Partial Resolution of Some Organic Racemates by Solvent Extraction

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Abstract: Partial resolutions of a series of organic racemates[1] have been achieved by partitioning the racemates between an aqueous phase and an optically active ester of *d*-tartaric acid. A semiquantitative treatment of the data indicates that the observed results are in agreement with those predicted from the normal relationships dealing with solvent extractions.

Although the differences in chemical interactions between an optically active compound and the enantiomers of a *dl* pair form the basis of most of the classical methods of resolution, the use of physical interactions to achieve such separations has been a rather recent development. Some methods which have been employed to achieve partial resolutions involve the use of clathrates, dialysis, crystallizations, and chromatography. Thus, for example, 2-chlorooctane has been resolved through the formation of an inclusion complex with urea,[2] while a partial resolution of *dl*-tartaric acid has been achieved by dialysis through an optically active membrane.[3] The use of crystallization to separate optical antipodes has received considerable attention. These resolutions are normally carried out in ternary systems involving *d* isomer, *l* isomer, and an optically inactive solvent; preferential crystallization of one of the enantiomers is induced in the supersaturated solution by the addition of an optically active seed crystal. Secor[4] has considered the theoretical possibilities and limitations of this method in some detail. More recently Luttringhaus and Berrer[5] have reported partial resolutions of racemates by recrystallizations from an optically active medium. Paper, gas–liquid partition, and column chromatography as well as ion-exchange resins involving optically active materials have also been employed with varying degrees of success.[6]

We have recently communicated[7] the partial resolution of neutral, inorganic coordination compounds by the use of multicomponent, two-phase solvent extraction techniques. The purpose of the present study was to demonstrate a broadened applicability of this method and to investigate some of the parameters which influence the extent of resolution achieved.

Results

Preliminary investigations revealed that in certain cases partition of a racemate between two phases, one of which was optically active, yielded a solute on isolation which possessed an optical rotation. Before stating that a partial resolution has been achieved by the solvent extraction technique, it was necessary to demonstrate that (1) the observed rotational values possessed some degree of reliability and (2) the origin of the partial resolution was an actual consequence of the partitioning technique. To test these points, quantitative equilibrium relationships were derived from solvent extraction equations. The anticipated behaviors of optical rotations as various parameters are altered were then calculated on the basis of these equations. These relationships are developed below, and an intercomparison is made between the predicted rotational values and trends with those actually observed.

If a racemate is partitioned between two immiscible phases, the normal distribution relationship may be written

$$K_d = \frac{(c_d)_{org}}{(c_d)_{aq}} = \frac{(m_d)_{org}}{(m_d)_{aq}} \frac{V_{aq}}{V_{org}} \quad (1)$$

where K_d is the partition coefficient of the *d* isomer, *c* and *m* are respectively the concentration and mass of that isomer in the organic (org) and aqueous (aq) phases, and *V* is the phase volume. A similar expression applies for the *l* isomer. If both phases are optically inactive, $K_d = K_l$, and no resolution is obtained. However, if at least one of the phases is optically active, then it is possible that the two partition coefficients may no longer be equal. In this case a partial resolution will be achieved, and the per cent resolution, *R*, may be defined for the phase in which the *d* isomer is in excess as

$$R = [(m_d - m_l)/(m_d + m_l)]100 \quad (2)$$

A comparable expression will apply to the other phase in which there will be an excess of the *l* isomer.

For a single equilibration of a racemate between equal volumes of two phases, it is convenient to adopt the concept of a separation factor, *S*, which is chosen such as always to be greater than unity. In the present study, for the phase in which the *d* isomer is in excess, *S* is defined as

$$S = c_d/c_l = m_d/m_l \quad (3)$$

where all concentrations and masses relate to the same phase. Under the conditions of a single extraction employing equal phase volumes, it is readily shown from eq 2 that

$$S = (100 + R)/(100 - R) \quad (4)$$

(1) The term *racemate* is used throughout this presentation synonymously with "racemic pair" or "racemic modification," and does not necessarily imply a racemic compound.
(2) W. Schlenk, *Experientia*, **8**, 337 (1952).
(3) V. O. G. Klingmüller and G. Gedenk, *Nature*, **179**, 367 (1957).
(4) R. M. Secor, *Chem. Rev.*, **63**, 297 (1963).
(5) A. Luttringhaus and D. Berrer, *Tetrahedron Letters*, **No. 10**, 10 (1959).
(6) For a brief survey of these methods of resolution as well as some of those mentioned previously, see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 4.
(7) N. S. Bowman, V. G'ceva, G. K. Schweitzer, and I. R. Supernaw, *Inorg. Nucl. Chem. Letters*, 2, 351 (1966).

Table I. Per Cents Resolution (R) of a Series of Racemates

	d-Diisoamyl tartrate–water		*d*-Diisopropyl tartrate–water	
	Ester phase	Aqueous phase	Ester phase	Aqueous phase
dl-Bis-4-pyridylglycol	0.95 ± 0.17 (+)[a]	1.00 ± 0.35 (−)	0.51 ± 0.30 (+)	1.46 ± 0.72 (−)
dl-2,3-Dibromobutane-1,4-diol	1.00 ± 0.25 (−)	0.50 ± 0.25 (+)	0.75 ± 0.17 (−)	0.31 ± 0.17 (+)
dl-Isohydrobenzoin	2.00 ± 0.90 (+)			
dl-Camphoric acid	0.49 ± 0.33 (+)	1.37 ± 0.23 (−)	0.19 ± 0.04 (−)	0.28 ± 0.02 (+)

[a] The symbols in parentheses indicate the signs of rotation of the solutes isolated from the phases indicated.

Table I gives the per cent resolution (R) for a series of racemates as determined in two different two-phase solvent systems: *d*-diisopropyl tartrate–water and *d*-diisoamyl tartrate–water. The data were obtained from single extractions using equal phase volumes. R was calculated by comparing the specific rotation of the solute isolated from each phase with the literature values of the pure enantiomorphs as given in the Experimental Section. The resolutions given in Table I in the main represent averages of several experiments, and the range in R primarily reflects experimental errors in polarimeter readings; this is discussed more fully in the Experimental Section.

A gross partition coefficient, K_G, may be defined in terms of the total concentration of the two enantiomers present in each phase after equilibration.

$$K_G = \frac{(c_d + c_l)_{org}}{(c_d + c_l)_{aq}} \tag{5}$$

While this may also be expressed in terms of the partition coefficients of the individual antipodes, unlike these latter coefficients, K_G may be determined directly by numerous ordinary analytical means.

If a racemate is partitioned between two phases and partial resolution occurs, the excess of *l* molecules in one phase must be equal in number to the excess of *d* molecules in the other phase. It follows therefore that K_G can be determined from the specific rotations $[\alpha]$ of the solutes isolated from each phase through the relationship

$$K_G = -\frac{[\alpha]_{aq}}{[\alpha]_{org}}\frac{V_{aq}}{V_{org}} \tag{6}$$

using the same data employed to calculate the values in Table I. K_G may also be determined in the classical manner from the solubilities of the racemate in each of the two phases. Finally, if the racemate possesses a characteristic ultraviolet absorption, its concentrations in the two phases after equilibration may be found through previously prepared calibration curves. In order to assess the reliability of the rotational data, K_G was determined by all three of these methods for bis-4-pyridylglycol, and the results are summarized in Table II. This particular compound was selected because of its convenient aromatic absorption at 250 mμ.

Table I shows that partitioning racemic camphoric acid between *d*-diisoamyl tartrate and water yields a solute isolated from the ester phase which is dextrorotatory. Equations 1 and 2 may be combined to demonstrate a linear relationship between the reciprocal of the per cent resolution and the volume ratio of the phases.

Table II. Values of K_G for Bis-4-pyridylglycol in Two Different Two-Phase Systems as Determined by Various Methods

Resolving system	Optical rotation	Ultraviolet	Solubility
d-Diisoamyl tartrate–water	0.92 ± 0.14	1.14 ± 0.06	
d-Diisopropyl tartrate–water	3.06 ± 0.84	2.80 ± 0.20	3.31

$$\frac{1}{R_{org}} = \frac{K_d + K_l + 2K_dK_l(V_{org}/V_{aq})}{(K_d - K_l)100} \tag{7}$$

The experimentally determined values for this system are shown in Figure 1. The ratio of the partition coefficients for the two enantiomers may readily be determined by extrapolating the curve to $V_{org}/V_{aq} = 0$. For the system presently under consideration this value was found to be $K_d/K_l = 1.02$.

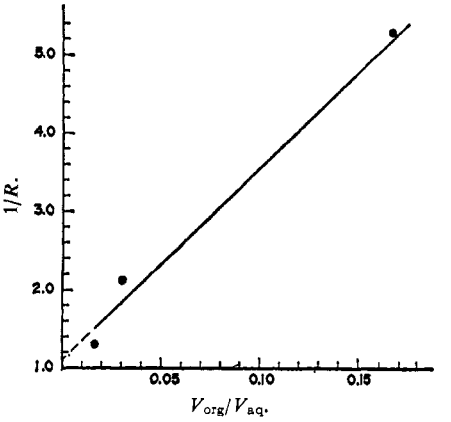

Figure 1. Relationship between the per cent resolution of camphoric acid isolated from the ester phase and the phase volume ratio of the resolving system diisoamyl tartrate–water.

A similar derivation involving the aqueous phase yields eq 8, and the experimental data for the camphoric acid–water–diisoamyl tartrate system are presented

$$\frac{1}{R_{aq}} = \frac{K_d + K_l + 2(V_{org}/V_{aq})^{-1}}{(K_d - K_l)100} \tag{8}$$

graphically in Figure 2. As before, extrapolation to zero volume ratio allows for a determination of K_d/K_l. From Figure 2 this value was found to be 1.04 which is in reasonable agreement with that obtained from the ester phase.

Table III. Values of Per Cent Resolution of Combined Aqueous Phases ($R_{\Sigma_{aq}}$) with Varying Numbers of Extractions for Different Racemate–Solvent Systems

Racemate	Organic phase	n = 1	4	6	10	12	33
dl-Camphoric acid	*d*-Diisopropyl tartrate	0.19 ± 0.10				0.42 ± 0.23	0.55 ± 0.23
dl-Camphoric acid	*d*-Diisoamyl tartrate	1.67 ± 1.39	1.40 ± 0.54			0.92 ± 0.31	
dl-2,3-Dibromobutane-1,4-diol	*d*-Diisopropyl tartrate	0.31 ± 0.14		0.34 ± 0.14	0.42 ± 0.15		

In passing, it might be noted that eq 5 may be related through eq 1 to yield an expression (9) involving K_G and the partition coefficients of the individual isomers. If

$$K_G = \frac{K_d\left(1 + K_1\frac{V_{org}}{V_{aq}}\right) + K_1\left(1 + K_d\frac{V_{org}}{V_{aq}}\right)}{2 + (K_1 + K_d)\frac{V_{org}}{V_{aq}}} \quad (9)$$

at any given value of V_{org}/V_{aq}, K_G is also known, then from the relationship between K_d and K_1 established by eq 7 or 8, it is possible in principle to determine the partition coefficients of the two isomers. In the present study, because of the lack of accuracy with which the various parameters have been determined, little confidence can be attached to values thus calculated for K_d and K_1.

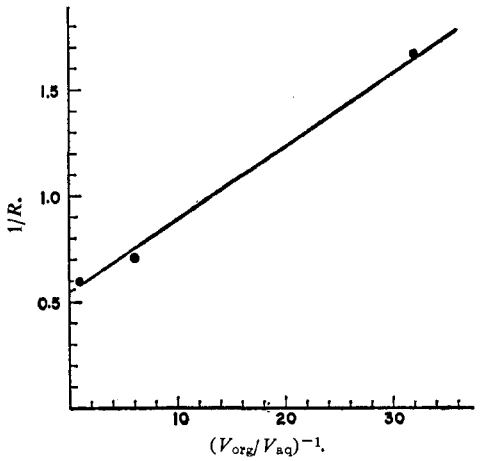

Figure 2. Relationship between the per cent resolution of camphoric acid isolated from the aqueous phase and the phase volume ratio of the resolving system diisoamyl tartrate–water.

Figure 3 summarizes the results obtained from two experiments involving multiple extractions. For these studies, equal phase volumes were used, and after each equilibration the ester phase was reequilibrated with fresh aqueous phase. Under these conditions it can be shown from eq 1, 2, and 3 that for the solute isolated from the ester phase

$$S_{org}{}^n = \frac{100 + (R_{org})_n}{100 - (R_{org})_n} \quad (10)$$

where $(R)_n$ is the per cent resolution after the nth equilibration. The slopes in Figure 3 yield log S, and from this a value of S of 1.001 was obtained for the camphoric acid system and 1.010 for the 2,3-dibromobutane-1,4-diol system. Data were also obtained on camphoric acid using *d*-diisopropyl tartrate rather than the diisoamyl ester. The two curves in these cases are essentially superimposable except, as can be seen from Table I, the rotations of the camphoric acid isolated from the two esters differ in sign.

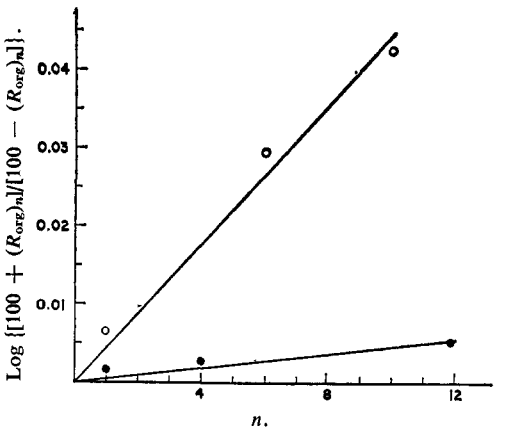

Figure 3. Relationship between the per cent resolution of solute isolated from the tartrate ester phase as a function of the number of multiple extractions: ○, 2,3-dibromobutane-1,4-diol from *d*-diisopropyl tartrate; ●, camphoric acid from *d*-diisoamyl tartrate.

In a similar fashion an expression may be derived relating the resolution found for the combined aqueous phases ($R_{\Sigma_{aq}}$) with the number of extractions. For those systems in which the solute isolated from the aqueous phase is levorotatory, the expression is

$$R_{\Sigma_{aq}} = \frac{\left[1 - \left(\frac{K_1}{1 + K_1}\right)^n\right] - \left[1 - \left(\frac{K_d}{1 + K_d}\right)^n\right]}{\left[1 - \left(\frac{K_1}{1 + K_1}\right)^n\right] + \left[1 - \left(\frac{K_d}{1 + K_d}\right)^n\right]} \quad (11)$$

This relationship reveals that with increasing n, $R_{\Sigma_{aq}}$ asymptotically approaches zero. The data for the aqueous phases for the three systems considered in conjunction with Figure 3 are given in Table III. While the data in this table would not appear for the cases involving *d*-diisopropyl tartrate to support strongly the anticipated trend previously mentioned, the behavior is in marked contrast to that displayed by the ester phase. Furthermore, it can be shown that for such small values of resolution, $R_{\Sigma_{aq}}$ would not be expected to change significantly over the values of n investigated.

Figure 4 depicts resolutions obtained for camphoric acid isolated from *d*-diisoamyl tartrate employing an extraction system in which both phases were optically active. Optical activity was imparted to the aqueous phase by adding varying amounts of *d*- or *l*-tartaric

acid which is essentially insoluble in diisoamyl tartrate. Since K_G for this particular system is such that a relatively small fraction of the racemate is extracted into the aqueous phase, a phase volume ratio organic: aqueous of 1:20 was employed for experimental convenience. A plot of the rotation of the camphoric acid isolated from the aqueous phase shows a similar behavior except the effect is opposite in sign; *i.e.*, with no tartaric acid in the aqueous phase, the isolated camphoric acid is levorotatory; with increasing concentrations of *l*-tartaric acid, the isolated camphoric acid becomes more levorotatory. Increasing the concentration of *d*-tartaric acid in the aqueous phase on the other hand yields increasingly dextrorotatory camphoric acid.

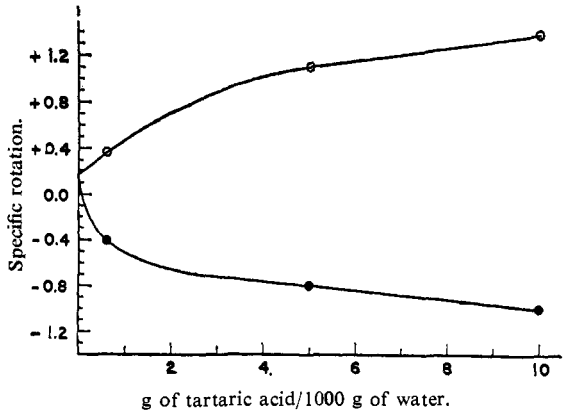

Figure 4. Specific rotation of the camphoric acid isolated from *d*-diisoamyl tartrate phase as a function of amount of tartaric acids present in the aqueous phase: ○, *l*-tartaric acid; ●, *d*-tartaric acid.

Discussion

It has been shown in the previous section that the observed results are in repeated agreement with those predicted from solvent extraction relationships as various parameters are altered. This can hardly be fortuitous in so many cases, and strongly supports the reliability of the rotational data and the origin of the partial resolutions being a consequence of the partitioning technique. It must be pointed out however that this manner of presentation was given only to demonstrate a general agreement between trends observed in experimental determinations and those predicted by the normal relationships involving solvent extractions when applied to the special case of a racemic mixture. It is not the intent of this study to ascribe any high degree of significance to the numerical values determined for various constants.

Investigators of the various physical methods of resolution when considering the origin of such separations have in general interpreted their results in a manner somewhat analogous to that proposed by Ogston[8] to account for the stereospecificity of enzymes. Thus it is assumed that some sort of bonding exists between the racemate and the resolving medium, and that because of differences in configuration, one enantiomer is geometrically more favorable for such bonding interactions than the other. This hypothesis has received additional support by the findings of Pirkle and Burlingame[9,10] who demonstrated through nmr that the enantiomorphs of a racemate may possess different environments in an optically active medium. Hydrogen bonding has been stressed as a primary type of interaction whenever such bonding is possible.

Our own results would lend empirical support to this conclusion, and would seem to suggest that at least two sites of hydrogen bonding are necessary for both the resolving medium and the substrate. Thus we could obtain no resolution when either optically active β-pinene or carvones were used in place of the tartrate esters. In addition, while partial resolutions were achieved with other racemates which possessed two potential hydrogen bonding sites such as mandelic acid and phenylephedrine, no resolutions were obtained for molecules such as epichlorohydrin or monools. Similarly when a two-phase system consisting of a tartrate ester and high molecular weight hydrocarbons or alkyl halides was employed, no resolutions were observed.

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(9) W. H. Pirkle, *J. Am. Chem. Soc.*, **88**, 1837 (1966).
(10) T. G. Burlingame and W. H. Pirkle, *ibid.*, **88**, 4294 (1966).

It should be pointed out, however, that experimental conditions limited the number of systems which could conveniently be studied. Because of the small resolutions obtained, it was necessary that the racemates selected display large specific rotations when resolved. Since most studies were conducted in conjunction with an aqueous phase, there was the additional requirement that the racemates display at least a limited water solubility. Two-phase systems which differed widely in their polarities, such as tartrate esters and hydrocarbons, besides seeming to be unpromising systems on their face, so overwhelmingly distributed the racemates investigated into one phase or the other that isolation and purification of the solute from both phases presented serious experimental difficulties. The number of potential phases to serve as resolving media was even more limited in view of the requirements that they both be liquids and readily available in large quantities.

In this respect while initial experiments were conducted with diisopropyl tartrate–water, this system suffers from the disadvantage that there is significant mutual solubility of the two phases. Not only does this lead to phases whose compositions depend upon the concentration of the racemate, but it also complicates the purification of the solute isolated from the aqueous phase, which for those compounds studied may be present in rather small amounts. To circumvent this problem, a series of tartrate esters through octyl was investigated as potential resolving media. It was found that while water solubility in general decreased with increasing molecular weight, the same trend applied for the solubility of the racemates under consideration in the ester phase. Optimum results were obtained with diisoamyl tartrate which is essentially insoluble in water and at the same time is a satisfactory solvent for the compounds studied.

Figure 4 indicates that the resolution of camphoric acid is enhanced by the addition of *l*-tartaric acid to the aqueous phase. No comparable effect could be observed on the extent of resolution of the other racemates given in Table I. In addition, while smaller resolutions of camphoric acid were still obtained using aqueous solutions of *l*-tartaric acid and optically inactive organic phases such as isoamyl alcohol or diethyl ketone, again no resolutions were observed under the same conditions with the other racemates in Table I. These findings

might suggest that *l*-tartaric acid in the aqueous phases functions in partial resolution of camphoric acid by preferential dimer formation with one of the enantiomorphs.

Experimental Section

All phases were subjected to preequilibration prior to extractions, and phase volumes of 50–100 ml were normally employed using typically 3.0 g of the racemates. Equilibrations of racemates between phases were carried out by mechanical shaking for 5–12 hr.

With the exception of *dl*-camphoric acid, the isolation of the partially resolved racemates followed similar procedures. After separation of the phases and removal of water, the residue was diluted with ligroin until precipitation of the solid was essentially complete. The diols were then crystallized to constant rotation using the following solvents: bis-4-pyridylglycol–methanol, 2,3-dibromobutane-1,4-diol–benzene, and isohydrobenzoin–methanol.

Camphoric acid was isolated by first removing the water from the separated phases, extracting the acid into 10% sodium bicarbonate, precipitating the camphoric acid by addition of hydrochloric acid, and repeating this procedure to constant rotation.

Optical rotations were measured on a Bendix automatic polarimeter Model 143A using a sodium filter and a 6.3-cm cell. Observed rotations varied from several millidegrees to over a hundred millidegrees. Although the reported sensitivity of this instrument is ±0.0002°, in determining error ranges we have assumed an accuracy in observed readings of ±0.005°. Sample concentrations were less than 200 mg/ml and rotations were taken in the following solvents: bis-4-pyridylglycol–acetic acid, 2,3-dibromobutane-1,4-diol–methanol, isohydrobenzoin–methanol, and camphoric acid–acetone. In determining the optical purity of the partially resolved compounds, the values used for the specific rotations were bis-4-pyridylglycol, 87.5°; 2,3-dibromobutanediol, 45.0°; isohydrobenzoin, 65.2°; camphoric acid, 47.7°.

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Branched Chain Sugars. The Synthesis of Adenine Nucleosides of 3-Deoxy-3-*C*-hydroxymethyl-D-erythrofuranose and 2-Deoxy-2-*C*-hydroxymethyl-D-erythrofuranose[1,2]

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Abstract: The reaction of methyl 3-amino-β-D-xylopyranoside (**5**) with nitrous acid effected a ring contraction to give methyl 3-deoxy-3-*C*-formyl-β-D-erythrofuranoside (**6**) as the main product along with small amounts of methyl 2-deoxy-2-*C*-formyl-β-D-erythrofuranoside (**16**). Reduction of the aldehyde function with sponge nickel to the diols **7** and **17** followed by esterification, acetolysis, and nucleoside condensation gave 9-(3-deoxy-3-hydroxymethyl-β-(and α)-D-erythrofuranosyl)adenine (**13**) and 9-(2-deoxy-2-hydroxymethyl-β-(and α)-D-erythrofuranosyl)-adenine (**21**). Intervention by a 1,2 ortho ester ion afforded a 5:1 ratio of **13b**:**13a**. No intervention by a 1,3 ortho ester ion was indicated by the 1:1 ratio of α and β anomers in the 2-branched series. Double-resonance nmr was used to identify the 3-branched series.

In recent years, branched chain sugars have been discovered as constituent parts of a number of antibiotics.[3] These discoveries have stimulated considerable interest in devising means of synthesis[4] of branched chain sugars. This could serve as the proof of structure of naturally occurring compounds. Also, new analogs could be made available to serve as useful intermediates for the preparation of analogs of biologically active materials.

The suggestion has been made[5] that the biological usefulness of a number of adenine nucleosides has been limited by facile conversion to the less active hypoxanthine analogs through the action of adenosine deaminase. It has been noted[6] that the replacement or substitution of the 5′-hydroxyl of adenosine or removal of the 4′-hydroxymethyl group invariably led to loss of substrate activity toward adenosine deaminase.

Recent reports[7] described the synthesis of 2′-*C*-methyl- and 3′-*C*-methyladenosine. Both compounds were

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(2) A portion of this work has been described previously. See E. J. Reist, *Chem. Ind.* (London), 1957 (1967).

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