C, 64.39; H, 4.92; ultraviolet spectrum, λ_{max} 259, 295 (broad) mμ (ε 11,800, 1,980); infrared C=O band in CCl_4: 1689 cm.$^{-1}$.

2-Benzyl-1-naphthol. a. From (III) with Morpholine.—One gram of 2-bromo-2-benzyl-1-tetralone (III) was allowed to stand with three equivalents of morpholine for 10 minutes, then heated for 2 minutes on a steam-bath. Isopropyl ether was added and a 96% yield of the hydrogen bromide salt was collected by filtration. Upon evaporation of the washed filtrate, treatment with charcoal and recrystallization from petroleum ether, a 60% yield of a colorless solid, m.p. 73–74°, was obtained. This compound was identical in m.p. and ultraviolet spectrum with 2-benzyl-1-naphthol secured by the Claisen[22] reaction. Poorer yields and the formation of polymeric substances were obtained when the reaction time was prolonged to 1.5 days.

b. By Reaction of 1-Naphthol with Sodium and Benzyl Chloride.—The reaction was carried out in toluene as described by Claisen.[22] Repeated purification from petroleum ether gave white crystals of 2-benzyl-1-naphthol, m.p. 74–74.5° (lit.[22] 73.5–74°). This compound gradually produced a red coloration with the formation of a golden glimmering precipitate when treated with aq. ferric chloride in ethanol solution; ultraviolet spectrum, λ_{max} 214, 220, 236, 270, 290–300, 310 and 326 mμ (ε 31,400, 33,000, 40,000, 3,000, 4,400, 3,150 and 2,300); infrared bands, γ_{max} in CCl_4: 3520, 3040, 2900, 1945, 1632, 1395, 1142, 1080, 915, 890, 690, 662 cm.$^{-1}$.

Attempted Reaction of III with N-Methylmorpholine.—When N-methylmorpholine was substituted for morpholine in the reaction with III as described above, only a 10% yield of its hydrobromide salt was isolated. Most of the α-bromo ketone III was recovered (80%), and only traces of an impure solid showing a positive ferric chloride test were formed.

LINCOLN, NEBRASKA

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Stereospecific Ring Formation by Means of Mercuric Salts

BY R. K. SUMMERBELL, GREGORY LESTINA AND HAL WAITE

RECEIVED JULY 23, 1956

Allyl ether has been condensed with aqueous mercuric acetate under various conditions of time, acidity and temperature to give, after the appropriate sequence of reactions, mixtures of *cis*- and *trans*-2,6-bis-(iodomethyl)-*p*-dioxane. Although the *cis* isomer was not formed exclusively when mercuric acetate was used, it was found that the proportions and yields of that isomer could be markedly increased by higher reaction temperature, higher acid concentration, and by longer elapsed time before workup. The maximum *cis/trans* ratio was sixteen to one. A reaction mechanism involving mercurinium (or carbonium) ions and equilibration is proposed to explain the observed results.

Introduction

Cyclization of allyl ether with aqueous mercuric acetate to form a substituted dioxane was first reported by Nesmeyanov and Lutsenko.[1] The product, after precipitation of the adduct as the halide followed by replacement of the halomercuri group with iodine, yielded 2,6-bis-(iodomethyl)-*p*-dioxane. This was shown to be the *cis* form by Summerbell and Stephens.[2] The latter workers always obtained some of the *trans* form which, although it was difficult to separate in a pure state, could hardly have been missed by Nesmeyanov and Lutsenko if their preparation had contained similar amounts.

A closely related reaction is the one discovered by Sand and Biilmann[3] who condensed allyl alcohol with mercuric nitrate, precipitated the halide, and treated the halide with iodine to obtain only the *trans* form of 2,5-bis-(iodomethyl)-*p*-dioxane.[4] This preparation has been repeated a number of times in our laboratory, and under the specified conditions the *cis* form had never been observed, and the yields of the *trans* form were invariably very high.

The most obvious difference between this reaction which is stereospecific and the closely related preceding one which yields a mixture of *cis* and *trans* isomers is the use of mercuric nitrate, the salt of a strong acid, in place of mercuric acetate, the salt of a weak acid. Since acid is generated in the mercuration of olefins, there can be obtained either a high or low hydrogen ion concentration during the reaction by the proper choice of a mercuric salt. In view of the current interest in ring closure methods that are, or can be made, stereospecific it seemed worthwhile to investigate the effect of acid concentration and other conditions on the stereospecificity of this reaction.

Discussion

The Stereochemistry of the Reaction.—In the present work allyl ether has been condensed with aqueous mercuric acetate under various conditions of time, acidity and temperature. Conditions were found which gave, after the appropriate sequence of reactions, good yields of *cis*-2,6-bis-(iodomethyl)-*p*-dioxane (I) almost uncontaminated with the *trans* isomer II. Although the *cis* isomer was never formed exclusively when mercuric acetate was used, it was found that proportions and yields of that isomer could be markedly increased by higher reaction temperature, higher acid concentration and by longer elapsed time before workup. The results have been summarized in Table I[5] and the effect of time on the yield and isomer ratio is shown in Fig. 1.

A Proposed Reaction Mechanism.—An acceptable mechanism must explain several facts: (a)

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[1] A. N. Nesmeyanov and I. F. Lutsenko, *Bull. acad. sci.* (*U.S.S.R.*) *Classe Sci. chim.*, 296 (1943).

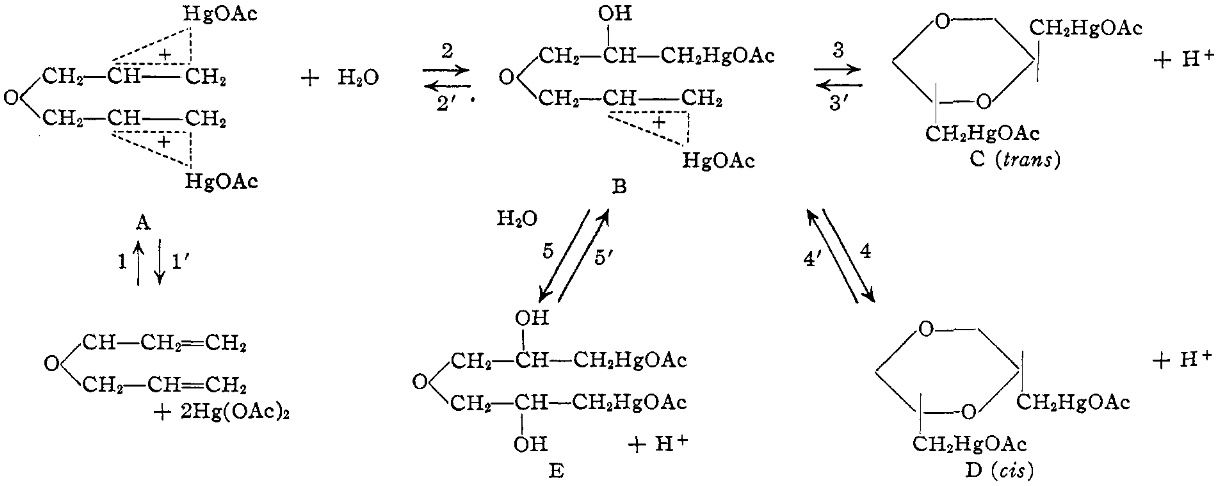
[2] R. K. Summerbell and J. R. Stephens, THIS JOURNAL, **76**, 731 (1954).

[3] J. Sand, *Ber.*, **34**, 1394 (1901); E. Biilmann, *ibid.*, **33**, 1644 (1900).

[4] R. K. Summerbell and J. R. Stephens, THIS JOURNAL, **76**, 6401 (1954); **77**, 6080 (1955).

(5) The referee has suggested the possibility that ". . . fractionation of isomers may occur in the conversion of the acetoxymercuric compounds to the iodides." The iodides are quite insoluble and excess iodide was always used. Some years ago, J. R. Stephens attempted a fractionation of the more soluble corresponding chlorides by partial precipitation, but with no success. As to the next step, the time of reaction with the excess of iodine had been found in preliminary experiments to give the maximum yield, and we believe that this reaction goes to virtual completion. Some small amount of fractionation during crystallization of the final product would be unavoidable by our procedure.

CHART I



A very rapid initial rate of dioxane formation is followed by a much slower rate. One-third of the total yield of dioxanes is formed in the first 15 minutes, the second third in the next seven hours (samples 1, 3, 4). (b) After ten minutes, no precipitate of mercuric oxide is obtained when excess sodium hydroxide is added to an aliquot of the reaction mixture.[1,6] Evidently, some sort of complexation of the mercuric ions is complete at a stage when only one-third of the final yield of dioxanes has been formed. (c) The *cis/trans* ratio of the produced dioxanes changes from 1.8/1 to 16/1 (samples 1, 4). (d) Increased acidity shortens the time necessary to produce maximum dioxane yields and maximum *cis/trans* ratio (samples 4, 5). (e) Increased temperature has the same effect (samples 3, 4, 7).

TABLE I

QUANTITATIVE DETERMINATION OF DIOXANE COMPOUND FROM THE MERCURATION OF ALLYL ETHER

Sample[a]	Time, hr.	Yield, %	M.p., °C.	*cis/trans*
1	0.25	32.8	65–76	1.8
2	2.5	42.5	65–78	1.8
3	7	61.0	70–85	3.2
4	48	89.3	84–89	16
5	7	86.7	85–90	16
6	48	86.0	83–90	16
7	7	86.0	86–90	16
8	48	86.0	84–90	16

[a] The total volume of the reaction mixtures as well as the moles of mercuric acetate and allyl ether were constant in all cases. In reactions 5 and 6, 36.0 g. of nitric acid was added. All reactions were run at 25°, except 7 and 8, which were run at 59°.

A mechanism which seems to us to explain these results is outlined in Chart I.

The immediate formation of mercuric ion–olefin complexes of some stable sort must be postulated to explain the lack of a test for uncomplexed mercuric ions on the addition of sodium hydroxide shortly after the reagents are mixed. Excellent kinetic evidence for the rapid formation of an ion of the type represented by A has been presented by Lucas, Hepner and Winstein[6] in the closely related case of cyclohexene. One of the mercurinium ions of A is assumed to hydrate very rapidly, generating a proton and B. The intermediate B can either solvate to form E[7] and protons, or condense with itself to form C or D and protons. Perhaps steric factors, among them the proximity of the mercurinium ion and the hydroxyl group, are of some importance in determining the ratio of these competing reactions. All of the reactions listed so far, 1, 2, 3, 4 and 5, are assumed to be quite rapid, to account for the very high initial rate of dioxane formation during some unknown portion of the first 15 minutes and the contrasting slow rate of dioxane formation that follows. Molecules E, D and C are assumed to be reconverted to B by proton attack. One would expect 5′ to be faster than 3′ or 4′, as the linear compound E would be much less stable than the six-membered ring compounds D and C. Thus, E serves as the reservoir providing raw material for the slow dioxane formation in the latter stages of the reaction. One would also expect 4′ to be slower than 3′, as D would be the very stable *cis* form[8] of the *meta* derivative of a six-membered ring comparable to cyclohexane.[2,4]

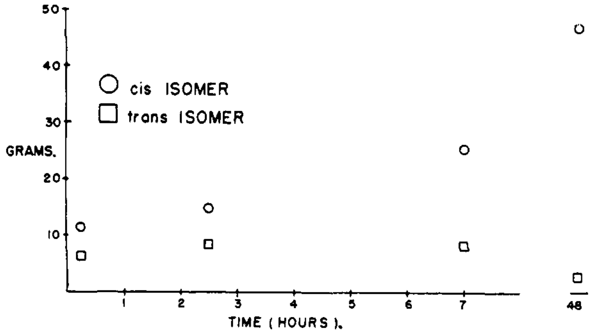


Fig. 1.—The formation of 2,6-bis-(iodomethyl)-*p*-dioxane at 25° with no added acid.

As time goes on, E and C would gradually be converted through B to D, producing a large pre-

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(6) H. J. Lucas, F. R. Hepner and S. Winstein, THIS JOURNAL, **61**, 3102 (1939).

(7) See J. Chatt, *Chem. Revs.*, **48**, 7 (1951), for a detailed evaluation of the chemical evidence concerning the existence of this type of compound.

(8) C. W. Beckett, K. S. Pitzer and R. S. Spitzer, THIS JOURNAL, **69**, 2488 (1947).

ponderance of that product, the most stable entity in this complex reversible system. Thus, our mechanism accounts for the changing ratio of *cis* to *trans* isomers, the increase to a maximum and then the decrease in the yield of *trans* isomer, and the eventual high yield of *cis* isomer.

Increased hydrogen ion concentration and elevated temperatures would have the effect of bringing the system to equilibrium in a shorter time.

Some Additional Effects of Acid Concentration.—The compound *cis*-2,5-bis-(iodomethyl)-*p*-dioxane (III) has never been reported as a direct product from the reaction of mercuric nitrate with allyl alcohol followed by the precipitation with iodide ion and subsequent treatment with iodine.[3,4] From the observed effects of time, acidity and temperature on the isomer distribution of the 2,6-disubstituted dioxanes, and from our mechanistic concepts, it seemed probable that some III should be produced with the proper selection of conditions. An experiment was performed in which there was used less time and less nitric acid than is usually employed in this reaction and under these conditions, after the usual workup, a small amount of the product was separated and identified as III. Spectral evidence indicated the presence of a small amount of a 2,6-isomer as well. Thus at least three, and perhaps all, of the four possible dioxanes were present before equilibration had reduced the concentration of the less stable isomers.

It was then necessary to show that the III isolated in this experiment was due to the specific reaction conditions rather than to increased care and improved isolation and identification procedures. The experiment was repeated, using the relatively high acid concentration and long time of Summerbell and Stephens.[4] No III could be found as a reaction product. We were somewhat surprised, however, when we isolated a little *cis*-2,6-bis-(iodomethyl)-*p*-dioxane (I). The compound was identified beyond question by its infrared spectrogram, and the absence of depression in melting point when mixed with authentic I. An impurity of allyl ether in the allyl alcohol used would account for this product, but none could be detected. Perhaps the derivative of the allyl alcohol analogous to E, $XHgCH_2CHOHCH_2OH$, is involved as an intermediate. It is worth noting that the 2,6-derivative actually isolated is the more stable *cis* isomer.

In another related experiment, high acid concentrations were used in the mercuric nitrate condensation of allyl ether. Under these circumstances, a considerable amount of *trans*-2,5-bis-(iodomethyl)-*p*-dioxane was produced. Evidently, at high enough acid concentrations, ether bonds can be formed or hydrolyzed[9] rather readily. Such experiments as the last two would have been very confusing if they had been encountered in the early stages of the work in our laboratory concerning the structure of these compounds.

Acknowledgment.—Our thanks are given to the Abbott Foundation of Northwestern University for a grant of financial aid and to the Allied Chemical and Dye Corporation for a fellowship held by G. L.

Experimental

A. The Preparation of 2,6-Bis-(iodomethyl)-*p*-dioxane. 1. The Reaction of Mercuric Acetate with Allyl Ether. a. In the Presence of Strong Acid.—To 191.3 g. (0.60 mole) of reagent mercuric acetate dissolved in 700 ml. of water containing 72 g. of concentrated nitric acid, 33.0 g. (0.34 mole) of freshly distilled allyl ether was added. The mixture was then vigorously shaken until all of the allyl ether was absorbed, and sufficient water was added to make a liter of solution. Then two 500-ml. aliquots were withdrawn to be designated as samples 5 and 6 and allowed to react at the time and temperature listed in Table I.

b. In the Absence of Strong Acid.—To 382.5 g. (1.2 moles) of reagent mercuric acetate dissolved in 1 liter of water, was added 66.0 g. (0.67 mole) of freshly distilled allyl ether. The mixture was shaken until the allyl ether was absorbed and sufficient water was added to make 2 liters of solution. Then four 500-ml. aliquots were withdrawn to be designated as samples 1, 2, 3 and 4 and were allowed to react at the time and temperature listed in Table I. Samples 7 and 8 were prepared in the same manner using only one-half the amounts of material listed previously and were allowed to react the designated times before workup.

2. The Preparation of 2,6-Bis-(iodomercurimethyl)-*p*-dioxane. a. From 1_a.—After the mixtures had been allowed to react the appropriate times, during which no precipitates formed, each sample was added to a solution of 80 g. of sodium hydroxide dissolved in 1.5 liters of water. Again no precipitates were formed and the solution remained basic to litmus. To each solution 50 g. (0.3 mole) of potassium iodide in 200 ml. of water was added with vigorous stirring and upon addition a copious white precipitate formed in each case. When the solution had been tested for completeness of precipitation by the addition of excess aqueous potassium iodide, the precipitates were collected by suction filtration, dried for 24 hours at 45°, and weighed.

b. From 1_b.—When the designated times had elapsed, each sample was added to a solution of 40 g. of sodium hydroxide dissolved in 1 liter of water. The remainder of the workup was identical to the procedure cited in 2_a.

3. Treatment of the Iodomercuri Compound with Iodine.—The samples of 2,6-bis-(iodomercurimethyl)-*p*-dioxane were separately suspended in a mixture of 800 ml. of chloroform and 200 ml. of water and refluxed in the presence of excess iodine (slightly more than twice the molar amount of the iodomercuri compound) for four hours. The two liquid phases along with the solid mercuric iodide were washed with 0.1 *M* sodium thiosulfate until the excess iodine was removed. The mercuric iodide was removed by shaking the mixture with a concentrated solution of potassium iodide. The chloroform layer was withdrawn, washed once with water, and evaporated to dryness by means of an air stream. A tan solid remained which was then recrystallized from methyl alcohol. When the first crop of crystals had been collected, the filtrate was evaporated to less than 25 ml. and there were deposited additional crystals along with some dark brown oil. The crystals were collected and subjected to the following analytical procedure.

B. Analytical Procedure.—Each sample to be analyzed was triturated in a Fisher grinder which had been fitted with an agate mortar and pestle.

The analyses were performed with the Baird infrared recording spectrophotometer which was equipped with sodium chloride cells.

The analytical method was based on absorption differences in the 10 to 11 μ region of the infrared spectrum. In carbon disulfide solution, *cis*-2,6-bis-(iodomethyl)-*p*-dioxane (I) possessed a sharp absorption at 11.0 μ (density 0.529 at 1.1901 g./5 ml. of solution while the *trans* isomer II had a density of 0.055 at this point at the same concentration). The infrared spectrum of II had a sharp band at 10.4 μ (density 0.268 for 1.190 g./5 ml. of solution while the *cis*

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(9) The referee has suggested that "... the apparent interconversion of allyl alcohol and allyl ether in these more acid reactions is not unexpected since the reaction would involve the relatively stable allylic carbonium ion ..." Published rates of the acid hydrolysis of comparable ethers at room temperature (R. L. Burwell, Jr., *Chem. Rev.*, **54**, 632 (1954)) seem to us to be too slow to account for the finite amounts of condensed material actually detected, and we believe that mechanisms involving the mercuric ion as well as the hydrogen ion must be involved.

isomer had a density of only 0.051 at this point for the same concentration).

Beer's law was found to be constant in the range of 50–75% *cis* compound. This was determined by making five known mixtures in this range and calculating their concentrations from the observed optical densities. The concentrations of the unknowns in this concentration range were obtained by direct calculations from their observed optical densities according to the procedure utilized by Zimmerman.[10] The analytical method proved accurate to within 3% when tested with mixtures of known composition.

For concentrations above 80% *cis* isomer there were large deviations from Beer's law. This was determined by making three knowns in this range and calculating their concentrations from the observed optical densities. Determinations in this range were performed according to the method described by Burwell and Shields.[11] The unknowns analyzed according to this method were adjudged accurate to within 3% of the actual value.

Some Additional Effects of Acid Concentration. 1. The Mercuration of Allyl Ether in the Presence of Excess Strong Acid.—To 95.6 g. (0.30 mole) of reagent mercuric acetate dissolved in 250 ml. of water containing 108 g. of concentrated nitric acid was added 16.5 g. (0.17 mole) of freshly distilled allyl ether. The mixture was shaken until all of the allyl ether was absorbed and sufficient water was added to make 500 ml. of solution. The solution was then allowed to stand for 48 hours at 25°, after which it was worked up as the preceding experiments. There was obtained 43.5 g. (0.118 mole) of material from which there was isolated 6.1 g. of *trans*-2,5-bis-(iodomethyl)-*p*-dioxane by recrystallization from carbon disulfide and methanol. The remainder of the material consisted of almost pure I.

2. The Preparation of *cis*-2,5-Bis-(iodomethyl)-*p*-dioxane (III).—In 300 ml. of water containing 171.0 g. (0.50 mole) of mercuric nitrate there was added slowly 30.5 g. (0.52 mole) of allyl alcohol and the mixture was vigorously stirred. After three hours the reaction was terminated and the precipitate which had formed was collected by filtration. There was thus obtained 61.5 g. of solid which was assumed to be *trans*-2,5-bis-(nitratomercurimethyl)-*p*-dioxane. The filtrate from the mercuration reaction was added to 1.5 liters of 1 M sodium hydroxide solution and considerable amounts of free mercury were formed. Upon addition of aqueous potassium iodide a precipitate was formed which after treatment with iodine as described in section A-3 yielded 9.8 g. (0.027 mole) of material which after recrystallization from methanol yielded 0.86 g. (0.0023 mole) of *trans*-2,5-bis-(iodomethyl)-*p*-dioxane and 1.0 g. (0.0027 mole) of III, m.p. 96–97° for a 0.93% yield of III. This latter substance did not depress the m.p. of authentic III in a mixed m.p. determination.

Evaporation of the filtrates from recrystallization yielded 7.5 g. of material which because of its infrared spectrogram in potassium bromide was presumed to contain *cis*- and *trans*-2,5-bis-(iodomethyl)-*p*-dioxane as well as some I or II.

Since both isomers of 2,6-bis-(iodomethyl)-*p*-dioxane absorbed strongly at 10.6 μ in the infrared, the presence of this peak indicated the presence of I or II or both. Since *cis*-2,5-bis-(iodomethyl)-*p*-dioxane possessed characteristic absorptions at 10.85 and 11.5 μ in the infrared whereas the *trans* isomer absorbed strongly at 11.1 μ, the presence of these absorbancies indicated the presence of *cis*- and *trans*-2,5-bis-(iodomethyl)-*p*-dioxane.

3. The Mercuration of Allyl Alcohol. The Isolation, after Workup, of *cis*-2,6-Bis-(iodomethyl)-*p*-dioxane (I).—To a solution containing 70 ml. of concd. nitric acid and 45 ml. of water there was added 108.3 g. (0.50 mole) of mercuric oxide. When solution was complete, 200 ml. of water was added and the solution was cooled to 0°. To this cooled solution was added 30.5 g. (0.52 mole) of allyl alcohol with vigorous stirring. This mixture stood for 6 hours and the precipitate which had formed was removed by filtration. The filtrate from the mercuration reaction was made basic by the addition of 4 N sodium hydroxide, and with addition of aqueous potassium iodide a precipitate formed which upon treatment with iodine yielded 3.3 g. (0.0089 mole) of I for a 1.8% yield. After recrystallization from methanol the compound melted at 91–92°, and when the compound was mixed with authentic *cis*-2,5-bis-(iodomethyl)-*p*-dioxane, the mixture melted at 73–77°. The infrared spectrogram of this compound in carbon disulfide was identical to that of authentic I. In a mixed melting point determination with authentic I the mixture melted at 91–92°.

4. The Reaction of Mercuric Acetate with Allyl Alcohol.—To 300 ml. of water containing 25 ml. of glacial acetic acid there was added 159.4 g. (0.50 mole) of mercuric acetate. Sufficient water was added to make 500 ml. of solution and then 30.5 g. (0.52 mole) of allyl alcohol was slowly added. The mixture was allowed to stand at 25° for 6 hours during which time no precipitate formed. Then the reaction mixture was poured into a liter of 1.5 M aqueous sodium hydroxide solution where a small amount of a yellow precipitate was formed. Aqueous potassium iodide was added and a gummy, gray precipitate was formed which was filtered, treated with iodine, and the product isolated in the manner described in section A-3. There was obtained 1.0 g. of material, m.p. 85–130°, which by virtue of its infrared spectrogram in potassium bromide was adjudged to contain only *cis*- and *trans*-2,5-bis-(iodomethyl)-*p*-dioxane.

The absence of an absorption at 10.6 μ indicated the absence of I and II in the product, whereas the presence of absorptions at 10.85, 11.5 and 11.1 μ indicated the presence of both *cis*- and *trans*-2,5-bis-(iodomethyl)-*p*-dioxane.

EVANSTON, ILL.

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[10] H. E. Zimmerman, THIS JOURNAL, **78**, 1172 (1956).

[11] R. L. Burwell and A. D. Shields, *ibid.*, **77**, 2766 (1955).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Synthesis of Substituted Penicillins and Simpler Structural Analogs. XII. 6-Benzylsulfonamidopenicillanic Acid

BY JOHN C. SHEEHAN AND DALE R. HOFF[1]

RECEIVED JULY 13, 1956

An acid-stable, biologically active "sulfonyl analog" of benzylpenicillinic acid (penicillin G) has been synthesized as a crystalline tertiary amine salt. This analog, a racemate, differs from the natural antibiotic structurally only in the replacement of the carbonyl group of the side-chain amide with a sulfonyl function, and the configuration corresponds to that of the natural penicillins. A promising intermediate for the synthesis of penicillin analogs and penicillanic acids, *t*-butyl 4-carbobenzyloxy-5,5-dimethyl-α-amino-2-thiazolidineacetate hydrochloride (VI), was prepared. Acylation of VI with benzylsulfonyl chloride, followed by acid cleavage of the *t*-butyl ester and cyclization, yielded benzyl 6-benzylsulfonamidopenicillanate (IIb), which afforded the free penicillanic acid (IIc) upon catalytic hydrogenolysis.

Recently, the synthesis has been reported[2] of the methyl ester of the "sulfonyl analog" of benzylpenicillin (penicillin G) in which the phenylacetamido side chain was replaced with the benzylsulfonamido group. Cyclization of isomeric benzylsulfonamidopenicilloates (Ia) produced the corresponding isomeric 6-benzylsulfonamidopenicil-

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[1] National Science Foundation Predoctoral Fellow, 1953–1954 and 1954–1955.

[2] J. C. Sheehan and P. A. Cruickshank, THIS JOURNAL, **78**, 3683 (1956).