N–N distances. However, it is not possible to determine the direction of the covalent bonds, since the differences[6] in the interatomic distances are not significant in most cases. This is so because the x-coordinates were not directly determined and also because the standard deviations of the remaining parameters are rather large. An accurate determination of bond distances will have to wait until three-dimensional neutron data can be obtained.

Acknowledgment.—Thanks are due to Dr. J. V. R. Kaufman for bringing this problem to my attention and to Mr. I. Kluger for performing all the computer calculations. The author also is grateful to Dr. H. Danner, Brookhaven National Laboratory, for the neutron data and for the information on the work done at Pennsylvania State University.

(8) The Atlantic Refining Company, Philadelphia, Pa.

EXPLOSIVES & PROPELLANTS LABORATORY
FELTMAN RESEARCH LABORATORIES G. L. GLEN[8]
PICATINNY ARSENAL
DOVER, NEW JERSEY

RECEIVED JUNE 1, 1963

The Mechanism of the Dehydrochlorination of β-Benzene Hexachloride[1]

Sir:

Cristol proposed that the marked unreactivity of the β-isomer of benzene hexachloride (relative to that of the other isomers) is due to the absence, in that and only that isomer, of hydrogen and chlorine atoms *trans* to each other and on adjacent carbon atoms.[2] Although this proposal seems generally accepted, there is less agreement concerning the mechanism of the *cis*-dehydrochlorination of β-benzene hexachloride. Cristol and Fix[3] pointed out that in a deuterated solvent the intermediate carbanion suggested for the reaction could either be deuterated with retention of configuration to yield labeled starting material, be deuterated with inversion of configuration to give labeled δ-benzene hexachloride, or lose a chloride ion to give a pentachlorocyclohexene. Either the δ-isomer or the pentachlorocyclohexene would then be rapidly dehydrochlorinated to a mixture of trichlorobenzenes.

$$\beta\text{-}C_6H_6Cl_6 + OEt^- \longrightarrow C_6H_5Cl_6^- + EtOH$$
$$C_6H_5Cl_6^- + EtOD \longrightarrow \beta\text{-}C_6H_5DCl_6 + EtO^-$$
$$C_6H_5Cl_6^- + EtOD \longrightarrow \delta\text{-}C_6H_5DCl_6 + EtO^-$$
$$C_6H_5Cl_6^- \longrightarrow C_6H_5Cl_5 + Cl^-$$

As evidence for the intermediacy of a carbanion, Cristol and Fix reported 0.08% deuterium present in the β-benzene hexachloride isolated after about 50% dehydrohalogenation in 70% EtOD–30% EtOH.

Cram has stated that the most probable path of decomposition of the carbanion is *via* the formation of δ-benzene hexachloride, *cis* elimination from the carbanion being improbable, and that deuterated trichlorobenzenes should be produced in a deuterated solvent, since the deuterium atom of any intermediate δ-benzene hexachloride could be removed in a *trans* elimination only *via* a conformation with five axial chlorine atoms.[4]

In relation to our interest in the carbanion mechanism for β-elimination reactions,[1] we have examined the trichlorobenzene mixture produced in deuterated methanol.[5] When 2.19 mmoles of β-benzene hexachloride was 70% dehydrohalogenated by 6.9 mmoles of sodium methoxide in 98% MeOD–2% MeOH, the trichlorobenzene mixture (containing 88% of the 1,2,4-isomer) produced had n.m.r. and infrared spectra almost identical with those of the trichlorobenzene mixture produced under very similar conditions in "light" methanol. From blank experiments we conclude that 3.1 ± 1.0% 1,2,4-trichlorobenzene-3-*d* and much less of any other deuterated trichlorobenzene were present in the products of reaction in MeOD. Determination of the rate constant for the dehydrochlorination of β-benzene hexachloride in methanol and comparison with that for the exchange of 1,2,4-trichlorobenzene-3-*d*[1b] showed that between 1 and 5%[6] of the 1,2,4-trichlorobenzene produced in the reaction in MeOD would have been transformed to 1,2,4-trichlorobenzene-3-*d*.

We therefore conclude that if the alkaline dehydrochlorination of β-benzene hexachloride is initiated to any major extent by carbanion formation, the intermediate carbanions almost always lose chloride ions and are only rarely reprotonated. The possibility that the reaction proceeds only to a minor extent *via* intermediate carbanions but consists largely of a concerted *cis* elimination from a conformation, like the boat form, in which the dihedral angle between the hydrogen and chlorine atoms being removed is quite small[7] has not been ruled out. However, in view of the slow rate of such *cis* eliminations[8] and the added energy that would be required in the present case to reach such a conformation, the dehydrohalogenation of β-benzene hexachloride seems surprisingly fast to be a reaction of this type.

Acknowledgment.—We wish to thank the National Science Foundation for partial support of this investigation.

it seems that intermediate carbanions should be captured more efficiently in this solvent than in ethanol. If k_H/k_D is 5.0, 9% of the captured intermediates will escape deuteration in 98% MeOD but 68% will in 70% EtOD.

(6) Assuming that k_H/k_D is between 1 and 5.

(7) *Cf.* C. H. DePuy, R. D. Thurn, and G. F. Morris, *J. Am. Chem. Soc.*, **84**, 1314 (1962).

(8) Some of the data of Cristol and co-workers[9] provide maximum values for the rates of such processes.

(9) S. J. Cristol and N. L. Hause, *J. Am. Chem. Soc.*, **74**, 2193 (1952); S. J. Cristol and E. F. Hoegger, *ibid.*, **79**, 3438 (1957).

SCHOOL OF CHEMISTRY JACK HINE
GEORGIA INSTITUTE OF TECHNOLOGY RICHARD D. WEIMAR, JR.
ATLANTA 13, GEORGIA PAUL B. LANGFORD
O. BERTRAND RAMSAY

RECEIVED OCTOBER 28, 1963

Photochemical and Thermal Rearrangement of α,β-Epoxyketones

Sir:

Investigations during the past decade have revealed the carbonyl group as an important and versatile chromophore in photochemical reactions.[1,2] In view of the many acid- and base-catalyzed rearrangements exhibited by α,β-epoxyketones,[3] it is surprising that the photochemical behavior of these substrates has not been widely studied.[4] A recent investigation[5] of the photolysis of some steroidal epoxyketones represents the only published case in which skeletal rearrangement occurs. We take this opportunity to report[6]

(1) (a) Part V in the series "The Carbanion Mechanism for β-Elimination Reactions"; (b) for part IV see J. Hine and P. B. Langford, *J. Org. Chem.*, **27**, 4149 (1962).

(2) S. J. Cristol, *J. Am. Chem. Soc.*, **69**, 338 (1947); *cf.* S. J. Cristol, N. L. Hause, and J. S. Meek, *ibid.*, **73**, 674 (1951).

(3) S. J. Cristol and D. D. Fix, *ibid.*, **75**, 2647 (1953).

(4) D. J. Cram in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 321.

(5) In view of the greater acidity and ion-solvating power of methanol

(1) P. de Mayo, *Advan. Org. Chem.*, **2**, 367 (1960).

(2) P. de Mayo and S. T. Reid, *Quart. Rev.* (London), **15**, 393 (1961).

(3) R. Parker and N. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(4) The first of a few recent endeavors is that by H. E. Zimmerman, Abstracts of the Seventeenth National Organic Chemistry Symposium, June, 1961, Bloomington, Indiana, p. 31.

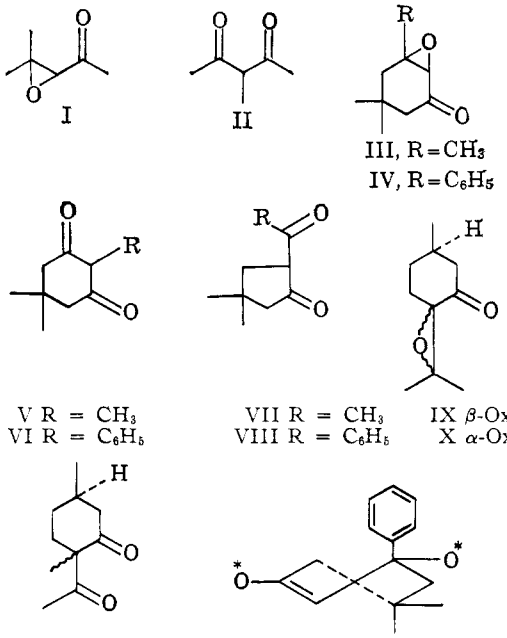
(5) C. Lehmann, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **45**, 1031 (1962).

(6) Part of this work was presented by W. Reusch and C. K. Johnson,

similar reactions for several simple epoxyketones and to discuss the mechanistic implications of these rearrangements.

Irradiation[7] of 3,4-epoxy-4-methyl-2-pentanone (I) in the gaseous state, neat, or in a variety of solvents produced a slight coloration after exposure for periods of 6 to 24 hr. Analysis by v.p.c. indicated a 10–16% conversion to volatile substances; in most cases the major product (2–12%) was 3-methylpentane-2,4-dione (II). The poor yield in this reaction is due in part to the sensitivity of the α-diketone II to the photolysis conditions. Acetaldehyde, acetone, methyl ethyl ketone, methyl isopropyl ketone, and 2-butenyl acetate have been identified among the rearrangement products from the photolysis of both I and II. Since I reacts more rapidly than II, the latter cannot be the sole source of these minor products. Large amounts of higher boiling compounds and tar are formed during the gas phase irradiations, but constitute only 0–12% of the material recovered from the liquid phase experiments.

The photolysis of benzene, ether, and acetic acid solutions of isophorone oxide (III) gave similar transformations. A 9:1 mixture of 2-acetyl-4,4-dimethylcyclopentanone (VII)[8] and 2,5,5-trimethylcyclohexane-1,3-dione (V)[9] was isolated in 9–10% yield by base extraction of the crude photolysis mixture. Analysis (v.p.c.) did not disclose any additional volatile products; however, higher boiling materials were definitely formed.



The stereoisomeric pulegone oxides IX and X[10] are of particular interest in this discussion, since isomerization[11] would imply the reversible formation of a reactive intermediate.[12] When an ether solution of X was irradiated, rearrangement to the stereoisomeric 2-acetyl-2,5-dimethylcyclohexanones (XI and XII) and isomerization (to IX) were both observed. The rate of isomerization appears to be slightly greater than the rate of rearrangement; however, subsequent photochemical decomposition of the rearrangement products (XI and XII) makes an accurate comparison impossible. The steady-state concentration of XI and XII is roughly 7% with XI predominating.

The previous examples parallel the findings of the Zurich investigation[5] in that β-diketones are formed as a consequence of an alkyl group shift from C-β to C-α. This transformation is consistent with a mechanism recently suggested by Zimmerman,[4] but is clearly open to a number of other interpretations. Although our work is not complete enough to warrant a critical discussion of different mechanisms, we wish to report some additional facts which are relevant to this subject.

First, mercury-sensitized photolysis[13] of I in the gas phase gave a 10% yield of II plus considerable tar formation after exposure for only 3.5 hr. It is thus conceivable that these reactions proceed *via* triplet intermediates.

Second, a 24-hr. irradiation of an ether solution of 3-phenyl-5,5-dimethyl-2,3-epoxycyclohexanone (IV)[14] produced a 15% yield of 2-benzoyl-4,4-dimethylcyclopentanone (VIII), m.p. 85°, and no detectable quantity of isomer VI.[15] The remarkable absence of phenyl migration in this rearrangement might be attributed to steric factors which prevent the required orientation of the aromatic ring in the intermediate; however, inspection of a Dreiding model discloses a twist conformation (XIII) lacking such restrictions. Consequently, we prefer to consider the preferential shift of alkyl groups rather than aryl groups to be a fundamental characteristic of this reaction[16] instead of a special case. This suggests considerable bond breaking in the transition state for rearrangement, or possibly a fragmented intermediate.[17]

Finally, an investigation of the thermal chemistry of pulegone oxide introduces the possibility that these photochemical reactions proceed by way of vibrationally excited species.[18,19] A thermal reaction of pulegone oxide was described over 35 years ago[20] and confirmed recently by Pigulevsky and Mironova[21]; however, the interpretation offered by the latter workers has been shown to be erroneous.[10] When degassed samples of IX and X are heated in carefully cleaned Pyrex vials

Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 89Q.

(7) Gaseous and neat samples in Vycor or quartz vessels were exposed to a Hanovia Type SH, 100-w., mercury lamp. Solutions were photolyzed by a Hanovia Type S, 200-w., water-cooled mercury lamp in an immersion apparatus equipped with a Corex filter.

(8) Identified by comparison with authentic material prepared by acylating 3,3-dimethylcyclohexanone according to C. Hauser, F. Swamer, and B. Ringler, *J. Am. Chem. Soc.*, **70**, 4023 (1948).

(9) T. Voitila, *Ann. Acad. Sci. Fennicae*, **A49**, **1**, 110 (1938).

(10) W. Reusch and C. K. Johnson, *J. Org. Chem.*, **28**, 2557 (1963).

(11) H. E. Zimmerman[4] has reported isomerization in the photolysis of *trans*-dypnone oxide.

(12) Evidence concerning isomerization does not necessarily apply to the rearrangement process. Nevertheless, we favor *a priori* a stepwise mechanism for the latter reaction as well, since the transition state for a concerted path would be rather contorted in order to achieve even poor overlap of orbitals.

(13) A Vycor flask containing I and mercury at 2 mm. and 40° was irradiated by two 15-w. General Electric germicidal lamps. In the absence of mercury, very little reaction was observed. Liquid phase sensitization by benzophenone proved not to be successful.

(14) Prepared by epoxidation of 3-phenyl-5,5-dimethylcyclohex-2-en-1-one: G. F. Woods, *J. Am. Chem. Soc.*, **69**, 2549 (1947).

(15) F. M. Beringer, P. Forgione, and M. Yudis, *Tetrahedron*, **8**, 4963 (1960).

(16) It is hoped that current work with open-chain analogs will substantiate this conclusion. The lack of phenyl migration in the epoxyketone photolyses reported by Zimmerman[4] supports this viewpoint.

(17) The presence of ionic or radical fragments is being investigated by scavenging experiments.

(18) J. P. Simons, *Quart. Rev.* (London), **13**, 3 (1959); R. Srinivasan, *J. Am. Chem. Soc.*, **84**, 3432, 3982 (1962).

(19) H. E. Zimmerman and D. I. Schuster, *ibid.*, **84**, 4527 (1962), have remarked that n → π^* photochemical reactions do not in general parallel thermal reactions.

(20) M. N. Prileschaev, *Bull. Soc. Chim. France*, (IV) **41**, 687 (1927).

(21) G. V. Pigulevsky and I. K. Mironova, *Zh. Obshch. Khim.*, **27**, 1101 (1957).

at 200°, extensive rearrangement, isomerization, and fragmentation occurs. A 2:1 mixture of XII, disemicarbazone, m.p. 222°, and XI, semicarbazone, m.p. 213°, was obtained in 75% yield after heating X for 10 hr. The diastereoisomer IX is slower to react, giving 43% rearrangement to a similar mixture in the same period. An independent preparation of XI and XII by ozonolysis of a mixture of 4-methylisopulegone diastereoisomers[22] completed the proof of structure and enabled us to assign configurations to these isomers. Appropriate experiments have established that this unusual thermal rearrangement[23] is not catalyzed by acids or radical initiators and is insensitive to increases in surface area.

(22) C. Djerassi, J. Osiecki, and E. J. Eisenbraum, *J. Am. Chem. Soc.*, **83**, 4433 (1961). In our hands the methylation of pulegone yielded a mixture of 76%(−)-4-methylisopulegone and 24% of the dextrorotatory diastereomer, identified by semicarbazone derivatives.

(23) Epoxyketones I and III do not exhibit similar thermal reactions, but are transformed instead by a high temperature, free-radical decomposition initiated by oxirane hydrogen abstraction: W. Reusch and C. K. Johnson, *J. Am. Chem. Soc.*, **84**, 1759 (1962).

(24) Holder of a National Science Foundation Cooperative Graduate Fellowship, 1962–1963.

(25) National Science Foundation Undergraduate Research Participant.

(26) This investigation was supported in part by a research grant, AM 04936-03, from the National Institutes of Health.

KEDZIE CHEMICAL LABORATORY
MICHIGAN STATE UNIVERSITY
EAST LANSING, MICHIGAN
CALVIN KEITH JOHNSON[24]
BERYL DOMINY[25]
WILLIAM REUSCH[26]

RECEIVED SEPTEMBER 9, 1963

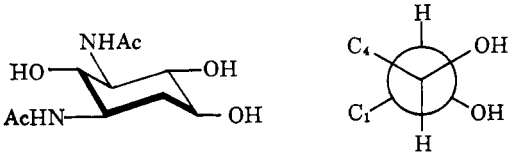
The Absolute Configuration of Streptidine in Streptomycin

Sir:

The gross structural features of the potent antibiotic substance streptomycin were derived[1] many years ago. The component fragments are N-methyl-L-glucosamine, the elusive L-streptose (which has been assigned the structure 5-deoxy-3-C-formyl-L-lyxose),[2] and streptidine. The configuration of the glycosidic linkage between N-methyl-L-glucosamine and streptose has been shown to be α,[3] that between streptose and streptidine has been shown to be β.[3] Streptidine was shown to be a *meso* form of 1,3-diguanido-2,4,5,6-tetrahydroxycyclohexane[4] and, furthermore, by synthesis[5] and degradation[6] to possess the all *trans* configuration. The streptobiosamine moiety of streptomycin has been shown to be attached to position 4[7] of streptidine in *either* the R or S[9] absolute configuration by the degradation of streptomycin of optically active ($[\alpha]_D$ −4° (*c* 1.1, 50% acetic acid)) N,N′-dibenzoyl-4-deoxystreptamine (I).[10] Although streptidine is a *meso* form, the asymmetric attachment of streptobiosamine to it causes each of the ring carbons of streptidine in streptomycin to be asymmetric. We wish to report the determination of the absolute configuration of N,N′-diacetyl-4-deoxystreptamine, derived from N,N′-dibenzoyl-4-deoxystreptamine and, hence, the complete configurational assignment of streptomycin and other members of the streptomycin antibiotic group.

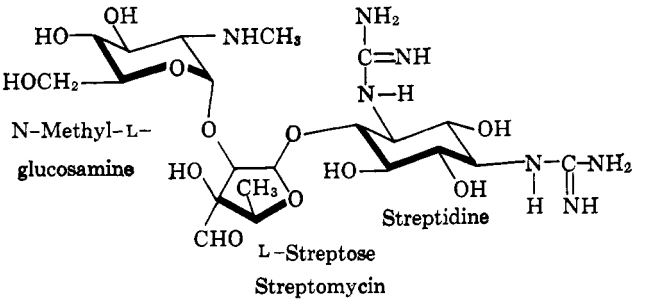
Acid hydrolysis of N,N′-dibenzoyl-4-deoxystreptamine (I), m.p. 284–286° dec. (lit.[10] m.p. 287–289°), furnished 4-deoxystreptamine, which on acetylation gave pentaacetyl-4-deoxystreptamine (II), m.p. 319–320° (*Anal.* Calcd. for $C_{16}H_{24}O_8N_2$: C, 51.60; H, 6.50; N, 7.52. Found: C, 51.39; H, 6.47; N, 7.48). The polyacetate II, on treatment with methanolic ammonia, gave N,N′-diacetyl-4-deoxystreptamine (III), m.p. 291–292°, $[\alpha]^{29}_D$ +5° (*c* 0.97, water) (*Anal.* Calcd. for $C_{10}H_{18}O_5N_2$: C, 48.77; H, 7.36; N, 11.37. Found: C, 48.50; H, 7.29; N, 11.15).

The absolute configuration of III was determined by the application of Reeves' cuprammonium method.[11] Compound III showed $[\alpha]^{29}_{436}$ +5° (*c* 0.97, water) and $[\alpha]^{29}_{436}$ −970° (*c* 0.88, Cupra B); this gives the result $\Delta[M]_{\text{Cupra B}}$ −2400°.[12] The strong negative increment is similar to that obtained for the 2,3-glycol complex of D-glucosides ($\Delta[M]_{\text{Cupra B}} \sim -2075°$) but opposed to that obtained for the 3,4-glycol complex of D-glucosides ($\Delta[M]_{\text{Cupra B}} \sim +2150°$).[11] Interferences from a potential *trans* 1,3-glycol complex are not observed,[11] and interference from acetamido groups does not occur.[13] Thus, the dihedral angle of the 5,6-glycol grouping (formed from the planes of HO–C_5–C_6 and C_5–C_6–OH) of N,N′-diacetyl-4-deoxystreptamine (III) is *clockwise*[11] 60° and III has the absolute configuration shown *rather* than its mirror image.[14]



III

Using this configurational assignment, the structure of streptomycin in complete stereochemical detail may be written as indicated.[15] This stereochemical result also establishes the complete structure



Streptomycin

(1) R. U. Lemieux and M. L. Wolfrom, *Advan. Carbohydrate Chem.*, **3**, 337 (1948), and references cited therein.

(2) F. A. Kuehl, Jr., R. L. Clark, M. N. Bishop, E. H. Flynn, and K. Folkers, *J. Am. Chem. Soc.*, **71**, 1445 (1949).

(3) M. L. Wolfrom, M. J. Cron, C. W. DeWalt, and R. M. Husband, *ibid.*, **76**, 3675 (1954).

(4) H. E. Carter, R. K. Clark, Jr., S. R. Dickman, Y. H. Loo, P. S. Skell, and W. A. Strong, *Science*, **103**, 540 (1946).

(5) M. L. Wolfrom, S. M. Olin, and W. J. Polglase, *J. Am. Chem. Soc.*, **72**, 1724 (1950).

(6) O. Wintersteiner and A. Klingsberg, *ibid.*, **73**, 2917 (1951).

(7) The numbering system used here is that suggested by Rinehart, *et al.*,[8] for the 2-deoxystreptamine moiety of the neomycin antibiotic group. For streptomycin, this attaches the streptobiosamine fragment at C-4 of streptidine.

(8) K. L. Rinehart, Jr., M. Hichens, A. D. Argoudelis, W. S. Chilton, H. E. Carter, M. P. Georgiadis, C. P. Schaffner, and R. T. Schillings, *J. Am. Chem. Soc.*, **84**, 3218 (1962).

(9) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(10) F. A. Kuehl, Jr., R. L. Peck, C. E. Hoffhine, Jr., and K. Folkers, *J. Am. Chem. Soc.*, **70**, 2325 (1948). The hydroxyl group of streptidine that is replaced by hydrogen in this degradation sequence is that to which streptobiosamine is glycosidically attached in streptomycin.

(11) R. E. Reeves, *Advan. Carbohydrate Chem.*, **6**, 107 (1951), and references cited therein.

(12) $\Delta[M]_{\text{Cupra}} = ([\alpha]_{436}$ Cupra − $[\alpha]_{436}$ water) × (mol. wt./100).

(13) M. Hichens and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **85**, 1547 (1963).

(14) Using the R, S[9] convention, the absolute configuration of III may be written 1(R),3(R)-diacetamido-2(S),5(S),6(S)-trihydroxycyclohexane.

(15) The asymmetry of the streptidine ring in streptomycin is thus 1(R),-2(R),3(S),4(R),5(R),6(S). This assignment is in agreement with the suggestion of Tatsuoka,[16] which was based on the fact that N,N′-diacetyl-2,5,6-tri-O-methylstreptamine, derived from dihydrostreptomycin, has the same sign (positive) of rotation as N,N′-diacetyl-5,6-di-O-methyl-2-deoxystreptamine, derived from pseudoneamine. We thank Dr. K. L. Rinehart, Jr., for bringing this suggestion to our attention.

(16) S. Tatsuoka and S. Horii, *Proc. Japan Acad.*, **39**, 314 (1963).