has been suggested several times.[2,3,4] Among the post-transition metal–metal halide systems, the variations in metal solubility both within the group and with change in halide ion are consistent with such an interpretation, and, moreover, there is a direct correspondence between appreciable solubility in the molten halide and the existence of a known gaseous subhalide.[5] However, with the possible exception of CaCl,[6] the isolation of lower oxidation states from these melts apparently has not been achieved; the systems characteristically revert to the original components on solidification.

The effect of certain foreign salts on the metal solubility has been reported for the cadmium[7] and bismuth[8] systems. An interpretation of the results that appears more satisfactory than those previously presented[3,7] can be obtained from a consideration of the possible acid-base or "complexing" interactions between the added salt and the two oxidation states present. Added base, *i.e.*, halide ion, would be expected to reduce the amount of subhalide formed through stabilization of the more acidic, higher oxidation state. Conversely, addition of an acid capable of complexing halide ion would increase the amount of subhalide formed. Use of the strongly acidic $AlCl_3$ in such systems has resulted in the preparation of stable Bi(I), Cd(I) and Ga(I) compounds.

The solubility of Bi in $BiCl_3$ at 260° corresponds to 46% conversion to BiCl; a black, asphalt-like mixture is obtained on solidification. At the same temperature, addition of $AlCl_3$ results in the reaction $BiCl_3 + 2Bi + 3AlCl_3 = 3BiAlCl_4$ taking place quantitatively [56.3, 55.7% Bi, 55.3% theor.]. The product, m.p. *ca.* 253°, is maroon in bulk and reddish-brown as a powder. It disproportionates to metal and trihalide essentially quantitatively in water, dioxaneor alcohol, and darkens rapidly in air.

Similarly, the solubility of Cd in $CdCl_2$ at 740° corresponds to 17.6% conversion of Cd_2Cl_2; a black mixture is obtained on quenching. With $2AlCl_3/CdCl_2$, the solubility of cadmium at 330° indicates 71.5% conversion to the Cd(I) oxidation state. The solid, very light gray in bulk, white as a powder, also readily disproportionates in contact with the above solvents. Similar results have been obtained in the iodide system.

The compound Ga_2Cl_4, which has been found to be $Ga(I)[Ga(III)Cl_4]$,[5] is an example of such an acid-stabilized lower oxidation state. Further reduction of the Ga(III) therein by metal gives a solution containing 7.4% GaCl at 180°.[4] In the presence of sufficient $AlCl_3$ the amount of metal dissolved at 180° is within 0.1% of that for the reaction $Ga(GaCl_4) + 2Ga + 4AlCl_3 = 4GaAlCl_4$. The white product, m.p. 175°, is, as expected, physically very similar to $Ga(GaCl_4)$.

(2) G. von Hevesy and E. Löwenstein, *Z. anorg. allgem. Chem.*, **187**, 266 (1930).

(3) K. Grjotheim, F. Grönvold and J. Krogh-Moe, THIS JOURNAL, **77**, 5824 (1955).

(4) J. D. Corbett and S. von Winbush, *ibid.*, **77**, 3964 (1955).

(5) S. von Winbush, R. K. McMullan and J. D. Corbett, to be published.

(6) (a) P. Ehrlich and L. Gentsch, *Naturwiss.*, **40**, 460 (1953); (b) The compound has been found to be CaHCl, P. Ehrlich, B. Ait, and L. Gentsch, *Z. anorg. allgem. Chem.*, **283**, 58 (1956).

(7) D. Cubicciotti, THIS JOURNAL, **74**, 1198 (1952).

(8) G. Cleary and D. Cubicciotti, *ibid.*, **74**, 557 (1952).

All the solid products described are diamagnetic, and give powder pattern lines different from those obtained with any binary mixture of the components.

INSTITUTE FOR ATOMIC RESEARCH
DEPARTMENT OF CHEMISTRY JOHN D. CORBETT
IOWA STATE COLLEGE RICHARD K. MCMULLAN
AMES, IOWA

RECEIVED MAY 3, 1956

THE STRUCTURE OF THE ANTIBIOTIC METHYMYCIN

Sir:

Methymycin[1] belongs chemically to a class of antibiotics[2] which contains such therapeutically important representatives as erythromycin[3] and carbomycin (magnamycin)[4] and partial structures have been advanced for two of them (erythromycin[3] and pikromycin[5]). We should now like to report certain degradation experiments which, coupled with earlier results,[6] lead us to propose structure I as a complete expression for methymycin.

Mild hydrolysis of methymycin with aqueous sulfuric acid led to the desosamine free fragment II (m.p. 163–165°, $[\alpha] + 79°$ (all rotations in chloroform), λ_{max}^{EtOH} 225 mμ, log ε 4.03, $\lambda_{max}^{CHCl_3}$ 2.80, 2.95, 5.76, 5.91 and 6.08 μ; Found: C, 65.17; H, 9.11; C—CH_3, 19.34) which was further characterized as the acetate III (m.p. 198–200°, $[\alpha]_D + 93°$; Found: C, 64.39; H, 8.29; acetyl, 12.11) and as the ketone IV (m.p. 173–179°, $[\alpha]_D +177°$, λ_{max}^{EtOH} 224 mμ, log ε 3.96; Found: C, 65.87; H, 8.47; C—CH_3, 19.95). The ketone IV gave a negative Schiff test and yielded 58% of carbon dioxide upon treatment with alkali followed by acidification (a parallel experiment with II furnished no carbon dioxide).

When methymycin or II was treated with methanolic sulfuric acid, there was produced the spiroketal V (m.p. 79–81°, $[\alpha]_D - 68°$, no high selective ultraviolet absorption, $\lambda_{max}^{CHCl_3}$ 5.77 μ; Found: C, 66.51; H, 9.25; OCH_3, 9.81; active hydrogen, 0.00), which upon lithium aluminum hydride reduction led to the corresponding diol (m.p. 159–161°, $[\alpha]_D + 118°$; Found: C, 65.77: H, 10.17; OCH_3, 9.40).

Permanganate oxidation of II in acetone solution furnished three products: VI (m.p. 164–172°, $[\alpha]_D +52°$ (acetone), λ_{max}^{KBr} 2.90, 5.66 and 5.78 μ; Found: C, 58.35; H, 7.79; C—CH_3, 21.01; neut. equiv., 318), VII (m.p. 55–56°, $[\alpha]_D + 69°$, $\lambda_{max}^{CHCl_3}$ 5.68–5.76 μ (broad); Found: C, 63.40; H, 8.39; C—CH_3, 22.51) and VIIIa (m.p. 126–128°,

(1) M. N. Donin, J. Pagano, J. D. Dutcher and C. M. McKee, "Antibiotics Annual 1953–1954," Medical Encyclopedia, Inc., New York, p. 179.

(2) For leading references see R. Corbaz, L. Ettlinger, E. Gäumann, W. Keller-Schierlein, F. Kradolfer, E. Kyburz, L. Neipp, V. Prelog, A. Wettstein and H. Zähner, *Helv. Chim. Acta*, **39**, 304 (1956).

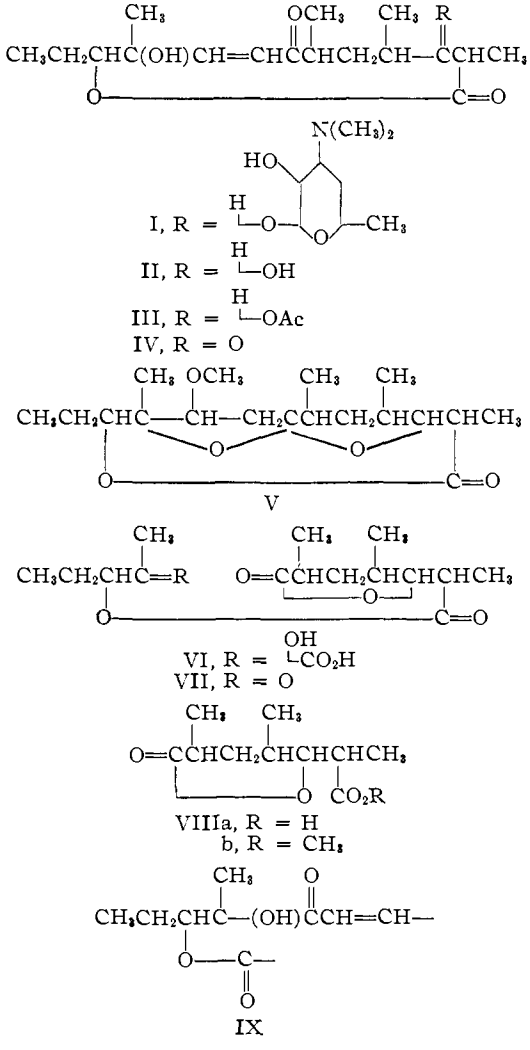
(3) *Cf.* P. F. Wiley, K. Gerzon, E. H. Flynn, M. V. Sigal and U. C. Quarck, THIS JOURNAL, **77**, 3677 (1955).

(4) R. L. Wagner, F. A. Hochstein, K. Murai, N. Messina and P. P. Regna, *ibid.*, **75**, 4684 (1953).

(5) H. Brockmann and R. Oster, *Naturwiss.*, **42**, 155 (1955).

(6) (a) C. Djerassi, A. Bowers and H. N. Khastgir, THIS JOURNAL, **78**, 1729 (1956); (b) C. Djerassi, A. Bowers, R. Hodges and B. Riniker, *ibid.*, **78**, 1733 (1956).

$[\alpha]_D$ +38°, λ_{max}^{KBr} 3.05 (broad), 5.68 and 5.76 μ; Found: C, 59.91; H, 8.05; neut. equiv., 199 (immediate titration), 100 (after standing for 2 hours in excess base)). Lead tetraacetate oxidation of the hydroxy acid VI gave the methyl ketone VII (positive iodoform test), which in turn upon alkaline saponification led to the lactone acid VIIIa and 3-hydroxy-2-pentanone (isolated and identified as the bis-2,4-dinitrophenylhydrazone of pentane-2,3-dione).[7]



It is clear that 2,4,6-trimethylcyclohex-2-en-1-one, isolated[6b] from the alkali fusion of methymycin (I), must have arisen by a cyclization process involving a fragment containing the carbon sequence of VIIIa. Since methymycin cannot contain the partial structure IX[8] (which would also have led to the oxidation products VI, VII and VIII), the trimethylcyclohexenone precursor can, for all practical purposes, be attached only in the manner shown in II and this in turn would lead to formulation VIIIa for the lactone acid. This acid (as well as its methyl ester VIIIb, m.p. 79–81°) proved to be identical with a specimen isolated by Prof. V. Prelog and colleagues[9] from some related antibiotics. Since the Swiss investigators[9] have shown that decarboxylation of VIIIa followed by oxidation yields acetaldehyde and meso-α,α'-dimethylglutaric acid, this fully confirms structures VI and VII and consequently also II.

The placement of the desosamine fragment as shown in I rather than attaching it to the tertiary hydroxyl function follows from three lines of evidence: (a) methymycin amide[6a] is recovered unchanged under conditions where II is oxidized to the ketone IV in good yield; (b) since the lithium aluminum hydride reduction product of methymycin[6b,8] was processed under non-acidic conditions prior to periodate oxidation, a glycosidic linkage involving desosamine and the tertiary hydroxyl group would almost certainly not have been cleaved and consequently no periodate would have been consumed; (c) the alternative structure would not explain the resistance[6b] to periodate of the lithium aluminum hydride reduction product of tetrahydrodesoxymethymycin.[6a]

Acknowledgment.—We are greatly indebted to the Squibb Institute for Medical Research for generous fellowship support and to Mr. Joseph F. Alicino (Squibb Institute) for his outstanding microanalytical contributions.

(7) Comparison with an authentic sample (P. F. Wiley, K. Gerzon, E. H. Flynn, M. V. Sigal and U. C. Quarck, THIS JOURNAL, **77**, 3676 (1955)) was kindly carried out by Dr. K. Gerzon.

(8) Lithium aluminum hydride reduction of methymycin (ref. 6b) or of II followed by periodate oxidation results in consumption of only one equivalent of reagent and formation of propionaldehyde which is only compatible with structures I and II. Furthermore, IX is also excluded by the formation of the spiroketal V.

(9) We are greatly indebted to Prof. V. Prelog (E. T. H., Zurich) for carrying out the direct comparison and for informing us of his results prior to publication.

(10) Squibb Postdoctorate Research Fellow at Wayne University, 1955–1956.

DEPARTMENT OF CHEMISTRY
WAYNE UNIVERSITY
DETROIT, MICHIGAN
CARL DJERASSI
JOHN A. ZDERIC[10]

RECEIVED APRIL 18, 1956

USE OF GAS PHASE CHROMATOGRAPHY FOR THE SEPARATION OF MIXTURES OF CARRIER FREE RADIOACTIVE SUBSTANCES: PRODUCTS OF CHEMICAL REACTIONS ACTIVATED BY NUCLEAR PROCESSES

Sir:

When organic bromides are irradiated with neutrons, the Br^{82}(36 hr.) formed with high kinetic energy by the $Br^{81}(n,\gamma)Br^{82}$ process ruptures the parent bond and reënters combination as a variety of compounds.[1] Such compounds are present at mole fractions of the order of 10^{-12}. By gas–liquid partition chromatography we have separated over twenty different radioactive organic compounds from a drop of neutron irradiated *n*-propyl bromide and detected their presence with the aid of a scintillation counter (curve A, Fig. 1), thus demonstrating that: (1) the gas chromatographic technique is as effective for materials at tracer concentrations as at macro concentrations; (2) the number of products from the (n,γ) reaction in n-C_3H_7Br is at least twice as great as formerly suspected. Curve B, Fig. 1, shows a similar chromatogram of the organic products containing Br^{80}

(1) For a discussion of chemical reactions activated by nuclear processes see J. E. Willard, *Ann. Rev. of Nuc. Sci.*, **3**, 193 (1953).