

stant, and T = absolute temperature. For such solutions, as $x \rightarrow 0$, $\rightarrow \exp(\omega/RT)$. For the surfactant component, the activity coefficient f' is given by:

$$\ln f' = x^2\omega/RT \quad (\text{Eq. 15})$$

so that $f' \rightarrow 1$ as $x \rightarrow 0$.

In Fig. 2, a plot of x versus c shows the pronounced deviation from Henry's law at high x values. By using the activity coefficient from the regular solution theory, with $\omega/RT = -1.64$, the product xf , however, varies linearly with c within an average variation of about 2.5%, which is of the order of the experimental error. The distribution law (Eq. 11) is thus obeyed. The solubilization data are thus in good accord with a simple picture of nonideality. It should be stressed that the regular solution theory uses two parameters to relate the x versus c data, namely, K_D' and ω/RT , just as the Langmuir-type analysis does.

The success of the regular solution approach suggests that even fairly severe nonidealities in solubilized systems may be amenable to analysis in terms of the distribution law.

REFERENCES

- (1) D. G. Davies and C. R. Bury, *J. Chem. Soc.*, **1930**, 2263.
- (2) J. Grindley and C. R. Bury, *ibid.*, **1929**, 679.
- (3) G. S. Hartley, "Aqueous Solutions of Paraffin-Chain Salts," Hermann, Paris, France, 1936.
- (4) P. Mukerjee, *Advan. Colloid Interface Sci.*, **1**, 241(1967).
- (5) P. Mukerjee, *J. Phys. Chem.*, **74**, 3824(1970).
- (6) P. Mukerjee, in "Encyclopaedic Dictionary of Physics," J. Thewlis, Ed., Pergamon, Oxford, England, 1961.
- (7) P. Mukerjee and K. J. Mysels, *J. Amer. Chem. Soc.*, **77**, 2937(1955).
- (8) P. Mukerjee and K. J. Mysels, "Critical Micelle Concentra-

tions of Aqueous Surfactant Systems," NSRDS-NBS 36, U. S. Govt. Printing Office, Washington, DC 20402, 1971.

- (9) T. Nakagawa, in "Nonionic Surfactants," M. J. Schick, Ed., Marcel Dekker, New York, N. Y., 1967.
- (10) K. Shinoda, T. Nakagawa, B. Tamamushi, and T. Isemura, "Colloidal Surfactants," Academic, New York, N. Y., 1963.
- (11) S. J. Rehfeld, *J. Phys. Chem.*, **71**, 738(1967).
- (12) M. E. L. McBain and E. Hutchinson, "Solubilization and Related Phenomena," Academic, New York, N. Y., 1955.
- (13) N. K. Patel and H. B. Kostenbauder, *J. Amer. Pharm. Ass., Sci. Ed.*, **47**, 289(1958).
- (14) M. Donbrow, P. Molyneaux, and C. T. Rhodes, *J. Chem. Soc., A*, **1967**, 561.
- (15) T. L. Hill, "Thermodynamics of Small Systems," vols. 1 and 2, Benjamin, New York, N. Y., 1963.
- (16) D. G. Hall and B. A. Pethica, in "Nonionic Surfactants," M. J. Schick, Ed., Marcel Dekker, New York, N. Y., 1967.
- (17) K. J. Mysels, *J. Colloid Sci.*, **10**, 507(1955).
- (18) S. J. Rehfeld, *J. Phys. Chem.*, **74**, 117(1970).
- (19) I. M. Kolthoff and W. Stricks, *J. Phys. Colloid Chem.*, **52**, 915(1948).
- (20) *Ibid.*, **53**, 424(1949).
- (21) I. M. Kolthoff and W. F. Graydon, *J. Phys. Colloid Chem.*, **55**, 699(1951).
- (22) E. A. Guggenheim, "Thermodynamics," 2nd ed., North Holland, Amsterdam, The Netherlands, 1950.
- (23) P. Mukerjee, *J. Pharm. Sci.*, **60**, 1528(1971).
- (24) P. Mukerjee, *Kolloid-Z. Z. Polym.*, **236**, 76(1970).

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Bis-Quaternary Ammonium Compounds: Derivatives and Congeners of Bicyclo[2.2.2]octane

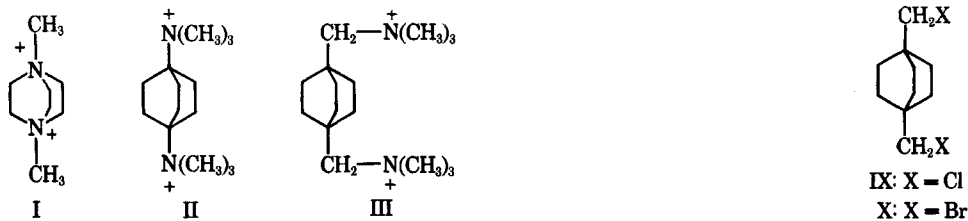
JOSEPH G. CANNON*, KIM WENN YANG*, MELITA RODRIGUEZ†‡, and JOSEPH P. BUCKLEY†

Abstract □ A series of rigid congeners of hexamethonium was prepared, based upon bicyclo[2.2.2]octane, in which the interquaternary distance is varied and in which this distance is known with some degree of certainty. Data on hypotensive activities, taken as an index of ganglionic blocking potency, are consistent with earlier proposals that an interquaternary distance of 6.5–7.5 Å is optimum for polyalkylene bis-quaternary ganglionic blocking agents.

Keyphrases □ Hexamethonium congeners—bicyclo[2.2.2]octane, hypotensive activity □ Bicyclo[2.2.2]octane derivatives—interquaternary distances correlated with hypotensive effects □ Hypotensive activity—bis-quaternary ammonium compounds of bicyclo[2.2.2]octane □ Bis-quaternary ammonium compounds—interquaternary distance correlated with hypotensive effects

There has been controversy in the literature for many years concerning the validity of the "two-point attachment" hypothesis of Barlow and Ing (1) for explaining the ganglionic blocking mechanism of bis-quaternary ammonium salts, typified by hexamethonium. The attractive theory that the length of the most active bis-quaternary polyalkylene molecule corresponds to, or

even is a measure of, an interreceptor distance is complicated by the fact that these flexible compounds can assume an infinite number of conformations and, consequently, their "molecular length" cannot be defined precisely. Gill (2) concluded that ganglionic blocking molecules must possess a "range" of interquaternary distances between the limits of 6 and 7.8 Å. Biel and DiPierro (3) introduced a triple bond into a series of C₅ and C₆ bis-quaternary compounds and found that these derivatives (in which the rigid carbon-carbon triple bond limits somewhat the flexibility of the carbon chain and forces it into a more extended form) were more potent than their saturated parent compounds in producing hypotension, which was considered to be at least in part due to an action at autonomic ganglia. This effect of the acetylenic link on blood pressure was verified in somewhat similar C₅ and C₆ bis-quaternary polyalkylene systems by Neumeyer *et al.* (4). They reported that when the triple bond was reduced to a *cis*-olefinic group, hypotensive activity diminished, but that reduction to a *trans*-olefin increased activity above that observed for the parent saturated molecule. It was concluded that the



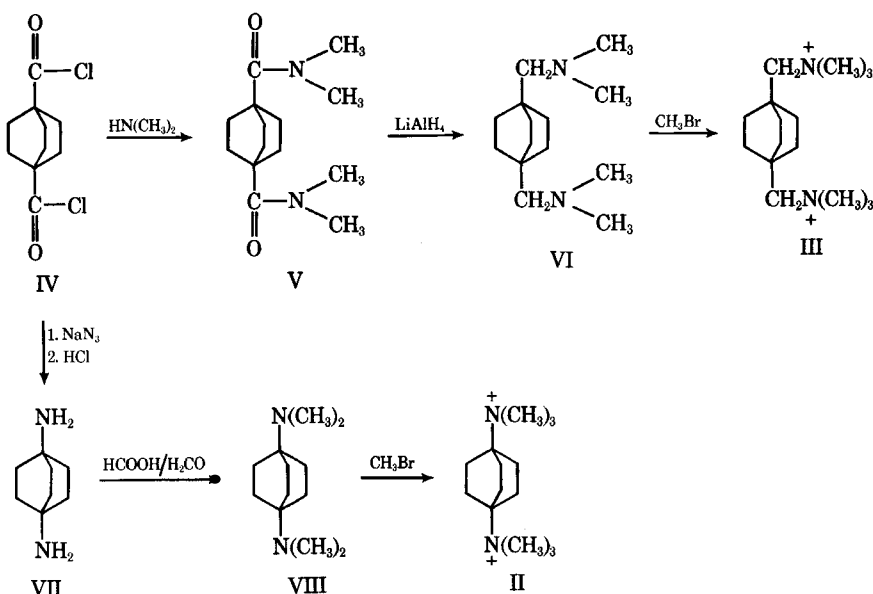
geometry of the *cis*-double bond, in which the polyalkylene chain is folded back over itself, is detrimental to hypotensive effect, whereas the imposition of a more extended conformation upon the chain (by acetylenic or *trans*-olefinic groups) tends to enhance hypotensive activity. Neumeyer (5) concluded that maximal hypotensive activity is manifested when the distance between the two quaternary centers is restricted between 6.5 and 7.5 Å.

A fundamental problem common to all of these compounds is that, despite the introduction of some degree of rigidity into the systems, a considerable amount of flexibility yet remains in the chains joining the quaternary heads and, hence, the interquaternary distances at *in vivo* receptors cannot be precisely defined. In addition, many of the moieties introduced into bis-quaternary compounds to impart rigidity and some degree of conformational integrity [benzene rings (6), acetylenic links (3, 4), and cyclopropane rings (7)] contain π -electrons or possess some degree of unsaturated character. These moieties might well influence physical and chemical properties of the molecule to the extent that they could affect biological activity. The bicyclo[2.2.2]octane system represents a rigid, relatively nonstrained system, lacking a π -electron cloud and having no unsaturated character. 1,4-Diazabicyclo[2.2.2]octane has a similar character, and it was the purpose of the work described here to utilize these two ring systems as the method of imparting a greater rigidity to bis-quaternary systems related to hexamethonium, such that the interquaternary distances could be determined with some degree of con-

fidence and so that attempts could be made to correlate these distances with hypotensive effects.

Specifically, three compounds, I, II, and III, seemed of interest. Inspection of Dreiding models revealed that the interquaternary distances in the diazabicyclooctane derivative (I) and in the 1,4-bis-quaternary ammonium bicyclo[2.2.2]octane system (II) are fixed and rigidly held, being approximately 2.60 and 6.12 Å, respectively. The bis-1,4-(trimethylammoniummethyl)bicyclo[2.2.2]octane system (III) possesses somewhat more flexibility; the range of interquaternary distances in the two conformational extremes of this molecule is between 6.5 and 7.7 Å. Thus, it might be predicted that, on the basis of Gill's (2) and Neumeyer's (5) proposals, Compound III would exhibit the greatest hypotensive effect; Compound II, being on the borderline of optimal interquaternary distance, might show some hypotensive effect; and Compound I should be inert.

The commercial availability of 1,4-diazabicyclo[2.2.2]octane made possible the facile preparation of Compound I.



Scheme 1—Preparation of Diaminobicyclo[2.2.2]octane Derivatives

Compounds II and III were prepared (Scheme I) from bicyclo[2.2.2]octane-1,4-dicarbonyl chloride (IV), which was prepared by a combination of literature methods. An alternate route to the diamide (V) involved aminolysis of diethyl bicyclo[2.2.2]octane-1,4-dicarboxylate (XV) with dimethylamine in the presence of *n*-butyllithium; this procedure is described in a separate article (8).

Attempts to prepare Compound III by alkylation of trimethylamine with 1,4-dichloromethylbicyclo[2.2.2]octane (IX) or with its dibromo analog (X) were unsuccessful; the starting halogen systems were inert toward trimethylamine at steam bath temperatures. The bicyclo[2.2.2]octane ring system exhibits many of the chemical properties of a neopentyl group. It was reported (9) that neopentyl halides are extremely unreactive toward many reagents in bimolecular reactions. Holtz and Stock (10) showed that 1-tosyloxymethylbicyclo[2.2.2]octane has neopentyl character and reacts in bimolecular reactions only with powerful nucleophiles.

1,4-Diazabicyclo[2.2.2]octane was diquaternized with a bulky group, benzyl bromide, as was 1,4-bis-(dimethylamino)bicyclo[2.2.2]octane (VIII); these bis-quaternary compounds (XI and XII) were submitted for biological evaluation.

DISCUSSION

Hypotensive effects are summarized in Table I. Compounds I, II, and III exhibited relative potencies consistent with the predictions based upon the interquaternary distances cited previously. Compound III, having an interquaternary distance range of 6.5–7.7 Å, was the only compound in the series effective at 1 mg./kg. Insofar as hypotensive effect is a measure of ganglionic blocking potency, these data support the proposal that optimal interquaternary distance for ganglionic blockade is in the region 6.5–7.5 Å. The low order of activity of XI and XII can be ascribed, at least in part, to their possessing interquaternary distances below the optimal range. Compound VI, the tertiary amine analog of the most active bis-quaternary, III, exhibited moderate hypotensive effects which may merit further investigation.

EXPERIMENTAL¹

Diethyl 2,5-Diketobicyclo[2.2.2]octane-1,4-dicarboxylate (XIII)—This compound was prepared in 45% yield by the method of Holtz and Stock (11), m.p. 112° [lit. (11) m.p. 111–112°].

Bis-Ethylenethioetal of Diethyl 2,5-Diketobicyclo[2.2.2]octane-1,4-dicarboxylate (XIV)—This compound was prepared from XIII in 95% yield by the method of Roberts *et al.* (12), m.p. 90.5–92° [lit. (12) m.p. 91.8–92.7°].

Diethyl Bicyclo[2.2.2]octane-1,4-dicarboxylate (XV)—This compound was prepared in 82% yield by Raney nickel desulfurization of XIV, as described by Roberts *et al.* (12), b.p. 90–105° (0.01 mm.), n_D^{25} 1.4660 [lit. (12) b.p. 113–115° (0.3 mm.), n_D^{25} 1.4667].

Bicyclo[2.2.2]octane-1,4-dicarbonyl Chloride (IV)—This compound was prepared in 89% yield from XV by the procedure of Kauer *et al.* (13), m.p. 96–98° [lit. (13) m.p. 97.5–98.5°].

1,4-Diaminobicyclo[2.2.2]octane (VII)—This compound was prepared from IV by the method of Kauer *et al.* (13), m.p. 67–68.5° [lit. (13) m.p. 67.5–68.5°].

1,4-Bis(dimethylamino)bicyclo[2.2.2]octane (VIII)—This procedure was adapted from a method of Baltzly and Buck (14). A

Table I—Hypotensive Effects of Bis-Quaternary Compounds in Anesthetized Rats^a

Compound Number	Number of Rats	Decrease in Mean Blood Pressure, mm. Hg				
		Dose Levels, mg./kg.				
		1.0	2.5	5.0	7.5	10.0
I	4	—	2.0	10.0	14.0	29.0
II	4	—	20.2	40.2	52.7	72.0
III	4	16	36.0	85.0	— ^b	—
XI	4	—	13.1	19.2	20.2	25.0
XII	4	—	4.0	13.2	17.2	46.2
VI ^c	4	—	3.0	10.0	25.0	53.0
Mecamylamine	6	—	—	34.0	—	—
Hexamethonium	8	—	—	35.0	—	—

^a Urethan, 1.2 g./kg. i.p. ^b All rats died with this dose. ^c Ditertiary amine analog of III.

mixture of 15.0 g. (0.07 mole) of VII, 70 ml. of 37% formaldehyde solution, and 0.2 ml. of 90% formic acid was heated in a bomb at 135–145° for 24 hr. The resulting clear, colorless solution was treated with 10 ml. of concentrated HCl and evaporated to dryness under reduced pressure from a water bath. The solid residue was suspended in 100 ml. of CHCl₃ and shaken with 50 ml. of H₂O containing 10 g. of KOH. The organic layer was separated, dried (Na₂SO₄), filtered, and evaporated to leave a white solid, which was recrystallized twice from H₂O to give 11.8 g. (86%) of product, m.p. 47–48°.

Anal.—Calc. for C₁₂H₂₄N₂: C, 73.41; H, 12.32; N, 14.22. Found: C, 73.24; H, 12.21; N, 13.99.

A picrate salt was recrystallized from EtOH, m.p. 240.6° dec.

Anal.—Calc. for C₂₄H₂₀N₈O₄: C, 44.04; H, 4.62; N, 17.12. Found: C, 44.28; H, 4.80; N, 16.76.

1,4-Bis(hydroxymethyl)bicyclo[2.2.2]octane (XVI)—Compound XV (21 g., 0.083 mole) was added dropwise to a refluxing suspension of 9 g. (0.24 mole) of LiAlH₄ in 200 ml. of purified tetrahydrofuran, and the resulting mixture was refluxed for 10 hr. The excess LiAlH₄ was decomposed with 10 ml. of H₂O, and the resulting mixture was filtered; the solid on the filter was washed with three 50-ml. portions of Et₂O which were added to the clear filtrate. This solution was dried (Na₂SO₄) and filtered; removal of the volatiles from the filtrate resulted in a viscous, liquid residue which solidified upon standing and was recrystallized from benzene; yield, 10.5 g. (72%); m.p. 108.2° [lit. (11) m.p. 107–108°].

1,4-Bis(chloromethyl)bicyclo[2.2.2]octane (IX)—Thionyl chloride (15 ml., 25 g., 0.21 mole) was added dropwise to a solution of 5.4 g. (0.032 mole) of XVI in 10 ml. of dry pyridine. Then the reaction mixture was refluxed for 12 hr. Volatiles were removed under reduced pressure on a steam bath, and the residue was extracted with Et₂O. After evaporation of the ethereal extract, the liquid residue was distilled, b.p. 74–77° (0.1 mm.), to afford 3.6 g. (53%) of material, n_D^{25} 1.4619.

Anal.—Calc. for C₁₀H₁₆Cl₂: C, 57.98; H, 7.79; Cl, 34.23. Found: C, 57.82; H, 7.82; Cl, 34.23.

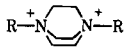
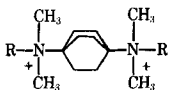
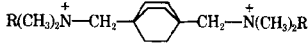
1,4-Bis(bromomethyl)bicyclo[2.2.2]octane (X)—Phosphorus tribromide (10 ml., 28.5 g., 0.106 mole) was added dropwise to 5 g. (0.030 mole) of XVI, and the reaction mixture was refluxed for 10 hr. The excess phosphorus tribromide was decomposed with H₂O; a large amount of tar separated. This mixture was extracted with CHCl₃; the extract was dried (Na₂SO₄) and filtered, and the filtrate was taken to dryness on a steam bath. The dark-brown viscous residue was chromatographed on a 20 × 2-cm. neutral alumina column and was eluted with CHCl₃. The residue from evaporation of the eluate was distilled at 110–120° (1.0 mm.) to yield 1.2 g. (13%) of product, n_D^{20} 1.5573.

Anal.—Calc. for C₁₀H₁₆Br₂: C, 40.57; H, 5.41; Br, 53.99. Found: C, 40.69; H, 5.78; Br, 53.24.

***N,N,N',N'*-Tetramethylbicyclo[2.2.2]octane-1,4-dicarboxamide (V)**—To 6.0 g. (0.02 mole) of IV in 40 ml. of anhydrous acetone, cooled in an ice water bath, was added with stirring an excess of anhydrous dimethylamine. The reaction mixture was filtered, and the solid that collected on the filter was washed with a small volume of anhydrous acetone which was added to the filtrate. The combined organic solutions were evaporated, and the residue was recrystallized from EtOH–H₂O, m.p. 161–162°; yield, 6 g. (92%); IR (KBr) 1605 cm.⁻¹ (amide C=O).

¹ All boiling points are uncorrected; melting points were determined with a Du Pont 900 differential thermal analyzer and/or in open glass capillaries in a Thomas-Hoover Uni-Melt apparatus and are corrected. Elemental analyses were performed by Hufmann Laboratories, Wheatridge, Colo., and Galbraith Laboratories, Knoxville, Tenn. IR spectra were recorded on Beckman IR-5-A and IR-10 instruments.

Table II—Bis-Quaternary Ammonium Compounds

Compound Number	R	Melting Point	Yield, %	Formula	Analysis, %	
					Calc.	Found
						
I	CH ₃ ^a	300–301 ^{ob}	75	C ₈ H ₁₈ Br ₂ N ₂	C, 31.81 H, 6.01 N, 9.27	C, 31.88 H, 6.04 N, 9.61
XI	CH ₂ C ₆ H ₅	274–275 ^{oc}	55	C ₂₀ H ₂₀ Br ₂ N ₂	C, 52.88 H, 5.77 N, 6.17	C, 52.72 H, 6.08 N, 6.25
						
II	CH ₃	Above 300 ^{ob}	52	C ₁₄ H ₃₀ Br ₂ N ₂	C, 43.54 H, 7.83 N, 7.25	C, 43.54 H, 7.84 N, 6.89
XII	CH ₂ C ₆ H ₅	280–281 ^{oc}	46	C ₂₈ H ₃₈ Br ₂ N ₂	C, 57.94 H, 7.11 N, 5.20	C, 57.82 H, 7.13 N, 4.89
						
III	CH ₃	Above 300 ^{ob}	64	C ₁₆ H ₃₄ Br ₂ N ₂	C, 46.39 H, 8.27 N, 6.77	C, 46.58 H, 8.25 N, 6.87

^a 1,4-Diazabicyclo[2.2.2]octane obtained from Aldrich Chemical Co. ^b From methanol. ^c From ethanol.

Anal.—Calc. for C₁₄H₂₄N₂O₂: C, 66.60; H, 9.59; N, 11.10. Found: C, 66.58; H, 9.45; N, 11.17.

1,4-Bis(dimethylaminomethyl)bicyclo[2.2.2]octane (VI)—A solution of 6.3 g. (0.025 mole) of the diamide (V) in 30 ml. of purified tetrahydrofuran was added dropwise to a suspension of 5 g. of LiAlH₄ in 50 ml. of purified tetrahydrofuran, and the resulting mixture was refluxed for 2 hr. Excess LiAlH₄ was decomposed with 5 ml. of H₂O, and the resulting mixture was filtered. The solid on the filter was washed with three 50-ml. portions of Et₂O which were added to the filtrate. This combined solution was dried (Na₂SO₄), filtered, and evaporated to afford a white solid residue, which was recrystallized from EtOH to yield 5.0 g. (89%) of product, m.p. 60–61°.

Anal.—Calc. for C₁₄H₂₈N₂: C, 74.91; H, 12.57; N, 12.51. Found: C, 74.91; H, 12.56; N, 12.24.

Bis-Quaternary Compounds—The appropriate diamine (0.02 mole) and an excess of methyl bromide or benzyl bromide in 10–15 ml. of 2-propanol were heated in a sealed tube on a steam bath for 4 hr. The reaction mixture was cooled, and the solid that separated was collected on a filter and recrystallized (Table II).

Pharmacology—Male Wistar rats, weighing between 200 and 250 g., were divided into six groups of four rats each. The animals were anesthetized with urethan, 1.2 g./kg. i.p., and secured to an operating board, ventral side up. A midline incision was made into the neck area, and the trachea was catheterized to permit free breathing. One of the carotid arteries was cannulated with a polyethylene catheter connected to a Statham pressure transducer, using the system filled with heparinized saline (5000 units/100 ml.). Blood pressure was recorded on a polygraph, and the femoral vein was catheterized for administration of the compounds. Each of the six groups of rats was treated with one of the compounds, using a dose schedule of 1.0, 2.5, 5.0, 7.5, and 10.0 mg./kg. with a minimum period of 10 min. between doses.

REFERENCES

- (1) R. B. Barlow and H. R. Ing, *Brit. J. Pharmacol. Chemother.*, **3**, 298(1948).
- (2) E. W. Gill, *Proc. Roy. Soc., Ser. B*, **150**, 381(1959).
- (3) J. H. Biel and F. DiPierro, *J. Amer. Chem. Soc.*, **80**, 4609(1958).
- (4) J. L. Neumeyer, J. G. Cannon, and J. P. Buckley, *J. Med. Pharm. Chem.*, **5**, 784(1962).
- (5) J. L. Neumeyer, *Diss. Abstr., Sec. B*, **22**, 3001(1962).
- (6) R. Wien, *Arch. Int. Pharmacodyn. Ther.*, **97**, 395(1954).
- (7) A. Burger and G. R. Bedford, *J. Med. Chem.*, **6**, 402(1963).
- (8) J. G. Cannon and K. W. Yang, to be published.
- (9) F. C. Whitmore and G. H. Fleming, *J. Amer. Chem. Soc.*, **55**, 4161(1933).
- (10) H. D. Holtz and L. M. Stock, *ibid.*, **87**, 2404(1965).
- (11) *Ibid.*, **86**, 5183(1964).
- (12) J. D. Roberts, W. T. Moreland, Jr., and W. Frazer, *J. Amer. Chem. Soc.*, **75**, 637(1953).
- (13) J. C. Kauer, R. E. Benson, and G. W. Parshall, *J. Org. Chem.*, **30**, 1431(1965).
- (14) R. Baltzly and J. S. Buck, *J. Amer. Chem. Soc.*, **62**, 161(1940).

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