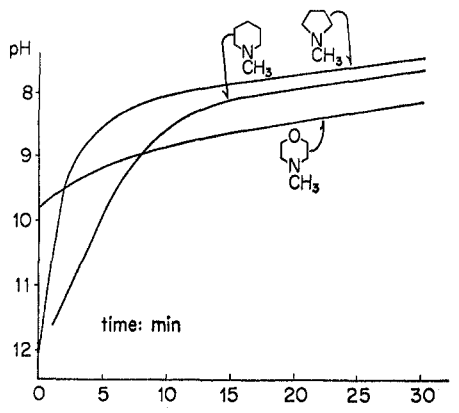

Figure 1.—Quarternization of tertiary amines with methyl iodide.

sured at 1-min intervals for 15 min and after 20, 25, and 30 min. A plot of the data is shown in Figure 1.

C to N Alkylation Ratios.—An enamine (6–7 ml) from Table I was added to about 80 ml of dry dioxane. From this mixture three 25-ml samples were drawn. One sample was diluted with 50 ml of dioxane and enough water to increase the volume to 100 ml. From this 10-ml aliquots were drawn, diluted with water, and titrated with standard hydrochloric acid to determine the total enamine per 25-ml sample. Each of the other 25-ml samples was refluxed for 18 hr, or cooled in ice, and then stored for 24 hr at 25° with <1 equiv of a different alkylating agent, under nitrogen. After cooling, 5 ml of water was added and the mixture refluxed for 1 hr. The cooled reaction mixtures were diluted with 50 ml of dioxane in volumetric flasks and diluted with water to 100 ml. The amount of unreacted enamine was determined by titrating 10-ml aliquots, dissolved in water, with standard hydrochloric acid. The amount of amine acid salt, which equals the amount of C alkylated products, was determined by titrating 10-ml aliquots, dissolved in 50 ml of alcohol, with standard sodium hydroxide. Amount of N alkylated product = total enamine − unreacted enamine − C alkylated product. Titrations were carried out with the pH meter described above and end points determined[17,18] from the following equation: endpoint volume = maximum volume + $0.05\Delta(\Delta pH/\Delta V)_{max}/[\Delta(\Delta pH/\Delta V)_{max-1} + \Delta(\Delta pH/\Delta V)_{max+1}]$. The results are listed in Table I.

Registry No.—5/5, 7148-07-4; 5/6, 1125-99-1; 5/7, 14092-11-6; 5/h, 23516-90-7; 5/n, 3494-04-0; 6/5, 1614-92-2; 6/6, 2981-10-4; 7/6, 23430-63-9; m/5, 936-52-7; m/6, 670-80-4; methyl acrylate, 96-33-3; acrylonitrile, 107-13-1; benzyl bromide, 100-39-0; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; *sec*-butyl bromide, 78-76-2.

(17) D. A. Skoog and D. M. West, "Fundamentals of Analytical Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1963, p 556.

(18) J. J. Lingane, "Electroanalytical Chemistry," 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1958, p 93.

Alkylation of Amines. A New Method for the Synthesis of Quaternary Ammonium Compounds from Primary and Secondary Amines

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Primary and secondary amines have been exhaustively alkylated to their quaternary stage in a one-step procedure. The observation that protonation of sterically hindered amines is only slightly affected by steric hindrance, whereas nucleophilicity as measured by the rate of alkylation is considerably decreased, has been synthetically utilized. An organic base of greater base strength than the reactant amines has been employed to bind the acid generated in alkylation reactions. Aniline and aniline derivatives with pK_a values of 3.86–5.34 have been completely methylated in the presence of the stronger, but sterically hindered base, 2,6-lutidine (pK_a = 6.77). The mild and homogeneous reaction conditions resulted in good yields with minimal laboratory manipulations and effort. As an example of the applicability of the method to amines that possess labile functions, the bisquaternary carbamate, 5-(dimethylcarbamoyloxy)-1,3-phenylenebis(trimethylammonium iodide), has been prepared from 3,5-diaminophenyl dimethylcarbamate in a one-step procedure.

Quaternary ammonium compounds are prepared in most cases from tertiary amines, primary or secondary amines being used only occasionally as the starting materials.[1–3] The methods previously available for direct alkylation of primary and secondary amines to the quaternary stage require relatively harsh reaction conditions and give rise to undesirable side reactions, and, hence, are limited to stable amines and alkylating agents. These methods were developed by A. W. Hofmann in the nineteenth century and are still employed without significant changes. The reaction of a primary or secondary amine with an alkylating agent, such as an alkyl halide, involves the liberation of a hydrohalic acid which combines with the reactant amines to form a mixture of amine hydrohalide salts. Consequently, very low concentrations of free amines remain for subsequent alkylation. To increase the concentration of the free amines, inorganic bases are utilized as the proton acceptors.

The general procedure for the direct alkylation of primary or secondary amines to their quaternary ammonium salts is to reflux a mixture of the amine, an excess of the alkyl halide, and sodium carbonate or sodium hydroxide in water or alcohol. Under these heterogenous reaction conditions prolonged heating is needed leading to numerous side reactions and low yields. Consequently, this method is of value only in those instances where both the amines and the alkylating agents are thermally stable and are insensitive to strong inorganic bases. Further complications arise from the fact that the physical properties of quaternary ammonium salts closely resemble those of inorganic salts. Thus, the purification of quaternary compounds in the presence of inorganic salts can be very laborius, since their solubilities in most common solvents are very similar. In view of the above difficulties and in spite of the addi-

(1) For a review, see J. Goerdeler in "Methoden Der Organishen Chemie, Stickestoffverbindugen" (Houben-Weyl), Eugen Muller, Ed., Vol. XI/2, Georg Thieme Verlag, Stuttgart, Germany, 1958, pp 587–640.

(2) W. Krucker, "Synthese de Sels d'Ammonium quaternaires derives d'Aminophenols et Etude de leur Action sur la Transmission neuromusculaire," J. Peyronnet, Paris, 1951, pp 11–60.

(3) M. M. Markowitz, *J. Org. Chem.*, **22**, 983 (1957).

tional steps involved, the route usually chosen is the synthesis and isolation of the appropriate tertiary amine prior to quaternization.

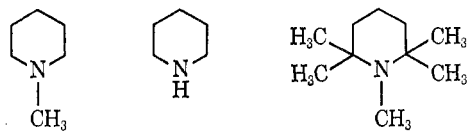
When primary amines react with alkylating agents a sequence of reactions occurs resulting in the formation of a mixture of products.[4] The composition of the product mixture depends on the molar concentration of the reactants, the temperature, the basicities of the starting and alkylated amines, the steric configuration of all the reacting species, and their solubilities in the various solvent media. In the complex series of equilibria the most readily controllable step is the final alkylation of the tertiary amine to the quaternary salt. The preparation of secondary and tertiary amines by this procedure is generally impractical because of the competing reactions and difficulty of separation. The equilibria can be shifted toward complete alkylation by the introduction of strong inorganic bases, but the disadvantages mentioned previously limit the scope of this approach.

In principle, the alkylation of a primary or secondary amine to the quaternary stage could be greatly simplified if an organic base could be used to bind the acid that is generated as the reaction proceeds. The organic base should have solubilities similar to those of the starting amines to attain homogeneous reaction conditions, it must be a stronger base (larger pK_a) than the reacting amines to combine preferentially with the acid produced, it must alkylate at a significantly slower rate than the reacting amines, and it should be readily available. Preferably, the acid salt of the organic base and the quaternary ammonium salt should be separable on the basis of solubility.

The seemingly contradictory requirement, that the organic base have a larger pK_a, yet react at a slower rate than the amines to be alkylated, led us to examine more closely the relationship between basicity and nucleophilicity.

Correlations between basicity and nucleophilicity in amines have been extensively explored in the literature.[5-23] Even though a direct relationship has been demonstrated in most studies, the exceptions, attributable to steric hindrance, are of special interest.[7,11,13,14]

Hall[18] determined the basicities of the following piperidine compounds which are shown in the order of increasing pK_a values.



10.13 11.05 11.25

1-Methylpiperidine is a weaker base than piperidine, while 1,2,2,6,6-pentamethylpiperidine is the strongest of the three, in spite of the five methyl groups surrounding the nitrogen. These examples indicate that, whereas steric factors can weaken basicity, polar effects, however, overcome severe steric hindrance.

Such compensation is not encountered when the parameters that govern nucleophilicity are evaluated. Clarke and Rothwell,[7] studying the effects of substituents on the rate of formation of alkylpyridinium halides, showed that the basicity of the pyridine nitrogen is enhanced by the inductive effects of alkyl substituents on the aromatic ring and that the influence of steric hindrance is insignificant. The pK_a values of the monosubstituted 2- and 4-methylpyridines (5.97 and 6.02) are essentially identical and greater by approximately 0.8 pK_a unit than pyridine (5.17). Dimethyl substitution, both in the 2, 4 and 2,6 positions, likewise results in very similar pK_a values (6.72 and 6.77). The pK_a of collidine, the 2,4,6-trimethylpyridine derivative, rises to a value of 7.48. The additive effect of the methyl groups on base strength, an increase of about 0.8 pK_a unit/methyl group from mono- to di- to trimethyl substitution, clearly demonstrates the electron-donor feature and rules out steric hindrance as a significant factor in protonation.[11,13,14]

In sharp contrast, steric hindrance greatly affects nucleophilicity in these alkyl-substituted pyridines. Of the cases cited by Clarke and Rothwell, only 4-methyl- and 4-ethylpyridine quaternize faster than pyridine. Regardless of base strength, the amines with *ortho* substituents alkylate more slowly than pyridine. 2,6-Lutidine (pK_a = 6.77) quaternizes with methyl iodide 18.6 times and 2,4,6-collidine (pK_a = 7.48) 9.1 times as slowly as pyridine (pK_a = 5.17). With allyl bromide the differences in alkylation rates are 260 and 150, respectively.

When both steric and electrical effects have to be considered, it seems evident that the latter is the dominant contributor in the determination of base strength, exemplified by the extremely hindered 1,2,2,6,6-pentamethylpiperidine, which is 13 times as strong a base as 1-methylpiperidine.[18] Steric effects, however, play the major role in the determination of nucleophilicity, strikingly demonstrated by the comparison of base strengths and alkylation rates of 2,6-lutidine and pyridine. 2,6-Lutidine is about 40 times as strong as pyridine in base strength, yet reacts with methyl iodide approximately 19 times as slowly.[7] Thus, competing strong electron donor and pronounced steric effects result in an increase of basicity and decrease of nucleophilicity.

In light of these observations the interaction between a proton and a hindered amine and the interaction of the same amine with an alkylating agent must be substantially different. The proton, owing to its small size and its electron deficiency, appears to be able to approach the nitrogen of an amine and form a chemical bond in spite of steric hindrance. On the other hand, a sterically hindered nucleophile is hampered or even completely blocked in its attack on the alkylating agent.

(4) P. Karrer "Organic Chemistry," 4th English ed, Elsevier, Amsterdam, 1950, p 128.
(5) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).
(6) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **78**, 2570 (1956); **79**, 5441 (1957).
(7) K. Clarke and K. Rothwell, *J. Chem. Soc.*, 1885 (1960).
(8) D. P. Evans, *et al.*, *ibid.*, 1345 (1939).
(9) A. I. Biggs and R. A. Robinson, *ibid.*, 388 (1961).
(10) E. Folkers and O. Runquist, *J. Org. Chem.*, **29**, 830 (1964).
(11) H. C. Brown and X. R. Mihm, *J. Amer. Chem. Soc.*, **77**, 1723 (1955).
(12) H. C. Brown and R. R. Holmes, *ibid.*, **77**, 1727 (1955).
(13) H. C. Brown and A. Cahn, *ibid.*, **77**, 1715 (1955).
(14) H. C. Brown, *et al.*, *ibid.*, **78**, 5375 (1956).
(15) G. W. Ceska and E. Grunwald, *ibid.*, **89**, 1371, 1377 (1967).
(16) M. M. Fickling, *et al.*, *ibid.*, **81**, 4226 (1959).
(17) A. Fischer, *et al.*, *J. Chem. Soc.*, 3591, 3596 (1964).
(18) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5444 (1957).
(19) H. P. Crocker and B. Jones, *J. Chem. Soc.*, 1808 (1959).
(20) D. P. Evans, *et al.*, *ibid.*, 1348 (1939).
(21) W. G. Brown, *et al.*, *J. Amer. Chem. Soc.*, **61**, 2597 (1939).
(22) W. G. Brown and S. Fried, *ibid.*, **65**, 1841 (1943).
(23) D. H. McDaniel and H. C. Brown, *ibid.*, **77**, 3756 (1955).

Whereas electron-donating groups favor the protonation of the amine, the inherent bulk of these groups retards alkylation. Severely hindered amines, it can be concluded, exhibit an inverse relationship between basicity and nucleophilicity.

In the search for an organic base that is readily protonated, yet is a relatively poor nucleophile, an appropriate hindered amine can now be chosen which can successfully serve as the proton acceptor in direct alkylation reactions of primary or secondary amines to their quaternary stage. The quaternization of aniline and its substituted derivatives with methyl iodide in the presence of 2,6-lutidine has been selected in the present study to test the validity and practical implementation of the above concept. 2,6-Lutidine fulfills the requirements outlined for the organic base. Its pK_a (6.77)[7] is greater than that of aniline (4.65),[10] N-methylaniline (4.89),[10] and N,N-dimethylaniline (5.07),[10] and is alkylated at a slower rate.[24] It is soluble in most common organic solvents and commercially available, and the separation of trimethylphenylammonium iodide and 2,6-lutidine hydroiodide is feasible on the basis of solubility differences, as shown in Table I.

TABLE I[a]

SOLUBILITIES OF $C_6H_5\overset{+}{N}(CH_3)_3I^-$ AND 2,6-LUTIDINE SALTS

Compound	DMF, 25°, g/100 ml	Acetone, 25°, g/100 ml	Acetone, 56° g/100 ml
$C_6H_5\overset{+}{N}(CH_3)_3I^-$	13	0.15	0.5
2,6-Lutidine HI	60	2.5	7.0
2,6-Lutidine MeI	6	0.16	0.4

[a] The data were obtained by saturating the solvent with a known quantity of the salt and weighing the undissolved material.

The concentrations of the reactants and the selection of the solvent are important for separation and purification of the quaternary ammonium salt. Table II lists the yields of trimethylphenylammonium iodide obtained at various concentrations in several solvents. A solution of aniline (1 equiv), 2,6-lutidine (2 equiv), and methyl iodide (excess) was allowed to stand at room temperature until precipitation of the product was complete. The product was collected and its purity was determined by its melting point and its mixture melting point with lutidine methiodide and lutidine hydriodide.

Aniline generates 2 equiv of hydriodic acid when it is alkylated to the quaternary state with methyl iodide. Therefore, 2 equiv of 2,6-lutidine are required to free the intermediate secondary and tertiary amines from their hydroiodides. While an excess of the alkylating agent is desirable, an excess of the proton acceptor should be avoided to minimize the formation of 2,6-lutidine methiodide.

The above method has been successfully applied to aromatic amines in the pK_a range from 3.86 (4-bromoaniline)[9] to 5.34 (4-methoxyaniline),[9] as shown in Table II. The reaction with 3-nitroaniline (pK_a of 2.45)[25] resulted in a mixture of the desired product, together with significant amounts of 2,6-lutidine methiodide. Hence, the lower limit of the usefulness of 2,6-lutidine in this quaternization method appears to be for amines with pK_a values between 2.45 and 3.86. The upper limit is determined by the basicity of 2,6-lutidine, *i.e.*, pK_a of 6.77.

TABLE II

YIELDS OF $C_6H_5\overset{+}{N}(CH_3)_3I^-$ AS A FUNCTION OF CONCENTRATION IN VARIOUS SOLVENTS AT 25°

Solvent	Molar concentration of aniline	Yield, %
Acetone	0.054	0
Acetone	0.108	76
Acetone	0.215	Mixture[a]
DMF[b]	0.54	0
DMF[b]	0.90	28
DMF[b]	1.28	49
DMF[b]	1.54	59
DMF[b]	2.69	Mixture[a]
MeOH	0.54	22
MeOH	0.72	29
MeOH	2.15	49
MeOH	3.58	52
MeOH	10.0	Mixture[a]
CH_3CN	0.54	29
CH_3CN	0.67	29
CH_3CN	0.90	Mixture[a]
EtOAc	0.108	Mixture[a]
EtOAc	0.215	Mixture[a]
Benzene	0.154	Mixture[a]

[a] The mixture consists of $C_6H_5\overset{+}{N}(CH_3)_3I^-$ and 2,6-lutidine HI. [b] N,N-Dimethylformamide.

At the concentrations indicated in Table III the quaternary ammonium product precipitates from the reaction solution. Higher concentrations often lead to mixtures and lower concentrations allow a substantial portion of the product to remain in solution.

Amines can also be employed in the form of their salts, in which case 3 equiv of 2,6-lutidine is used. The additional equivalent liberates the amine before alkylation proceeds. (4-Bromophenyl)trimethylammonium iodide has been prepared in this manner from 4-bromoaniline hydrochloride.

When N-phenylbenzylamine (pK_a of 4.04) was alkylated to form benzyldimethylphenylammonium iodide a mixture containing 25% 2,6-lutidine methiodide was obtained. In this instance, the steric hindrance of the starting secondary amine apparently is sufficient to decrease the alkylation rate to a level where 2,6-lutidine methiodide formation becomes significant. However, the mixture is easily separated on the basis of the relatively low solubility of 2,6-lutidine methiodide in methanol.

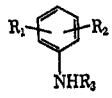
As examples for direct quaternization of amines possessing labile functions, 3-(dimethylcarbamoyloxy)-phenyltrimethylammonium iodide (Prostigmine iodide) and the bisquaternary carbamate 5-(dimethylcarbamoyloxy)-1,3-phenylenebis(trimethylammonium iodide) (IV) were synthesized. The former was prepared from the dimethylcarbamate ester of 2-aminophenol and the latter as shown in Scheme I.

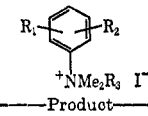
(24) K. J. Laidler and C. N. Hinshelwood, *J. Chem. Soc.*, 858 (1938); K. J. Laidler, *ibid.*, 1786 (1938).

(25) P. Pascal, *Compt. Rend.*, **262C**, 1196 (1966).

TABLE III

ANILINE DERIVATIVES QUATERNIZED WITH METHYL IODIDE IN THE PRESENCE OF 2,6-LUTIDINE



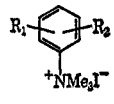


					Molar concentration of aniline derivatives	Product			
R_1	R_2	R_3	pK_a	Solvent		R_1	R_2	R_3	Yield,[a] %
H	H	H	4.65[b]	Acetone	0.054	H	H	Me	76
4-Me	H	H	5.08[c]	Methanol	2.16	4-Me	H	Me	53
4-OMe	H	H	5.34[d]	DMF[e]	1.53	4-OMe	H	Me	87
4-Br	H	H, HCl		Acetone	0.108	4-Br	H	Me	76
4-Br	H	H	3.86[d]	DMF	2.09	4-Br	H	Me	97
4-OH	H	H	5.31[f]	DMF	2.18	4-OH	H	Me	60
3-OH	H	H	4.31[c]	DMF	2.18	3-OH	H	Me	66
H	H	Me	4.89[b]	Methanol	2.70	H	H	Me	67
H	H	Benzyl	4.04[b]	Methanol	2.20	H	H	Benzyl	71
$3\text{-}NH_2$	H	H	4.88[g]	DMF	2.15	$3\text{-}\overset{+}{N}Me_3I^-$	H	Me	67
$3\text{-}NH_2$	5-OCONMe$_2$	H		DMF	0.40	$3\text{-}\overset{+}{N}Me_2I^-$	5-OCONMe$_2$	Me	63
3-OCONMe$_2$	H	H		Methanol	0.58	3-OCONMe$_2$	H	Me	94

[a] Analytically pure material. [b] Reference 10. [c] Reference 25. [d] Reference 9. [e] N,N-Dimethylformamide. [f] M. Gillois and P. Rumpf, *Bull. Soc. Chim. Fr.*, 112 (1954). [g] L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Van Nostrand-Reinhold Co., New York, N. Y., 1961, p 709.

TABLE IV

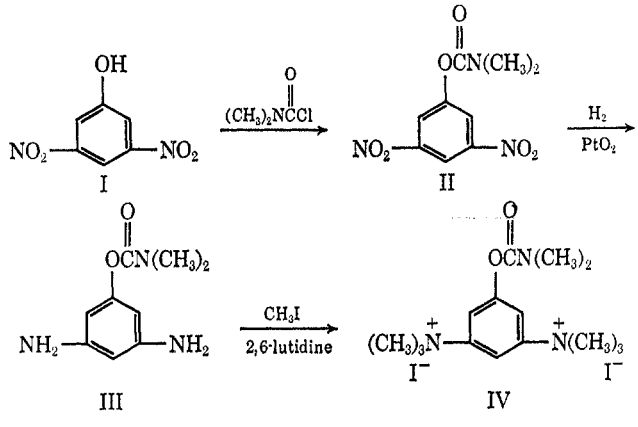
ANALYTICAL DATA



				Calcd, %				Found, %			
R_1	R_2	Mp, °C[a]	Formula	C	H	I	N	C	H	I	N
4-OMe	H	228–229	$C_{10}H_{16}INO$[b]	41.0	5.5	43.3	4.8	41.2	5.6	43.2	4.9
$3\text{-}\overset{+}{N}Me_3I^-$	H	182–183	$C_{12}H_{22}I_2N_2$[c]	32.2	5.0	56.6	6.2	32.0	5.2	56.6	6.3
$3\text{-}\overset{+}{N}Me_3I^-$	5-OCONMe$_2$	183–184	$C_{15}H_{27}I_2N_3O_2$	33.7	5.1	47.4	...	33.7	5.3	47.0	...

[a] Melting points are uncorrected. [b] Registry no. 17310-99-5. [c] Registry no. 23649-60-7.

SCHEME I



If an anion other than iodide is desired, the quaternary ammonium iodide is easily exchanged by conventional ion-exchange procedures.[3]

This study is being continued to extend the applicability of the method described herein to a wider range of amines and alkylating agents.

Experimental Section

Materials.—The aniline derivatives were distilled or recrystallized as required. 2,6-Lutidine and the solvents were dried and distilled before use.

General Procedure.—Methyl iodide (excess) is added to a solution of equimolar quantities of aniline or the aniline derivative and 2,6-lutidine in an appropriate solvent (see Table II). Since the reactions are exothermic and are generally completed in a few minutes, gradual addition of methyl iodide or external cooling of the reaction mixture is advisable. After the reaction has taken place, the mixture is allowed to stand at room temperature for a few hours to ensure complete precipitation of the quaternary product. The product is collected on a filter, washed with acetone, and vacuum dried. To obtain analytically pure materials the quaternary ammonium salts are stirred with additional acetone to remove any remaining 2,6-lutidine hydriodide or are recrystallized from acetone or a methanol–ether mixture. Dry solvents are essential since the presence of water greatly increases the solubility of quaternary ammonium compounds in organic solvents.

The known quaternary ammonium iodides were identified by their elemental analyses and melting points.[26,27] Analytical data and melting points of compounds not found in the literature are given in Table IV.

4-(Methoxyphenyl)trimethylammonium Iodide.—4-Methoxyaniline (2.8 g) was dissolved in 15 ml of N,N-dimethylformamide and cooled in an ice–water bath. 1,6-Lutidine (4.9 g) and methyl iodide (16 g) were added and the reaction mixture was allowed to stand in the cooling bath for approximately 0.5 hr. After additional standing at room temperature for 1.5 hr, the precipitate that formed was collected on a filter. The crude product thus obtained melting between 219 and 220° was stirred in 150

(26) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th Ed., John Wiley & Sons, Inc., New York, N. Y., 1964, pp 335–337; "Tables for Identification of Organic Compounds," C. D. Hodgman, Editor-in-Chief, Chemical Rubber Publishing Co. Cleveland, Ohio, 1960, pp 183–188.

(27) A. Deutsch and O. Fernö (Aktiebolaget Leo), Swedish Patent, 128,292 (1950); *Chem. Abstr.*, **44**, 9477 (1950).

ml of acetone for 10 min at room temperature. After filtration and drying, 5.8 g (87% yield) of white crystalline product was obtained, mp 228–229°.

For analysis, see Table IV.

5-(Dimethylcarbamoyloxy)-1,3-phenylenebis(trimethylammonium Iodide) (IV).—A solution of 3.95 g of 3,5-dinitrophenol (I), 2.33 g of dimethylcarbamoyl chloride, and 4 ml of triethylamine in 100 ml of benzene was refluxed for 4 hr. Triethylamine hydrochloride was removed by filtration and the filtrate washed with 0.1 *N* sodium hydroxide and dried (Na_2SO_4). Addition of 20 ml of ethanol precipitated crude 3,5-dinitrophenyl dimethylcarbamate (II). Recrystallization from ethanol–water gave 2.83 g (52%) of yellow crystals, mp 78–79°.

Anal. Calcd for $C_9H_9N_3O_6$: C, 42.4; H, 3.5; N, 16.5. Found: C, 42.7; H, 3.5; N, 16.3.

A mixture of 510 mg of 3,5-dinitrophenyl dimethylcarbamate (II) and 200 mg of platinum oxide in 20 ml of absolute ethanol was hydrogenated in a Parr apparatus (Parr Instrument Co., Inc., Moline, Ill.). Absorption of 6 mol of hydrogen was complete in 20 min. The catalyst was removed by filtration and the filtrate was evaporated to give 3,5-diaminophenyl dimethylcarbamate (III) as a residue. The residue was dissolved in 5 ml of N,N-dimethylformamide. 2,6-Lutidine (0.9 ml) and methyl iodide (3 g) were added and the solution was allowed to stand at room temperature for 12 hr. The precipitate that formed was collected on a filter. Recrystallization from methanol–ether gave 670 mg (63%) of 5-(dimethylcarbamoyloxy)-1,3-phenylenebis(trimethylammonium iodide) (IV).

For analysis, see Table IV.

Registry No.—Trimethylphenylammonium iodide, 98-04-4; II, 15925-97-0; IV, 23649-61-8.

Acknowledgment.—The authors are indebted to Mr. Ronald D. Deibel for his valuable assistance in the experimental work.

Studies of Benzonorbornene and Derivatives. II. The *ac*-Bromobenzonorbornenes and -dienes[1]

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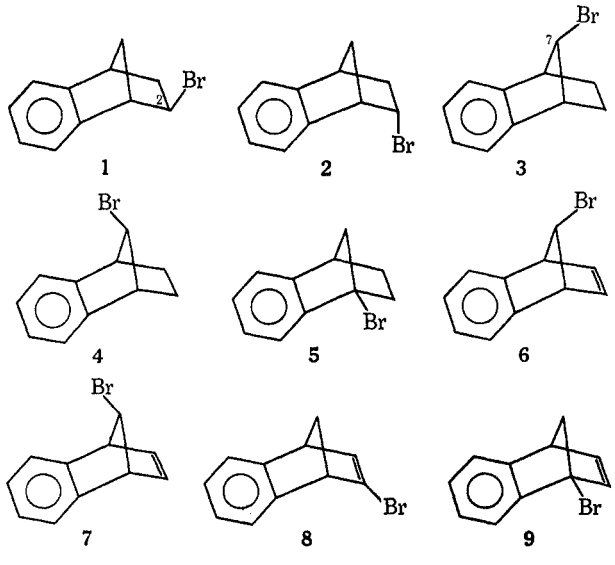
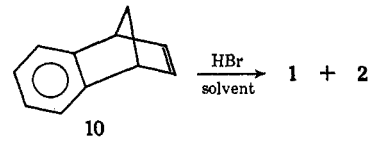
The synthesis and properties of the nine *ac*-bromobenzonorbornenes and -dienes are described. Addition of hydrobromic acid to benzonorbornadiene (**10**) produced the *exo*-2 bromide **1**. Its *endo* epimer **2** was prepared by diimide reduction of the vinylic bromide **8**. The *anti*-7 bromide **3** was obtained most simply by hydrogenolysis of the *exo*-2,*anti*-7 dibromide **13**, itself the addition product of **10** and bromine. Reaction of 1,2-dibromotetrachloroethane with **10** added bromine to afford the *trans*-2,3 dibromide **15** predominantly. Its rearrangement in hydrobromic acid produced some *exo*-2,*syn*-7 dibromide **17**, which was treated with zinc in ethanol to form the *syn*-7 bromide **4**. Application of the Hunsdiecker reaction on the corresponding acid afforded the bridgehead bromide **5**. The olefinic *anti*-7 bromide **6** resulted from **13** upon dehydrobromination. The highly reactive olefinic *syn*-7 bromide **7** was difficult to obtain, finally being synthesized *via* the tosylhydrazone of the *syn*-7-bromo ketone **24**. The vinylic bromide **8** was made from **15** by dehydrobromination. Treatment of **8** with hydrobromic acid produced some 1,*exo*-2 dibromide **27**, which could be dehydrobrominated to the bridgehead olefinic bromide **9**. The spectra of these compounds are tabulated and discussed briefly. Certain miscellaneous transformations in this system are mentioned as well.

There are nine *ac*-bromobenzonorbornenes and -dienes as shown (**1**–**9**), numbered according to Bartlett and Giddings.[3] Certain of them have been previously reported. Wiley and Barstow[4] have reported the preparation of **1** and **2** as mixtures. An earlier paper of this series[1a] has described the synthesis of **3** and **6**. Bromides **6** and **7** have also been prepared by Cristol and coworkers.[1d] The bridgehead bromide **5** was part of another study[5] and it is included here for completeness. Likewise, a preliminary report[1c] mentioning the sequence leading to **7** is here given in detail.



exo-2-**Bromobenzonorbornene** (**1**).—Wiley and Barstow[4] reported that the reaction of benzonorbornadiene (**10**) with hydrogen bromide in various solvents led to mixtures of **1** and the *endo* epimer **2**. Independently,



(1) (a) Paper I of this series: J. W. Wilt, G. Gutman, W. J. Ranus, Jr., and A. R. Zigman, *J. Org. Chem.*, **32**, 893 (1967). (b) The present paper is taken from the dissertation of P. J. C., Loyola University of Chicago, 1969. (c) Certain portions have appeared in preliminary form: J. W. Wilt and P. J. Chenier, *J. Amer. Chem. Soc.*, **90**, 7366 (1968), and the Great Lakes Regional Meeting of the American Chemical Society, Milwaukee, Wis., June 1968, Abstracts of Papers, p 36. (d) For related work, *cf.* S. J. Cristol and G. Nachtigall, *J. Org. Chem.*, **32**, 3727 (1967); S. J. Cristol and A. L. Noreen, *J. Amer. Chem. Soc.*, **91**, 3969 (1969).

(2) National Science Foundation Trainee, 1965–1968; University Fellow, 1968–1969.

(3) P. D. Bartlett and W. P. Giddings, *ibid.*, **82**, 1240 (1960).

(4) G. A. Wiley and L. E. Barstow, Abstracts of the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, paper 5K; L. E. Barstow, *Tetrahedron Lett.*, 6309 (1968).

(5) H. F. Dabek, Jr., dissertation, Loyola University of Chicago, Chicago, Ill., 1969.