The Kinetics and Mechanism of Symmetrization of *t*-Butyl α-Bromomercuriphenylacetate by Ammonia[1]

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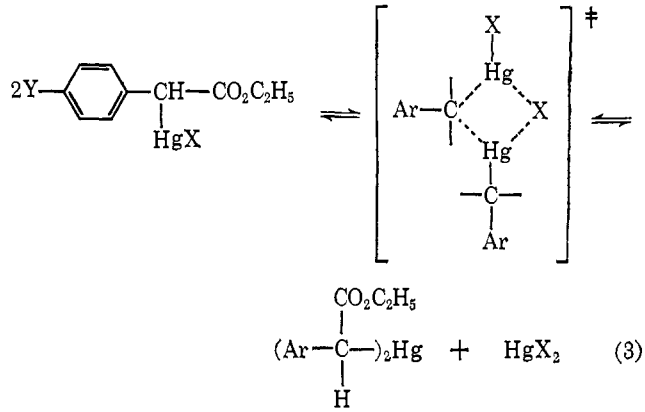
Abstract: The kinetics of ammonia symmetrization of the title mercurial have been examined in chloroform solution. The reaction is over-all fourth order, second order in each reactant, and is not inhibited by product. Symmetrization is complete even at low ammonia concentrations. Two mechanisms are suggested which accommodate the data.

Certain types of organomercuric salts in the presence of ammonia undergo symmetrization, *i.e.*, disproportionation to dialkylmercury and mercuric salt. This reaction has been extensively investigated by Reutov and co-workers,[2,3] particularly with α-halomercuriphenylacetate esters. Certain mechanistic conclusions have been drawn based on the previously determined stereochemistry (retention)[3] of the ammonia symmetrization and on the kinetics of the reaction as determined nephelometrically.[2b,4,5] Specifically, Reutov, *et al.*,[5] have concluded that the reaction: (a) is second order in alkylmercuric halide; (b) is second order in ammonia; (c) is subject to inhibition (first order) by *added* product; (d) proceeds to completion only with a 15-fold excess of ammonia concentration; (e) does not occur at low ammonia concentration; and (f) is reversible over-all. The work reported here will show that only the first two of these conclusions are valid.

The mechanism proposed by Reutov[2,5] is shown in eq. 1 and 2, in which eq. 1 represents a rapid pre-equilibrium and eq. 2 the slow, rate-determining step. Subsequently, these workers have discussed the effects on rate of ring substituents (and variation of the alcohol portion of the ester) in terms of the suggested transition state (eq. 3) for the symmetrization reaction (eq. 1).[6] As we have noted earlier, the kinetic effects of substituents on the mechanism suggested by Reutov cannot be discussed in terms of the transition state of eq. 3 since rate constants provide no information regarding the transition state of a fast pre-equilibrium step. Rather, variation in rate constants would reflect changes in equilibrium 1 and in reaction 2 and provide no direct evidence regarding the transition state for the electrophilic aliphatic substitution reaction. We have also demonstrated[7] that the suggested mechanism (eq. 1 and 2) cannot be operative in this reaction; the essentially instantaneous rate of complex formation between mercuric halide and ammonia in chloroform solution obviates this step being rate controlling.

$$2RHgX \underset{}{\overset{K_1}{\rightleftharpoons}} R_2Hg + HgX_2 \qquad (1)$$

$$HgX_2 + 2NH_3 \overset{k}{\rightleftharpoons} HgX_2(NH_3)_2\downarrow \qquad (2)$$



$$(Ar-\underset{\underset{H}{|}}{\overset{\overset{CO_2C_2H_5}{|}}{C}}-)_2Hg + HgX_2 \qquad (3)$$

The kinetic expression used by Reutov and co-workers is that shown in eq. 4, while in fact the proposed mechanism requires eq. 5. According to these workers, the product dialkylmercury formed during the course of the reaction does not have an inhibitory effect, while product added prior to the start of reaction does depress the rate.

$$\text{rate} = k[RHgX]^2[NH_3]^2 \qquad (4)$$

$$\text{rate} = k[RHgX]^2[NH_3]^2/[R_2Hg] \qquad (5)$$

In view of the inconsistencies in the data and conclusions of Reutov, and the importance of reactions of this type to electrophilic substitution generally, we felt that a reinvestigation of the kinetics of symmetrization was in order.

Results

The symmetrization reaction in chloroform is inherently difficult to study kinetically, involving a gas dissolved in solution as one reactant, and with one of the

(1) Acknowledgment is made to the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

(2) (a) O. A. Reutov, I. P. Beletskaya, and R. E. Mardaleishvili, *Proc. Acad. Sci. USSR*, **116**, 901 (1957); (b) O. A. Reutov, I. P. Beletskaya, and R. E. Mardaleishvili, *Zh. Fiz. Khim.*, **33**, 152 (1959); (c) O. A. Reutov and I. P. Beletskaya, *Proc. Acad. Sci. USSR*, **131**, 333 (1960); (d) O. A. Reutov, I. P. Beletskaya, and G. A. Artamkira, *J. Gen. Chem. USSR*, **30**, 3190 (1960); (e) I. P. Beletskaya, G. A. Artamkira, and O. A. Reutov, *Izv. Akad. Nauk SSSR*, 765 (1963); (f) I. P. Beletskaya, G. A. Artamkira, and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, **149**, 90 (1963); (g) O. A. Reutov, I. P. Beletskaya, and G. A. Artamkira, *Russ. J. Phys. Chem.*, **36**, 1407 (1962).

(3) A. N. Nesmeyanov, O. A. Reutov, W. Yang-Chieh, and L. Ching-Chu, *Bull. Acad. Sci. USSR*, 1280 (1958).

(4) A copious precipitate, presumably $HgX_2(NH_3)_2$, is formed during the course of this reaction in chloroform.

(5) O. A. Reutov, I. L. Beletskaya, and R. E. Mardaleishvili, *Russ. J. Phys. Chem.*, **33**, 240 (1959); *Zh. Fiz. Khim.*, **33**, 1962 (1959).

(6) See, for example, I. P. Beletskaya, G. A. Artamkina, and O. A. Reutov, *Proc. Acad. Sci. USSR*, **153**, 939 (1963), and earlier papers referred to therein.

(7) F. R. Jensen and B. Rickborn, *J. Am. Chem. Soc.*, **86**, 3784 (1964).

products precipitating from solution. Reutov followed the reaction by nephelometry, although our experience suggests that the tendency of the mercuric halide–ammonia complex to aggregate may introduce considerable error into this technique. Nuclear magnetic resonance spectrometry seemed a potentially useful method since it is one of the few spectral methods unaffected by the formation of an insoluble solid during the course of reaction. The nine equivalent protons in *t*-butyl α-bromomercuriphenylacetate led us to choose this substrate, for reasons of greater sensitivity over a wide concentration range. Initial experiments indicated that the signals from these protons differed sufficiently in chemical shift between starting material and product to be used for analysis.

It is interesting to note that Reutov[8] has claimed that this *t*-butyl ester is symmetrized at a negligibly slow rate; our data indicate clearly that this is not the case.

Areas of the appropriate peaks in the n.m.r. spectra (rates were determined at the temperature of the probe, 31.4°) were obtained either by planimetry or through use of the spectrometer integrator. Rate constants for reactions in which the concentrations were unequal were determined from the slopes from plots of the integrated form (eq. 6) of eq. 4. For reactions in which the concentrations of reagents were equal, the rate constants were obtained from the expression, $(1/(a - x)^3 - 1/a^3 = 3k_4t$.

$$k_4t = \frac{1}{(a-b)}\left[\frac{1}{(a-x)(b-x)} + \frac{2}{(a-b)(a-x)} + \frac{2}{(a-b)^2}\ln\frac{(b-x)}{(a-x)}\right] \quad (6)$$

The data in Table I are shown in four groups. In runs 1–9 the ammonia concentration was kept constant and in excess of the amount required by the stoichiometry of the reaction, while the organomercurial concentration was varied by approximately a factor of 20. The reaction is clearly second order in *t*-butyl α-bromomercuriphenylacetate.

The second group (runs 10–14) in Table I contains data in which the initial mercurial concentration is held constant and the ammonia concentration is varied over a factor of approximately 10. A downward drift in rate constant is appreciable in these instances although the reaction is clearly second order in ammonia. This rate diminution may be simply due to changes in the media associated with decreasing concentrations of both reactants. The rate constants for runs 18–22, where the initial concentrations of both reactants are substantially lower than 1 *M*, thus range to even lower values.

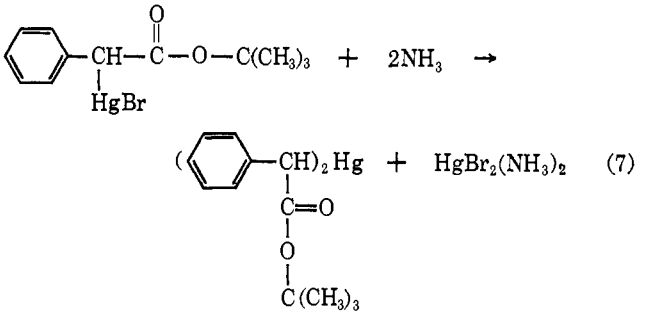
While, in fact, obtaining straight-line, fourth-order plots from eq. 6 obviates rate depression by product dialkylmercury, Reutov's claim that such depression occurs if product is added prior to reaction made it necessary to check this point. Runs 15–17 with varying initial amounts of product dialkylmercury give within experimental error identical rate constants with comparable runs 4 and 15 lacking the added product. Thus eq. 4, and not eq. 5, is the correct kinetic expression for the symmetrization reaction at all levels of dialkylmercury concentration.[9]

Table I. Rates of Symmetrization of *t*-Butyl α-Bromomercuriphenylacetate by Ammonia in $CHCl_3$ at 31.4°[a]

Run	$[NH_3]$	[RHgBr]	$[R_2Hg]$	$k_4 \times 10^4$ l.^{3} m.$^{-3}$ sec.$^{-1}$
1	1.05	0.396	...	16.6
2	1.00	0.401	...	16.6
3	0.992	0.182	...	14.6
4	0.997	0.0937	...	12.6
5	1.04	0.0805	...	13.0
6	0.990	0.0606	...	13.9
7	1.02	0.0408	...	11.4
8	1.00	0.0399	...	14.0
9	0.971	0.0202	...	15.6
10	0.828	0.101	...	14.8
11	0.608	0.101	...	11.5
12	0.397	0.102	...	10.3
13	0.0996	0.0996	...	9.6
14	1.06	0.100	...	14.8
15	1.06	0.100	0.026	14.5
16	1.07	0.0993	0.052	13.5
17	1.07	0.0995	0.104	14.7
18	0.40	0.40	...	9.8
19	0.305	0.396	...	6.6
20	0.199	0.393	...	6.2
21	0.204	0.399	...	7.5
22	0.0987	0.401	...	8.4

[a] Concentrations are in mole l.$^{-1}$.

Finally, we have demonstrated that even under conditions of limiting ammonia concentration (runs 18–22), the reaction goes to completion and is effectively irreversible. Although (as noted above) the fourth-order rate constant is somewhat lower than observed with higher concentrations of reactants, the observed infinity values were in good agreement with the values calculated from the stoichiometry of eq. 7.



(7)

Discussion

The data reported here indicate that the reaction consistently follows the kinetic expression of eq. 4 with either reagent limiting, that the reaction goes to completion, and that added product does not inhibit the reaction. Some decrease in k_4 is observed at low reagent concentrations. This decrease is not sufficiently large to indicate a change in kinetic order, but may reflect a change in the nature of the reaction medium or may be due to complex formation. The data reported here are not sufficiently precise to relate this change in rate constant as a meaningful function of change in concentration.

Reutov and co-workers have claimed that the reaction does not occur at low ammonia concentrations and that

(8) O. A. Reutov, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), 22, 1 (1961).

(9) Inhibition by product would require a tenfold decrease in k_4 over the concentration range employed in runs 14–17 of Table I.

the reactions in general do not go to completion. It is possible that Reutov and co-workers were deceived by the extreme falloff in rate with time which occurs in a fourth-order reaction. Also, it is required for their analytical procedure to be valid that the product which appears as a precipitate must remain suspended in solution for appreciable lengths of time. The controls reported to support the validity of the analytical procedure were very limited and were not carried out under conditions in which the ammonia concentration was limiting, or under conditions which correspond to the latter part of the reaction. Reutov and co-workers have reported that added dialkylmercury product inhibits the reaction but product formed in the reaction does not. The results reported here indicate that added or formed dialkylmercury product does not inhibit the reaction. No ready explanation appears possible to explain Reutov's results.

Consequently, the intervention of Reutov's mechanism (eq. 1, 2, and 3) for the reaction is precluded.

Reutov has offered in support of his mechanism the observation[10] that ethyl α-bromomercuriphenylacetate is also symmetrized by diphenylmercury, a reaction which he has proposed occurs by the scheme shown in eq. 8 and 9. The analogy with the suggested pathway

$$2RHgBr \rightleftharpoons R_2Hg + HgBr_2 \quad (8)$$

$$HgBr_2 + (C_6H_5)_2Hg \longrightarrow 2C_6H_5HgBr\downarrow \quad (9)$$

for ammonia symmetrization (eq. 1 and 2) is evident. However, simply weighing the precipitated phenylmercuric bromide demonstrates that the stoichiometry of the initial reaction is not $2RHgBr:1(C_6H_5)_2Hg$ as required by Reutov's mechanism but rather it is 1:1.[11] The reaction sequence[11] of diphenylmercury symmetrization is shown in eq. 10 and 11.

$$RHgBr + (C_6H_5)_2Hg \xrightarrow{fast} RHgC_6H_5 + C_6H_5HgBr\downarrow \quad (10)$$

$$RHgBr + RHgC_6H_5 \xrightarrow{slow} R_2Hg + C_6H_5HgBr\downarrow \quad (11)$$

Possible mechanisms for the ammonia symmetrization which are consistent with the observed kinetics involve complex formation between reactants prior to the rate-determining step. The mechanism shown in eq. 12 and 13 was actually considered by Reutov and rejected on the basis of erroneous conclusions regarding the mechanism of symmetrization by diphenylmercury (eq. 8 and 9). Although it is not possible on the basis of the kinetic data to distinguish between the processes represented by eq. 12 and 13, and 14 and 15,

$$RHgBr + NH_3 \underset{fast}{\overset{K}{\rightleftharpoons}} RHg(NH_3)Br \quad (12)$$

$$2RHgBr(NH_3) \xrightarrow[slow]{k} R_2Hg + HgBr_2(NH_3)_2 \quad (13)$$

$$RHgBr + 2NH_3 \underset{fast}{\overset{K}{\rightleftharpoons}} RHg(NH_3)_2Br \quad (14)$$

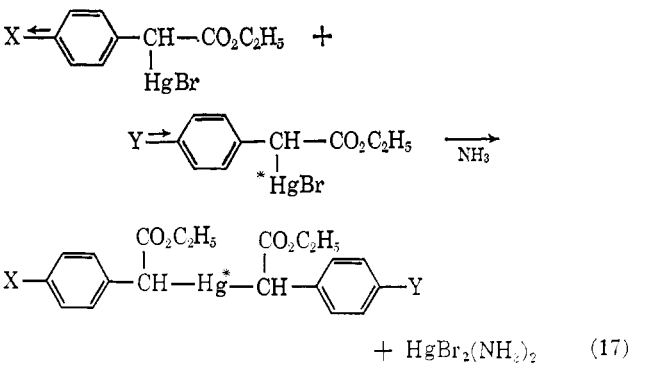
$$RHgBr(NH_3)_2 + RHgBr \xrightarrow[slow]{k} R_2Hg + HgBr_2(NH_3)_2 \quad (15)$$

respectively, we prefer the latter for reasons enumerated.[7] It is important to note that the rate expression for either mechanism involves the equilibrium constant for complex formation, *e.g.*, for eq. 14 and 15 the following applies.

$$\text{rate} = Kk[RHgBr]^2[NH_3]^2 \quad (16)$$

It is readily apparent that caution is required in deriving conclusions regarding the nature of the transition state from experimental rate constants which are actually products of true rate and equilibrium constants. In this connection, Reutov has argued that substituent effects in this reaction are anomalous since electron withdrawing groups accelerate the rate (ρ = 2.8) and he has concluded "that rupture of the old C–Hg bond rather than formation of the new is rate limiting, despite the fact that the reaction is an S$_E$2 type."[12] It is at least as probable that this "anomalous" effect is due to an increase in the complex equilibrium constant K caused by the electron-withdrawing groups.

Reaction between α-halomercuri esters with different *para* substituents has been termed cosymmetrization. When one *para* substituent is electron withdrawing and the other is electron releasing, it is found that the rate of symmetrization is enhanced over the rate for either reactant alone (the cosymmetrization effect). By use of Hg^{203} it has been demonstrated that the mercury atom of the ester containing the electron-donating group is found predominantly in the dialkylmercury product.[13]



$$+ HgBr_2(NH_3)_2 \quad (17)$$

These results again are compatible and readily explained by considering prior complex formation with ammonia.

Experimental Section

Materials. Chloroform was the fraction from P_2O_5 through a 60-plate Oldershaw column and then redistilled from CaH_2 taking a center cut prior to use. Only freshly purified chloroform was used.

t-Butyl α-bromomercuriphenylacetate was prepared in 59% yield according to the procedure given by Reutov, m.p. 103.5–104.5° (lit.[14] m.p. 141–142°). The n.m.r. spectrum in CS_2 shows a singlet (nine protons) at τ 8.59, a singlet (one proton) at 5.84, and a complex multiplet (five protons) centered at 2.8. *Anal.* Calcd. for $C_{12}H_{15}BrHgO_2$: C, 30.55; H, 3.20. Found: C, 30.53; H, 3.35.

Di-α-(*t*-butyl Phenylacetate)mercury. Chloroform (12 ml.) in a centrifuge tube was saturated with NH_3. To this solution 6.0 g.

(10) O. A. Reutov, I. P. Beletskaya, and L. R. Filippenko, *Nauchn. Dokl. Vysshei Shkoly, Khim. i Khim. Tekhnol.*, **4**, 754 (1958).

(11) F. R. Jensen and J. Miller, *J. Am. Chem. Soc.*, **86**, 4735 (1964).

(12) G. A. Artamkina, I. P. Beletskaya, and O. A. Reutov, *Proc. Acad. Sci. USSR*, **153**, 939 (1963).

(13) I. P. Beletskaya, G. A. Artamkina, and O. A. Reutov, *ibid.*, **149**, 181 (1963).

(14) O. A. Reutov, I. P. Beletskaya, and G. A. Artamkina, *J. Gen. Chem. USSR*, **30**, 3190 (1960). An explanation of the discrepancy in melting points is not apparent. The analytical and spectral data presented above indicate that the compound prepared in this work is as assigned and is pure.

(12.7 mmoles) of *t*-butyl α-bromomercuriphenylacetate was added, and the mixture was shaken to ensure dissolution of the alkylmercuric salt. Gaseous ammonia then was bubbled through the mixture for 30 min. The mixture then was centrifuged, and the mother liquor was decanted and evaporated to dryness on a rotary film evaporator. The residue was dissolved in $CHCl_3$ which was then evaporated to dryness. Crystallization of the residue from absolute ethanol gave 2.40 g (65%), m.p. 116–129°. Two further crystallizations raised the m.p. to 119.5–134°. The broad melting point is believed due to the presence of diastereoisomers. This is in agreement with the n.m.r. spectrum of this compound which is similar to that of the alkylmercuric salt excepting that the *t*-butyl and benzylic protons appear as doublets, the relative intensities of which change with crystallization.

This material slowly decomposes under the action of ammonia in chloroform to the hydrocarbon and an alkylmercuric salt. This side reaction has no effect on the kinetic determinations since (1) it is considerably slower than symmetrization and (2) the n.m.r. signal of the *t*-butyl protons of the decomposition products falls under that from the product *t*-butyl group.

Kinetic Method. A solution of NH_3 in $CHCl_3$ was prepared in an especially designed flask fitted with a side-arm buret and a Teflon valve. The concentration was determined by titration with HCl to the cresol red end point. Standard solutions were delivered into a 2-ml. volumetric flask fitted with a Teflon stopcock and a 3-mm. delivery tube. After mixing, about 1 ml. of the reaction solution was delivered into an n.m.r. tube. The space above the solution was filled with a piece of 4-mm. tubing. The tubes were then sealed and stored in an acetone–Dry Ice bath. For the kinetic runs, the tubes were placed in a bath at 31.4° until equilibrated. They were then placed in the n.m.r. probe and the rate was followed by appearance of the product *t*-butyl group. As the reaction proceeded, the formation of the ammonia–mercuric bromide precipitate caused broadening of the signal. Consequently, the tubes were removed from the probe and centrifuged periodically. The Varian Associates A-60 n.m.r. spectrometer was used for the analyses.

The Reaction of Diphenylmercury with Ethyl α-Bromomercuriphenylacetate. Standard solutions of the reactants in $CHCl_3$ were mixed in the proportions shown in Table II. A heavy precipitate formed immediately. After 2 min. the precipitate was filtered into a tared sintered-glass funnel and washed with a measured volume of cold $CHCl_3$. The identity of the precipitate was established by melting point, mixture melting point, and infrared spectrum.

Table II

Run	Ph_2Hg, mmole	mmole PhC(HgBr)-HCO_2Et	PhHgBr,[a] mmole	PhHgBr,[b] %
1	0.125	0.50	0.126	100
2	0.25	0.50	0.247	99
3	1.00	1.00	0.948	93
4	1.00	0.50	0.490	98

[a] Corrected for solubility of PhHgBr in $CHCl_3$ (0.0019 g./ml.). [b] Based on stoichiometry of eq. 10.

The n.m.r. spectrum of the mother liquor of run 3 (equimolar reactants) shows a triplet (three protons) at τ 8.75, a singlet (one proton) at 6.2, and a quartet (two protons) at 5.85. This splitting pattern is, of course, identical with that of di-α-(*t*-butyl phenylacetate)mercury. The two compounds are readily distinguished by their shifts in the n.m.r. spectrum. The peaks of the symmetrical compound are 1–5 c.p.s. upfield from those of the unsymmetrical dialkyl.

The fast step (eq. 10) is followed by a slow step which is represented by eq. 11. Run 2, for example, yielded after 1 week a second equivalent of phenylmercuric bromide and, within the limits of detection by n.m.r., pure di-α-(*t*-butyl phenylacetate)mercury. Run 3 yielded no phenylmercuric bromide after the initial fast reaction. The unsymmetrical dialkyl formed in run 3 slowly disproportionated into diphenyl mercury and di-α-(*t*-butyl phenylacetate)mercury. The ratio of the latter to the unsymmetrical material was approximately 2:1.

Intramolecular Catalysis. VIII.[1] General Base–General Acid Catalysis of Ester Solvolysis[2,3]

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Abstract: Evidence is presented for the argument that the solvolysis of 1,3-diaxial hydroxyacetates is an instance of concerted general base–general acid catalysis of ester solvolysis. Facilitation of the alkaline hydrolysis of an alicyclic axial acetate by a hydroxyl group bearing a 1,3-diaxial juxtaposition to the acetate had been established earlier. The buffer ratio–rate profile for the solvolyses of neogermitrine (I), strophanthidin 3-acetate (V), strophanthidol 3-acetate (VI), and coprostane-3β,5β-diol 3-monoacetate (X) indicated that the pseudo-first-order methanolysis of each is base catalyzed. The linear increase in rate with increasing buffer concentrations at constant buffer ratio and constant ionic strength support the view that the solvolyses of V and of X are catalyzed by a buffer component. Arguments for the view that the solvolysis is general base catalyzed are presented. Introduction of the 19-aldehyde group of strophanthidin 3-acetate (V) led to a fourfold increase of rate of solvolysis relative to X. The view is considered that the solvolyses of the acetate ester of V and of C-7 acetate esters in veratrum alkaloids such as I may be subject to general base and *bifunctional intramolecular* general acid catalysis.

Facilitation of the alkaline solvolysis of an alicyclic axial acetate by a hydroxyl group bearing a 1,3-diaxial juxtaposition to the acetate is a well-established fact.[4–7] Evidence is presented herewith for the argument that the solvolysis of 1,3-diaxial hydroxy-acetates

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(2) The investigations which form the subject of this paper were first outlined in a preliminary communication: S. M. Kupchan, S. P. Eriksen, and M. Friedman, *ibid.*, **84**, 4159 (1962).

(3) This work was supported in part by Public Health Service Research Grant HE-02275, from the National Heart Institute.

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(7) S. M. Kupchan and C. R. Narayanan, *J. Am. Chem. Soc.*, **81**, 1913 (1959).