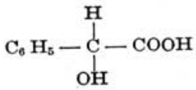
OPTICAL ISOMERISM OF BIPHENYL DERIVATIVES

HOWARD M. TEETER*

University of Illinois, Urbana, Illinois

Solutions of a large number of organic chemical compounds possess the power of rotating the plane of a beam of polarized light. Such compounds are said to be optically active. In order for optical activity to exist it is necessary that the molecule itself be constructed in an asymmetric manner, so that no plane or center of symmetry will be present. There are several ways in which this can be done. The most common is to provide the molecule with a carbon atom to which four different groups have been attached, resulting in the "asymmetric carbon atom". A simple example would be mandelic acid,



$$C_6H_5-\overset{\displaystyle H}{\underset{\displaystyle OH}{C}}-COOH$$

In the biphenyl type, however, asymmetry is obtained by restricting the rotation about the bond joining the phenyl groups. This is brought about by the mechanical interference[1] of groups *ortho* to the bond (i.e., groups in the 2,2′,6 and 6′ positions; the carbon atoms in one ring are numbered from 1 to 6, those in the other from 1′ to 6′). The rings are thus held in a coaxial, non-coplanar position, and if the rings are asymmetrically substituted, the compound will be optically active. Usually three or four *ortho* substituents are required, but occasionally two or even one will suffice.

Adam and Stanley[2] have calculated by means of X-ray data the internuclear distances from the ring to the center of various *ortho* substituents. If the average of the sums of the internuclear distances for the groups in the 2,2′ and 6,6′ positions be subtracted from 2.90 Å, the vertical distance between the 2,2′ carbon atoms, the interference value is obtained. The resistance of biphenyl derivatives to racemization upon heating is found to parallel the interference value very closely. If the interference value is zero, the compound can not be resolved; as the interference value becomes larger, the compound becomes optically more and more stable until finally it can no longer be racemized.

A close study of the interference effects of various groups has led to the conclusion that only the smaller groups, such as methyl, carboxyl, and halogen, behave in a simple fashion. In more complex groups, such as alkoxyl or substituted amide, apparent anomalies are observed. Because of the possibilities of free rotation within the grouping itself, the question has been raised whether or not the atom or group attached to the atom combined with the ring exerts any appreciable effect.

Thus, in the substituted amides of 2,2′-dimethoxy-6,6′-dicarboxybiphenyl, it was found[3] that the substituted amide groups were more effective than the simple amide grouping, $CONH_2$. The following order was observed for the various substituted amides studied:

$$CONHC_2H_5 > CONHCH_3 > CON(C_2H_5)_2 > CON(CH_3)_2.$$

Obviously the effect of the group attached to the $C=O$ is important; however, no completely satisfactory explanation has been given as to why the monomethyl should be more effective than the diethyl.

A smilar study[4] was made upon 2-nitro-6-carboxy-2-alkoxybiphenyl. The methoxy, ethoxy, and *n*-propoxy derivatives were compared. In this case the interference effect of the alkoxyl groups followed the expected order, methoxy being least and propoxy greatest. The extension of this series to include the comparison of hydroxyl and methoxyl has never been carried out. Calculations based upon Pauling's tables[5] of atomic radii indicate that hydroxyl should be smaller than methoxyl, while indirect experimental evidence intimates that the two groups should be practically equivalent.

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* Present address: Bradley Polytechnic Institute, Peoria, Illinois.

The writer, under the direction of Roger Adams at the University of Illinois, undertook a direct comparison of hydroxyl and methoxyl groups by studying 2-methyl-4-carboxy-6 - nitro-2′ - methoxybiphenyl and the corresponding hydroxy derivative. The first compound was prepared from *o*-iodoanisole and methyl 3-methyl-4-bromo-5-nitrobenzoate by the action of copper bronze at 270°. The hydroxy derivative was prepared from the methoxy compound by demethylation with hydrobromic acid. It was found that the methoxy acid could be prepared in an optically active form which was relatively unstable, the specific rotation falling to half its initial value during a period of 207 minutes. On the other hand, the hydroxy compound could not be resolved by the use of either brucine or strychnine.

On the basis of this experimental evidence it appears that hydroxyl is substantially smaller than the methoxyl group. A complete generality, however, must await the preparation and study of a larger number of similar compounds.

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