recently Jorgenson and Wright[37] have confirmed the very small activity of 3,5-dimethyl-3′-iodo-DL-thyronine (4% of Ia) which would seem to contradict the above statements. However, two possible explanations are available: (1) that it may be acting indirectly by blocking the degradation of endogenous hormone;[37] and (2) that a "reverse" CT complex is established since now the inner ring is a good donor due to the presence of three alkyl substituents, and the outer ring bearing the iodine is the acceptor. The total inactivity of tri- and tetraalkyl substituted analogs[37] is thus explained since they lack iodine. Furthermore, one iodine or bromine in the inner ring suffices for moderate activity provided there is another bulky substituent present.[7,38] This can be explained since the second substituent is required to stabilize the twisted conformation (VIIb). Thus in the hormones the second (inner ring) iodine has this role in addition to doubling the probability of formation of the π complex, and is possibly unavoidable biosynthetically.

The *ether oxygen* is necessary not only because it positions the donor and acceptor elements properly, but also because it insulates them from one another. The latter was established in a study[39] by esr of diphenyl ethers and thioethers which showed that electron transfer between rings is limited and proceeds mainly *via* random motions of the solvent molecules, and not through the linking atom as would have been expected. Although other bridges might

Table I. Measured and Calculated Dipole Moments of the Diphenyl Ethers V and VI



			V, X = I; Y = Me Measd DM = 6.55 D		VI, X = Y = Br Measd DM = 4.74 D	
Conformation	θ	θ'	Calcd DM, D	% dif	Calcd DM, D	% dif
Twisted	37	37	6.64	+ 1	5.18	+10
Skew, *o*-NO_2 *distal*	0	90	7.26	+11	5.57	+19
Skew, *o*-NO_2 *proximal*	180	90	4.82	−26	3.76	−20
Skew, *o*-X *proximal*	90	0	4.83	−26	3.87	−17

also result in appropriate geometries and insulation, no adequate analogs have been prepared and/or tested.[3,40,41] That aromatic character is required also in the inner ring is implicit in the requirement for a diphenyl ether or thioether nucleus; this has, however, never been tested adequately and activity may well be possible without it provided the iodine is positioned as required by other means.

The function of the *substituent at 3'* is twofold: (1) its ability to release electrons (which correlates well with thyromimetic activity[42]) increases the density of the π cloud in the outer ring, and (2) its bulk protects a biradical or free radical generated from the hormones from reacting prematurely through the phenolic oxygen. This explains why iodine and isopropyl groups are the most effective substituents at the 3' position.

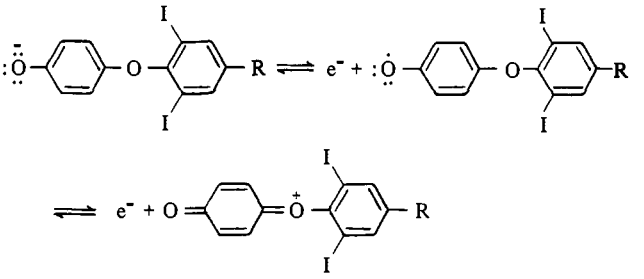
Only a *phenolic hydroxyl* which can participate easily in one-electron redox reactions is effective at the 4' position. Displacing it to the 2' position as in Niemann's "*o*-thyroxine"[43] is compatible with activity, but the analog is less active probably because the 2'-hydroxyl group competes with the π cloud as a donor,[44,45] and not because of its altered redox potential, since *o*-quinones have higher potentials than *p*-quinones.

The *alanine side chain* is probably necessary in transport to, and binding at the site, and might also represent the most "expedient" biosynthetic solution to this requirement.

The *fourth iodine (5')* present in thyroxine is biosynthetically unavoidable, but must be removed prior to acting, probably because interaction of the molecule with the receptor occurs at that part of the molecule.[6]

Mode of Action of the Thyroid Hormones. Extensive work has been carried out on the part played by the thyroid hormones in regulating energy metabolism and in searching for the exact point of interaction with the respiratory chain.[2,3] No clear picture has yet emerged but leads from several directions point toward its interaction with oxidative phosphorylation *via* redox processes. Earlier Niemann suggested[43] that the physiological activity in the case of thyroxine is in part dependent upon the equilibrium (XIV). All of the structure-activity relationships established since then do not in any way dispute this. Further, direct evidence has been obtained for the presence of free radicals generated from iodinated thyronines by one-electron oxidants[46] and in the presence of microsomal components.[47] Interaction of the hormones with receptors *via* intermolecular CT complexes has been suggested by different groups[5,6,26] and the intermediacy of long-lived triplet states§§ has been invoked in this context but without shedding light on the problem.

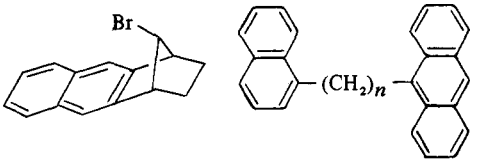
Another way of relating these observations is to consider them in an intramolecular context: formation of the intramolecular π complex makes the heavy-atom effect of iodine (which facilitates normally forbidden singlet-



R = $CH_2CH(NH_2)COOH$

XIV

triplet state transitions by spin-orbital coupling) extensive to the outer ring. That is, by "loosening" one of the π electrons, the interaction allows its spin to be reversed using much less energy than normally required, thus greatly increasing the probability of triplet state formation, as well as lengthening its lifetime. Striking confirmation is provided for this by the recent finding of Turro, *et al.*,[49] that the external heavy-atom-induced spin-orbital coupling in a series of bromonaphthonorbornanes is strongly dependent on the position of the bromine relative to the aromatic ring and that the triplet lifetime is longest for the 7-syn isomer (XV) in which the halogen is positioned directly above the π cloud. Direct evidence for the interannular transmission of spin state information is of course at hand in the demonstration of ^1H-^{19}F coupling described above.[33] Other work has shown[50,51] that intramolecular energy transfer occurs in molecules such as XVI.



XV XVI

This information makes it interesting to speculate that the thyroid hormones interact with the biochemical machinery in the form of a low-energy biradical which can easily give up an electron with high reduction potential. This would seem to receive support from Szent-Györgyi's observation[52] that 2,4-dinitrophenol uncouples oxidative phosphorylation due to its ability to quench the triplet state. Or, a free radical generated easily from these halothyronines through the biradical state, because of its stability and high reduction potential, could interact with the respiratory chain, accounting for the well-known antioxidant characteristics of the thyroid hormones. Thus Borg has demonstrated[46] that in contrast to free radicals generated from thyronine which are short-lived and show hyperfine splitting, those obtained from halogenated thyronines are much more stable and show no fine structure due to the presence of spin-orbital coupling.

An attractive alternative speculation is that triiodo-L-thyronine does not interact with a particular receptor in the cell, but that the mere presence of a triplet-state molecule there can, by Förster resonance coupling,[53] set off the biochemical changes associated with its action. Support for this may be found in the fact that despite numerous attempts[3] no effective peripheral antagonists have yet been found. The proposal made in this paper suggests that these be sought not in structurally similar molecules, but in species with appropriate electronic configurations for

§§Molecules in their lowest energy state have the spins of the paired electrons coupled so that there is no net magnetization, $S = 0$, and when placed in a magnetic field there are $2S + 1 = 1$ energy levels. This is termed a singlet state (S). In the first excited state the spins of one pair have been uncoupled by reversing the spin on one of them. Since the magnetic quantum number for such electrons is ½, $S = 1$ and $2S + 1 = 3$. Thus, when placed in a magnetic field, there are three different energy levels and such species are called triplet-state molecules (T). Normally transitions between S and T states (intersystem crossings) are highly improbable, *i.e.*, forbidden, because of the required spin reversal, and excitation by energetic means such as uv radiation is necessary. Essentially T-state molecules are highly reactive biradicals which decay to the ground state (S) principally by a relatively slow radiative process termed phosphorescence. For further details see Turro.[48]

Table II[a]

$\omega_2 \times 10^3$	ϵ_{12}	ν_{12}
0.0000	2.2756	1.14501
0.3602	2.2780	1.14469
0.6939	2.2816	1.14449
1.0904	2.2845	1.14426
1.4853	2.2879	1.14388
1.8492	2.2917	1.14363
2.2133	2.2959	1.14340
2.4706	2.2977	1.14331

[a] $\alpha = 8.99$; $(P_e + P_a)_D = 93.98$; mol wt = 526.00; $\epsilon_{12} = 2.2752$; $\beta = -0.709$; $\nu_{12} = 1.14498$; $P_{2\infty} = 957.10$; and $\mu = 6.55 \pm 0.08$ D.

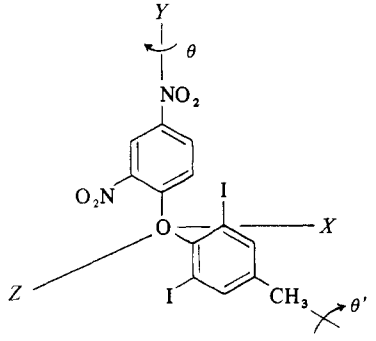
quenching the triplet state of the hormone within the cell.

Experimental Section

2,6-Diiodo-4-methylphenyl 2',4'-Dinitrophenyl Ether (V). This compound, originally prepared[54] according to Barnes, *et al.*,[55] could be obtained more conveniently and in higher purity using 2,4-dinitrofluorobenzene.[21] It shows the expected blue-violet color under Janovsky conditions.[56] It was purified by repeated recrystallizations from aqueous EtOH, passage through an alumina column in $CHCl_3$, and desiccation *in vacuo* until its purity was greater than 99.95% as determined by differential scanning calorimetry on a Perkin-Elmer DSC-13 instrument. Its mp of 196–198° (Kofler) was in agreement with that cited;[55] pmr (Varian A-60, $CDCl_3$, Me_4Si) δ 2.36 (s, 3 H), δ 6.71 (d, J = 9.2 Hz, 1 H), δ 7.75 (s, 2 H), δ 8.33 (dd, J = 9.2, 2.8 Hz, 1 H) and δ 8.94 (d, J = 2.8 Hz, 1 H).

Dipole Moment Determinations. The measured dipole moment was determined by the method of Halverstadt and Kumler[57] in benzene. The dielectric constants were obtained with a Model DM-01 Dipolemeter (Wissenschaftlich-Technische Werkstätten, G.m.b.H., Weilheim, Germany) using a DFL-2 cell maintained at 25.00 ± 0.02° (Colora Ultrathermostat NB, Lorch, Württemberg, Germany). The densities were measured using a calibrated pycnometer designed to permit rapid determinations of volatile solutions even under low atmospheric pressures (585 Torr).[54] Computation was carried out manually and checked with an IBM 1130 computer using a program kindly provided by N. L. Allinger.[58,59] Further details are given in an earlier publication of this series.[17] The experimental values are given in Table II.

Dipole Moment Calculations. The dipole moments calculated for various conformations were obtained by vector calculation with the following values and assumptions: (1) All valence angles are 120°. (2) Group moments are $ArNO_2$ = 3.98, ArI = 1.30, ArMe = −0.4, and Ar_2O = 1.16 D. (3) A mesomeric moment of M = 1.31 D was considered effective into the dinitro ring, 20° from the C_1–C_4 axis toward C_3, reduced by $\cos^2\theta$ on rotating θ.[17,18] (4) Twisting a nitro group out of coplanarity with the ring reduces its group moment to 3.10 D at $\theta_{NO_2} = 90°$; for intermediate angles it is 3.10 + 0.88 $\cos^2\theta$ D.[17] (5) θ and θ' are positive when the C_1–O and $C_{1'}$–O bonds are rotated clockwise (looking toward the ether oxygen) starting from the conformation shown as $\theta = \theta' = 0°$. Thus the overall dipole moment can be obtained by combining the contributions from the dinitro ring: $X = -1.005 - 0.342M\cos^3\theta - 3.447\cos\theta$; $Y = 1.41 + 0.94M\cos^2\theta$; $Z = -0.342M\cos^2\theta\sin\theta - 3.447\sin\theta$; with those from the other ring: $X = -1.47$; $Y = 0.85$; $Z = 0.00$.



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Notes

Synthesis and Oral Hypoglycemic Activity of *N*-(*p*-Deuteriomethylbenzenesulfonyl)-*N'*-*n*-butylurea, Deuterium-Substituted Tolbutamide[1]

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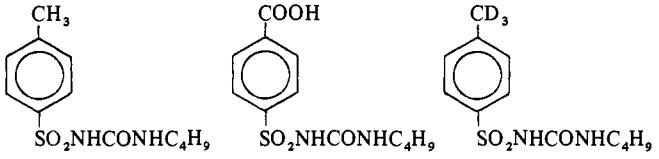
The primary metabolic pathway for the oral hypoglycemic agent, *N*-(*p*-methylbenzenesulfonyl)-*N'*-*n*-butylurea (I) (tolbutamide) is oxidation of the aromatic Me group to the inactive carboxylic acid (II) which is excreted.[1]



If the rate-determining step in the metabolic deactivation of the compound involved breaking of a C-H bond, then the rate of deactivation of *N*-(*p*-deuteriomethylbenzenesulfonyl)-*N'*-*n*-butylurea (III) would be slower due to the higher energy necessary to break the C-D bond of III.[2,3] This would result in a substantially increased duration of activity, which might enable the dosage necessary for a particular pharmacological result to be reduced appreciably with a corresponding decrease in the undesirable side effects of the drug.

III was prepared in a reaction sequence starting with toluene-d_8, which is commercially available in 99% isotopic purity.† The toluene-d_8 was sulfonated with HSO_3Cl and the resulting acid chloride was converted to the amide with concd NH_4OH, which was then converted to the disubstituted urea (III) with *n*-butyl isocyanate.[4] An nmr comparison of the residual protons of the *p*-deuteriomethylbenzenesulfonyl chloride with that of the 99 atom % toluene showed that the ring was only about 90% deuterated, indicating that some exchange had occurred during sulfonation. The Me group was still 99 atom % D in both the *p*-deuteriomethylbenzenesulfonyl chloride and in the final product, III. The D compound III melted at 126–127° as did the proteo compound and a mixture of the two.

The hypoglycemic activity of I and III was compared in male rats and found to be equiv (equal on a mole to mole basis). The deuterated material was not different in total activity or onset or duration of activity.

From these results, it can be concluded that the rate-determining step in the metabolic deactivation of I by its conversion to II does not involve the breaking of a C-H bond in the Me group ultimately oxidized to CO_2H.

Experimental Section

***p*-Deuteriomethylbenzenesulfonyl Chloride.** To a soln of 10 g (0.1 mole) of toluene-d_8 (99 atom % D)† was added 20 ml (0.33 mole) of HSO_3Cl dropwise with stirring. The temp rose 20°. Stirring was contd for 0.5 hr and the mixt was poured into ice. The org layer was sepd and the solvent was evapd. The solid was recrystd twice from hexane; yield 10.5 g (55%), mp 66–68° (lit.[5] proteo-*p*-toluenesulfonyl chloride, 69°). The nmr spectrum of the residual protons in this material in $DCCl_3$ compared to an equimolar soln of toluene-d_8 (99 atom % D), showed the same CH_3 absorption, but showed about 8 times the arom H absorption.

***p*-Deuteriomethylbenzenesulfonamide.** *p*-Deuteriomethylbenzenesulfonyl chloride (9.8 g, 0.05 mole), was added to 100 ml of concd NH_4OH and the mixt was stirred overnight at room temp. The solid was collected on a filter; wt 3.2 g, mp 127–132°. The mother liquor was acidified with concd HCl. The solid was collected, washed twice

†Diaprep, Inc., Atlanta, Georgia 30301.