sind. Beginnt jedoch ein chemisches Agens nach der Neuverteilung zu wirken, dann wird das weitere Wachstum aller chemosensiblen Arten bzw. Varianten unterdrückt, und die Neuverteilung führt zu einer Erhöhung der Kolonienzahl nur der chemoresistenten Keime. Eine solche Zunahme der Kolonienzahl ist bei entsprechender Kleinheit der primären Mikrokolonien jedoch nicht zu erwarten, wenn chemoresistente Varianten erst unter der Einwirkung des chemischen Agens entstehen.

Bei Chemoresistenzen ist eine Modifikation des von NEWCOMBE zur Prüfung von Phagenresistenzen angegebenen Testverfahrens erforderlich, die eine gut definierte Änderung des Nährmediums ohne Läsion der Mikrokolonien gewährleistet. Man geht dabei am einfachsten so vor, daß die Bakterien nicht unmittelbar auf die Agaroberfläche, sondern auf sterile, bakteriendichte Membranfilter gebracht werden (zum Beispiel Membranfilter «mittel» ⌀ 9 cm der Firma Sartorius, Göttingen). Die Membranfilter lassen sich nacheinander auf halbfeste Nährböden verschiedener Zusammensetzung legen und bebrüten. Es kommt zu einem schnellen Austausch des Nährmediums. Die Bakterien wachsen auf den Filtern zu gut erkennbaren Kolonien aus.

Nach diesem Verfahren wurde der Entstehungsmechanismus chemoresistenter Bakterienvarianten geprüft. Über das Ergebnis dieser Untersuchung wird an anderer Stelle[1] berichtet werden. WOLFGANG DITTRICH

Universitäts-Frauenklinik Hamburg-Eppendorf, den 6. Juli 1951.

Summary

A new form of the Newcombe test is described which gives a good possibility of testing mechanism of the origin of chemoresistant bacteria.

[1] H. BORNSCHEIN, W. DITTRICH und G. HÖHNE Naturwissenschaften *38*, 383 (1951).

DISPUTANDUM

Concerning the Mechanism of the Silver Salt-Bromine Reaction

Introduction. In the course of synthetic and degradative work, extensive use has been made in this laboratory and elsewhere of the silver salt-bromine reaction (cf.[1] for a review). The question as to the mechanism of this useful reaction was of obvious interest, and this question still forms a subject of active controversy (cf.[2] for recent discussions). A study of the pertinent literature revealed that certain stereochemical considerations apparently have not as yet been put forward in connection with this reaction, and it therefore seems appropriate to give a brief review on the present state of the problem.

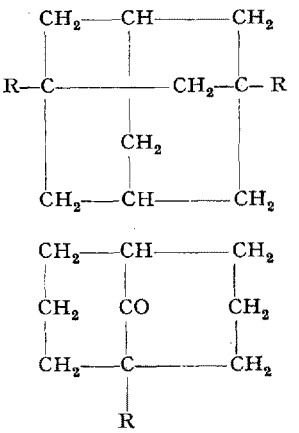
The overall reaction (A) of bromine with the silver salt of a carboxylic acid is known to proceed in two stages, (B) and (C)[1].

$$\text{(A)}\quad \underset{\text{(I)}}{RCOOAg} + Br_2 \rightarrow RBr + AgBr + CO_2$$

$$\text{(B)}\quad \underset{\text{(I)}}{RCOOAg} + Br_2 \rightarrow \underset{\text{(II)}}{RCOOBr} + AgBr$$

$$\text{(C)}\quad \underset{\text{(II)}}{RCOOBr} \rightarrow RBr + CO_2$$

The main question at issue has been whether in the decarboxylation step (C) the group R is attacked by a free bromine atom, $Br^{\cdot}$, or by a bromine cation, Br^{+}. Recent experiments[1] in the aromatic series (R = Ar) strongly indicate that in these cases the complex (II) can act as a source of free bromine atoms, and these cases will not be discussed here. In the aliphatic series, on the other hand, there is evidence of an ionic mechanism, and the last word in this respect appears to be the paper by ARCUS, CAMPBELL, and KENYON[2] which is consistent in itself and has remained unchallenged so far. On treating the silver salt of optically active α-phenylpropionic acid with bromine, the British authors obtained α-phenylethylbromide which was still optically active, the retention of asymmetry amounting to 43%, with *inversion* of configuration. The authors conclude from their experiment that the reaction of bromine with silver α-phenylpropionate is mainly or entirely a bimolecular substitution with inversion of configuration effected by the electrophilic reagent, positive bromine. Though the proposed mechanism satisfactorily explains the observations in that particular experiment, it follows from information available in the literature that still another mechanism or mechanisms must exist which can definitely not involve any configurational inversion. Thus, SMITH and HULL[3] converted the silver salt of *t*-butylacetic acid into neopentylbromide in 62% yield. Since the neopentyl system is known to be unusually stable and inert to substitution reactions involving inversion mechanisms[4], and since this inertness is of steric rather than of polar origin[5], the bimolecular course appears unlikely in this case. Furthermore, PRELOG and SEIWERTH[6] were able to secure, without difficulty, and in fair yield, the dibromide (IIIb) from adamantane–1,3-dicarboxylic acid (IIIa); and similarly, COPE and SYNERHOLM[7] obtained 1-bromobicyclo [3.3.1] nonan-9-one (IVb) from the acid (IVa) in 74% yield. The two last-named experiments constitute examples of successful transformations at highly hindered bridgehead positions.



(III)
a R = COOH
b R = Br

(IV)
a R = COOH
b R = Br

[1] W. G. DAUBEN and H. TILLES, J. Amer. Chem. Soc. *72*, 3185 (1950).—R. A. BARNES and R. J. PROCHASKA, J. Amer. Chem. Soc. *72*, 3188 (1950).—M. HEINTZELER, Ann. Chem. *569*, 102 (1950).

[2] C. L. ARCUS, A. CAMPBELL, and J. KENYON, J. Chem. Soc. *1949*, 1510.

[3] W. T. SMITH, Jr., and R. L. HULL, J. Amer. Chem. Soc. *72*, 3309 (1950).

[4] E. D. HUGHES, Trans. Faraday Soc. *37*, 620 (1941). – I. DOSTROVSKY, E. D. HUGHES, and C. K. INGOLD, J. Chem. Soc. 173 (1946). — P. D. BARTLETT and L. J. ROSEN, J. Amer. Chem. Soc. *64*, 543 (1942).

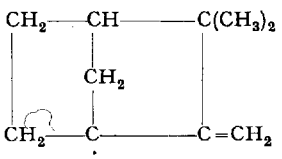
[5] P. D. BARTLETT and L. J. ROSEN, J. Amer. Chem. Soc. *64*, 543 (1942).

[6] V. PRELOG and R. SEIWERTH, Ber. Dtsch. chem. Ges. *74*, 1769 (1941).

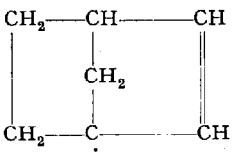
[7] A. C. COPE and M. E. SYNERHOLM, J. Amer. Chem. Soc. *72*, 5228 (1950).

(1) It follows that in these cases the silver salt reaction could *not* have taken the *bimolecular*, S_E2 course because BARTLETT and his co-workers[1] have shown that bimolecular substitution and Walden inversion are impossible at the bridgehead of a bicyclic structure of the apocamphane type, "attack from the rear" being excluded on steric grounds regardless of whether the carbon atom at which the substitution takes place carries a formal positive or negative charge in the transition state.

(2) It is tempting to discuss the possibility of a free radical mechanism on the evidence at hand, but the situation is confusing. On the one hand it is generally believed[2] that an aliphatic carbon radical has a planar configuration. This view is further substantiated by the experiments of ROBERTS and his co-workers[3]. These authors were unable to obtain any evidence of free radical intermediates (V) and (VI) from camphene or norbornylene respectively; treatment of the bicyclic olefins with N-bromosuccinimide in boiling carbon tetrachloride under irradiation and addition of benzoyl peroxide always resulted in abnormal products, and no bridgehead allylic bromide could be detected.



(V)



(VI)

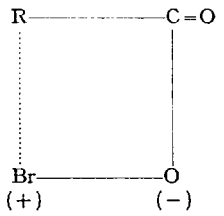
On the other hand KHARASCH, ENGELMANN, and URRY[4] provided strong evidence that the non-coplanar free radical, 1-apocamphyl, is capable of existence. When the diacyl peroxide from 1-apocamphylcarboxylic acid was subjected to prolonged boiling in carbon tetrachloride, the authors were able to isolate and identify, as by-products of the decomposition, 1-chloroapocamphane, 1,1'-biapocamphyl, and hexachloroethane, formation of coupling products and participation of solvent carbon tetrachloride both being characteristic of a free radical reaction. Thus the contradictory situation as outlined is a problem in itself and fails to provide any argument in favour of the occurrence or non-occurrence of free radical intermediates in the silver salt-bromine reaction.

(3) The *unimolecular*, S_E1 mechanism can be considered as a probable course of the silver salt reaction provided that HUGHES'[5] view of straightforward slow ionization rather than SWAIN'S[6] "concerted push-pull" mechanism is operative here. The intermediate carbanion would then be held rigidly in a stable pyramidal configuration in which carbanions in general are thought to occur[1]. The decomposition of the acyl hypobromite might then be formulated as to involve the following steps:

(*a*) formation of a carbanion by slow ionization of the C–C bond,

(*b*) splitting of the positive fragment into carbon dioxide gas and bromine cation, and

(*c*) formation of the C–Br bond from the oppositely charged parts, *with retention of configuration.*



An even more satisfactory picture would be obtained by assuming a concerted, intramolecular, cyclic modification of the scheme just outlined (S_i, Figure), in perfect formal analogy with the decomposition of chlorosulphinic esters[2] which appear as more or less stable intermediates in the transformation of alcohols into the corresponding alkyl halides by means of thionyl chloride, with retention of configuration. However, since BARTLETT and KNOX[3] were unable to bring about any reaction with thionyl chloride at the bridgehead of the bicyclic structure 1-apocamphanol this point requires further clarification.

The author's thanks are due to Professor SUNE BERGSTRÖM for his continuous interest.

MAX ROTTENBERG

Department of Physiological Chemistry, University of Lund, Sweden, August 22, 1951.

Zusammenfassung

An Hand der neueren Literatur wird der stereo- und strukturchemische Verlauf der Silbersalz-Brom-Reaktion bei aliphatischen Karbonsäuren diskutiert. KENYON und Mitarbeiter haben schon früher ihren Versuch als bimolekulare Substitution mit Waldenscher Umkehrung deuten können; die Tatsache jedoch, daß die besprochene Reaktion keiner sterischen Hinderung irgendwelcher Art unterworfen ist, schließt in andern Fällen KENYONS Chemismus mit Bestimmtheit aus und macht einen unimolekularen Reaktionsverlauf unter *Erhaltung der Konfiguration* wahrscheinlich.

[1] P. D. BARTLETT and L. H. KNOX, J. Amer. Chem. Soc. *61*, 3184 (1939).—P. D. BARTLETT and S. G. COHEN, J. Amer. Chem. Soc. *62*, 1183 (1940).

[2] H. C. BROWN, R. S. FLETCHER, and R. B. JOHANNESEN, J. Amer. Chem. Soc. *73*, 212 (1951).

[3] J. D. ROBERTS and E. R. TRUMBULL, J. Amer. Chem. Soc. *71*, 1630 (1949).—J. D. ROBERTS, E. R. TRUMBULL, W. BENNETT, and R. ARMSTRONG, J. Amer. Chem. Soc. *72*, 3116 (1950).

[4] M. S. KHARASCH, F. ENGELMANN, and W. H. URRY, J. Amer. Chem. Soc. *65*, 2428 (1943).

[5] E. D. HUGHES, J. Chem. Soc. 968 (1946).

[6] C. G. SWAIN, J. Amer. Chem. Soc. *70*, 1119 (1948).

[1] K. ZIEGLER and A. WENZ, Ber. Dtsch. chem. Ges. *83*, 354 (1950).—G. WITTIG, F. VIDAL, and E. BOHNERT, Ber. Dtsch. chem. Ges. *83*, 359 (1950).—M. HEINTZELER, Ann. chem. *569*, 97 (1950).—R. L. LETSINGER, J. Amer. Chem. Soc. *72*, 4842 (1950).

[2] W. A. COWDREY, E. D. HUGHES, C. K. INGOLD, S. MASTERMAN, and A. D. SCOTT, J. Chem. Soc. 1252 (1937).

[3] P. D. BARTLETT and L. H. KNOX, J. Amer. Chem. Soc. *61*, 3184 (1939).