be exceptions to Bell and Robin's theory such as sulfanilylurea, sulfanilylguanidine and sulfanalami-do-1,2,4-triazole, or compounds which do not fall within the scope of their theory such as the sulfones and the ring N-methyl and N1-methylsulfapyridine and sulfathiazole compounds can be adequately accounted for on the basis of this resonance theory.

4. These ideas appear to apply to other bacteriostatic compounds including the monoamino-acridines.

5. Whether the active species is an anion, cation or neutral molecule appears to be an incidental property as far as bacteriostatic activity of these compounds is concerned. The important factor is the contribution of the resonating form.

6. It is proposed that the reason for the maximum in the activity vs. pKa curve for the N1 mono-substituted sulfanilamides is that in these compounds neutral molecules are more effective in getting the agent to the site of action and once it gets there, the ion then interferes with essential metabolic processes resulting in bacteriostasis. It is suggested that this is also the reason the activities of various other types of bacteriostatic agents and local anesthetics are correlated with their acidic or basic dissociation constants.

San Francisco, California Received June 29, 1943

The Role of Neighboring Groups in Replacement Reactions. VII. The Methoxyl Group

BY S. WINSTEIN AND R. B. HENDERSON

Participation of a neighboring group in replacement reactions of the so-called Syl type has been demonstrated in a number of cases. On the qualitative side, we have been studying the generality of this participation with respect to variations in the nature of both the group and the rest of the reacting molecule. Any findings are not only of immediate interest but may prove equally useful in connection with other processes, for example, certain addition reactions. In the course of this work, most of which has been interrupted for the present, we studied the steric result of some reactions in the presence of a neighboring methoxyl group. These reactions involved the action of silver acetate in acetic acid on the threeo- and erythro-2-bromo-3-methoxybutanes II and VII and trans-1-bromo-2-methoxy-cyclohexane XII.

The diastereomeric 2-bromo-3-methoxybutanes were prepared by the addition of the elements of methyl hypobromite to the known compounds is of the oxide ring by methyl alcohol. Analogy with the reactions of oxides with water, acetic acid and malonic ester warrants the assumption of trans-opening of the oxide ring by methyl alcohol.

The cyclohexene derivatives, trans-1-bromo-2-methoxy-cyclohexane XII and trans-2-methoxy-cyclohexane XIV (acetate XIII) were prepared from cyclohexene XI and cyclohexene oxide XV, respectively. Configurations were assigned as in the case of the butene derivatives.

Comparison of the reaction products from the methoxylbromides with the known compounds is shown in Table I. Except for the preliminary

<p>| <strong>Table I</strong> |
| <strong>Comparison of Reaction Products with Known Compounds</strong> |</p>
<table>
<thead>
<tr>
<th><strong>Compound</strong></th>
<th><strong>%</strong></th>
<th><strong>B. p.</strong></th>
<th><strong>M. p. of derivative, °C</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Methoxy-2-butanol from cyclohexane</td>
<td>31.4-31.5</td>
<td>746</td>
<td>1.4105</td>
</tr>
<tr>
<td>Known cyclo-hydroxy-2-butanol</td>
<td>132.3-132.5</td>
<td>748</td>
<td>1.4107</td>
</tr>
<tr>
<td>2-Methoxy-2-butanol from cyclohexane</td>
<td>126.5-126.6</td>
<td>746</td>
<td>1.4076</td>
</tr>
<tr>
<td>Known trans-2-methoxy-2-butanol</td>
<td>126.4-126.5</td>
<td>752</td>
<td>1.4074</td>
</tr>
<tr>
<td>2-Methoxy-cyclohexylacetate from bromide</td>
<td>87-89</td>
<td>10</td>
<td>1.4437</td>
</tr>
<tr>
<td>Known trans-2-methoxy-cyclohexylacetate</td>
<td>87.5-88.0</td>
<td>10</td>
<td>1.4440</td>
</tr>
<tr>
<td>2-Methoxy-cyclohexanol from bromide</td>
<td>72.8-73.3</td>
<td>10</td>
<td>1.5856</td>
</tr>
<tr>
<td>Known trans-2-methoxy-cyclohexanol</td>
<td>72.5-73.2</td>
<td>10</td>
<td>1.5836</td>
</tr>
</tbody>
</table>

*α-Naphthylurethan. 4 5,5-Dinitrobenzoate.

(1) Weinstejn, Hess and Buckles, THIS JOURNAL, 64, 2796 (1942).
(2) Weinstein and Buckles, ibid., 64, 2780 (1942).
(3) Young, Dillon and Lucas, ibid., 61, 2528 (1929); (b) Brockway and Cross, ibid., 68, 2407 (1930); (c) Kistiakowsky, et al., ibid., 67, 876 (1935).
(4) Schmidt, Kaeling and Ascherl, Ber., 69, 1280 (1926).
(5) (a) Michael, J. prakt. Chem., 52, 344 (1895); (b) Terry and Bichelberger, THIS JOURNAL, 47, 1067 (1925); (c) Bartlett and Tabel, ibid., 58, 456 (1930); (d) Roberts and Kimbell, ibid., 58, 947 (1937); (e) Weinstein and Lucas, ibid., 61, 1576 (1939); (f) Lucas and Gould, ibid., 64, 601 (1942).
Nov., 1943

**The Methoxyl Group in Replacement Reactions**

**2197**

study of the reaction using the methoxybutyl bromide, it was most convenient to hydrolyze the ester product directly to methoxybutanol. This was the case because of the similarity in physical properties of the diastereomeric esters. From Table I it is clear that the product from erythro-methoxybutyl bromide is nearly pure erythro-methoxybutanol and that from threo-bromide is nearly pure threo-alcohol. Similarly the acetate and alcohol from trans-2-methoxycyclohexyl bromide agree closely in properties with the known trans-compounds.

In this work, as in previous cases, a reaction, which in the absence of a neighboring group gives rise to predominant inversion of configuration, proceeds with quite complete retention of configuration. Preliminary attempts to obtain XII in an optically active modification were without success and the work was interrupted before we could extend this phase of it. However, even without the supporting evidence, which could come from the use of optically active methoxybromides, it seems logical to ascribe the steric result of retention of configuration to the participation of the methoxyl group in the replacement process. There is formed, with the extraction of a bromide ion, intermediate XVI, carbon atom C-2 being inverted. The ring of intermediate XVI is opened, either acetate ion or acetic acid becoming attached to carbon atom C-1 or C-2. Two inversions of configuration occur in the whole process. It is interesting that we found no evidence of an attack by acetate ion on the methyl group of XVI to give rise to methyl acetate and an oxide (the latter being converted to glycol monoacetate). This can be reconciled either with an $S_N1$ type opening of the ring in XVI or an $S_N2$ type reaction in which unusual relative reactivities are ascribed to the primary and secondary carbon atoms because the latter are part of a strained ring.

It appears that the alkoxyl group should be classed with those groups which may participate in replacement reactions of the type used in this work. There is also some earlier evidence, in the cyclohexene series, that retention of configuration may turn out to be the steric result of a replacement reaction in the presence of a neighboring alkoxyl group. Brunel treated with silver

---

(8) Weinstein and Lucas, This Journal, 61, 2845 (1939).
(9) Brunel, Ann. chim., 8, 200 (1905).
oxide the 2-methoxy- and 2-ethoxycyclohexyl
iodide which he prepared from cyclohexene, iodine,
mercuric oxide and the proper alcohol. He ob-
tained, if his method of identification was reliable,
the monalkyl ether of what is now known to be
the trans-1,2-cyclohexanediol. Since Brunel's
procedure presumably gives iodo compounds
possessing the trans-configuration, the replace-
ment reactions must have proceeded with reten-
tion of configuration.
Intermediate XVI is a ring analog of the ter-
tary oxonium salts such as XVII which Meerwein
and co-workers have been able to prepare.

There is very considerable ionic character11 to
the carbon-oxygen bonds in the ring, forms XVIII
and XIX contributing significantly to the struc-
ture of the hybrid intermediate indicated by XVI.
We expect the contribution of form XX to be
smaller but nevertheless important.

In almost all cases of participation of neigh-
boring groups discussed in this series of papers
a three-membered ring intermediate is formed.
Whether the same participating groups may be
situated more remotely from the seat of sub-
stitution remains to be seen. Of course, other
kinds of ring closure have been extensively in-
vestigated. In our expectations with regard to
participation we can be guided some-
what by this general experience. However, a
few experiments are desirable with the type
replacement reaction we are stressing. These
would show which members of the class of
general intermediate XXI are important in de-
termining actual products and steric results.

In addition to functional groups whose par-
ticipation has been either investigated or dis-
cussed by us previously, the previous forms of

(10) Meerwein, et al., J. prakt. Chem., 147, 297 (1937); 154, 83
(1939); C. A., 34, 2325 (1940).
(11) In the case of the intermediate which is formed when an
alkoxycarboxylic acid group participates in a replacement reaction,
and which has been termed a betaine13 or an α-lactone,6 Professor Lucas
and one of us have been incorrectly credited (Chadwick and Pacsu,
This Journal, 63, 392 (1943)) with postulating a completely covalent α-
lactone. We hope sometime to deal further with the intimate
mechanism of formation of such intermediates. However, in regard
to the nature of the intermediate in question, Winstein and Lucas
had no idea of a completely covalent lactone. The latter authors
have always reasoned that, considering the ionic character of a usual
carbon-oxygen bond and allowing for the effects of resonance within
the carboxylate ion group and of ring strain, one arrives at the conclu-
sion that there is a very large ionic character to the new carbon-

(12) See, for example, Bennett, Trans. Faraday Soc., 37, 794 (1941).

the carboxyl group and the carbonyl group de-
serve consideration. A good deal of informa-
tion is available on the replacement reactions of acids
and their derivatives.12 In contrast to the α-
halogen-substituted carboxylate ions, the α-
halogen-substituted esters react with silver oxide
in alcohol with inversion of configuration.13
The most likely but not the unique expla-
nation of this is that the reaction is SN1 type but that
the carboxaloxyl group does not participate.
Perhaps, in special situations, the carboxalkoxyl
group will be found to give rise to such intermediates as
XXII or XXIII and will allow isolation of a
product such as XXIV from the reaction of
XXII.

With regard to reactions of substituted carboxyl
compounds, we might expect in certain favorable
situations such intermediates as XXV and XXVI.
Thus a product of the type XXVII might arise.

Experimental
cis- and trans-2-Butenes.—These were prepared from the
diacetoxybutanes by way of the dibromobutanes.6 The
meso-diacetate was prepared from meso-glycol, m. p. 34.2°,
which was obtained by recrystalsizing Lucidol Corp. glycol
from ether.64 Impure meso-diacetate from Lucidol glycol
was converted to impure dl-diacetate by conversion to
impure dl-dibromide with fuming hydrobromic acid and then
to impure dl-diacetate with silver acetate in acetic acid.1
Recrystalization from petroleum ether yielded dl-diacetate,
m. p. 42.7°, which was used in subsequent syntheses.

cis- and trans-2,3-Epoxybutanes.—These substances66 were prepared from the 3-chloro-2-butenol.64 The
latter substances were obtained from the treatment of the
pure diacetoxybutanes with fuming hydrochloric acid by
the general procedure used by Lucas and Gould64 with
meso-2,3-diacetoxybutane.
Acetomramide.—This substance was prepared in the
usual way.16 Yields in excess of 60% were obtained when the
potassium hydroxide was added slowly from a dropping
funnel to the well-stirred reaction mixture kept below 5°.
Four moles of acetamide were converted at one time.
The acetomramide, 70 mole % monohydrate by analy-
sis, was kept for nine months in an icebox, after which time
analysis showed a loss of 0.6% of oxidizing power. The partially hydrated material was used in the syntheses.

**erythro- and threo-2-Bromo-3-methoxybutanes.**—For the preparation of these substances the apparatus and method were applicable to prepare the 2-bromo-2-methoxybutanols from 2-butene and aqueous acetaemamide. To a ten-fold excess of cold anhydrous methanol containing an equivalent amount of acetaemamide and 2 drops of concd. sulfuric acid was added, followed by 0.4 mole of 2-butene. An ice–salt bath was used to control the vigor of the reaction for the first fifteen minutes. Stirring was continued one-half hour longer and then the reaction mixture was left overnight. It was then poured into aqueous sodium chloride and the organic layer separated with the aid of ether.

The ether extract was partially dried over potassium carbonate and the reaction mixture was distilled through the Weston-type column to yield approximately 80–82% of the 2-acetoxy-3-methoxybutanols.

**trans-2-Methoxycyclohexyl Acetate.**—From the acetylation of 26.0 g of methoxycyclohexyl bromide in the presence of other butene and cyclohexene derivatives previously investigated,8 no precautions were taken to use completely anhydrous acetic acid except with the cyclohexyl halide. A reaction time of eleven hours at 110°C was allowed, a preliminary experiment with a mixture of erythro- and threo-2-bromo-3-methoxybutanols having shown that virtually complete formation of silver bromo-methoxyacetate occurred in this time.

In the case of the butene derivatives, the esters were saponified and the reaction mixture was diluted with ether and the ether extract was neutralized with potassium carbonate. The organic layer was separated and then fractionated through the Weston-type column to yield 80–82% of the 2-acetoxy-3-methoxybutanols.8

**trans-2-Methoxycyclohexyl Acetate.**—From the acetylation of 26.0 g of methoxycyclohexyl bromide in the presence of other butene and cyclohexene derivatives previously investigated,8 no precautions were taken to use completely anhydrous acetic acid except with the cyclohexyl halide. A reaction time of eleven hours at 110°C was allowed, a preliminary experiment with a mixture of erythro- and threo-2-bromo-3-methoxybutanols having shown that virtually complete formation of silver bromo-methoxyacetate occurred in this time.

In the case of the butene derivatives, the esters were saponified and the reaction mixture was diluted with ether and the ether extract was neutralized with potassium carbonate. The organic layer was separated and then fractionated through the Weston-type column to yield 80–82% of the 2-acetoxy-3-methoxybutanols.8

**trans-2-Methoxycyclohexyl Acetate.**—From the acetylation of 26.0 g of methoxycyclohexyl bromide in the presence of other butene and cyclohexene derivatives previously investigated,8 no precautions were taken to use completely anhydrous acetic acid except with the cyclohexyl halide. A reaction time of eleven hours at 110°C was allowed, a preliminary experiment with a mixture of erythro- and threo-2-bromo-3-methoxybutanols having shown that virtually complete formation of silver bromo-methoxyacetate occurred in this time.
Identification of Alcohols.—This was carried out as indicated in Table I by a comparison of the physical properties of the alcohols and their derivatives with those of authentic specimens. Mixed melting points with the proper authentic derivatives gave no lowering. The physical properties of the alcohols and the melting points of the crude derivatives indicated small but appreciable stereoisomeric impurity.

Attempted Resolution of 2-Methoxycyclohexyl Bromide.—The halide, 0.3 mole, and 0.1 mole of brucine were mixed and left for twenty-four hours. The bromide, recovered in the usual way, was inactive. The recovered bromide was similarly inactive when the brucine-bromide mixture was kept at 120° for 26 hours.

Summary

The diastereomeric 2-bromo-3-methoxybutanes, 3-methoxy-2-butanol and 2-acetoxy-3-methoxybutane have been prepared.

The steric result of the reaction of silver acetate in acetic acid with the 2-bromo-3-methoxybutane and trans-1-bromo-2-methoxycyclohexane is retention of configuration. This steric result is ascribed to the participation of the neighboring methoxyl group in the replacement CH₃ process, \( \text{O} \) being an intermediate.

Possible participation of the carbomethoxy and carbonyl groups is briefly mentioned.

Los Angeles, California Received July 31, 1943

[CONTRIBUTION FROM THE IOWA AGRICULTURAL EXPERIMENT STATION]

The Configuration of Starch in the Starch–Iodine Complex. IV. An X-Ray Diffraction Investigation of Butanol-Precipitated Amylose

By R. E. Rundle and Frank C. Edwards

In the previous papers of this series evidence has been presented that both in the starch–iodine complex and in alcohol-precipitated starch the starch chains assume a helical configuration. X-Ray diffraction diagrams of the starch–iodine complex have revealed the type of packing of the helices and the dimensions of a turn in the helix. Similar diffraction diagrams of alcohol-precipitated starch might be expected to confirm the information obtained from the starch–iodine complex and perhaps supplement it by providing details of the structure not obtained from the starch-iodine complex, since diffraction patterns from the latter are largely the result of the scattering of the iodine molecules.

Bear has already discussed the possibility of a helical structure for Katz’s “V” modification of starch on the basis of three or four diffraction maxima obtained from a sample of ethanol-precipitated whole starch. It is now possible to get much better diffraction diagrams, and hence to obtain considerably more information than was possible at that time.

Preparation of Samples and Diffraction Diagrams.—There is evidence that many of the lower alcohols precipitate starch in the helical configuration. Thus starch precipitated by nearly any alcohol will absorb iodine vapor readily and Bear has shown that the dried precipitates yield identical or nearly identical X-ray diffraction patterns of the “V” type. In our experience, however, butanol precipitation produces very superior samples for diffraction purposes. Equally, or even more important in obtaining good diffraction diagrams is the use of amylose or the unbranched component of starch in place of whole starch.

The amylose used in this investigation was prepared by Sindic’s fractionation. Since in Sindic’s procedure the amylose is precipitated by butanol in excellent crystalline form, samples were taken directly from the precipitated fraction. The precipitated material occurs as highly birdfringent rosettes, an optical study of which has already been made. This amylose contains about 10% amylopectin. The purer “crystalline amylose” of Kerr was not superior for diffraction purposes.

Diffraction diagrams were prepared from both wet and dry samples. The wet samples dripping with the saturated butanol solution were sealed in thin glass capillaries. Other samples were dried to constant weight over phosphorus pentoxide in an Abderhalden drier. Diffraction diagrams from samples dried below 90° were best. The dried samples were very hygroscopic, and so were sealed in thin-walled glass capillaries.

Powder diagrams were prepared with Ni filtered Cu Kα radiation in a camera of 10-cm. radius. Exposure periods were varied from 300 to 1500 ma. hrs. at 40 Kv. peak.

The Unit Cells.—The pattern from the dried precipitate can be indexed on the basis of a hexagonal unit \( a₀ = 27.4 \, \text{Å}, \, c₀ = 8.05 \, \text{Å}, \) of an orthorhombic unit \( a₀ = 13.7 \, \text{Å}, \, b₀ = 24.8 \, \text{Å}, \, c₀ = 8.05 \, \text{Å} \) (Table I). The relation between the two unit cells is shown in Fig. 1. As will be seen later, the orthorhombic unit is probably the true unit. In either case the packing of the helices approximates the closest packing of cylinders, a packing very similar to that found for the starch–iodine complex. There are four helices running through the hexagonal unit, two through the orthorhombic unit.

Assuming 6 glucose residues per turn of the

(1) J. Katz, Z. physik Chem., A180, 60 (1930), applied this term to gelatinized starch precipitated by alcohol. Starch so treated produces a characteristic diffraction pattern, distinct from granular and retrograded starch.

(2) (a) R. Rundle and R. Baldwin, J. Amer. Chem. Soc., 66, 554 (1944); (b) R. Rundle and D. French, ibid., 66, 558 (1943); (c) R. Rundle and D. French, ibid., 66, 1707 (1944).

(3) R. S. Bear, ibid., 66, 1388 (1944).

