Reactions of Phenylazirines with Anilines

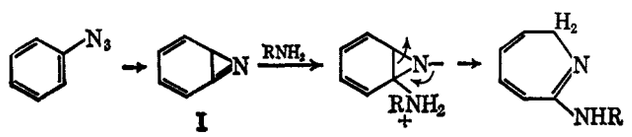
GERALD SMOLINSKY AND BERNICE I. FEUER

Bell Telephone Laboratories, Inc., Murray Hill, New Jersey 07971

Received September 9, 1965

Phenylazirine was heated for a short period with various substituted aniline derivatives. Following a mild aqueous acid work-up procedure, six types of products were identified: benzanilides, pyrazines, phenacylanilines, indoles, pyrroles, and enediamines. All but the first compound, benzanilide, can be obtained under suitable conditions from reactions of phenacylanilines with anilines. Mechanisms for the formation of the various products are presented.

Huisgen and co-workers reported[1] the interesting finding that the decompositions of phenyl azides in very dilute solutions of primary or secondary amines led to 2-amino-7H-azepines (II). They established that formation of the azepines involved ring expansion of the azides and postulated the following mechanism which invoked the formation of the unprecedented bicyclic azirine intermediate I. Since we have shown[2]



I II

that thermolysis of vinyl azides results in the formation of azirines, it seemed worthwhile to investigate reactions of phenylazirines with amines in the hope of gaining information about compounds related to I.

3-Phenyl-2H-azirine (IVa) or its precursor, α-azidostyrene (IIIa), was heated at 175° in a large excess of aniline for a short period. After mild acid hydrolysis it was possible to isolate a trace amount of 2,5-

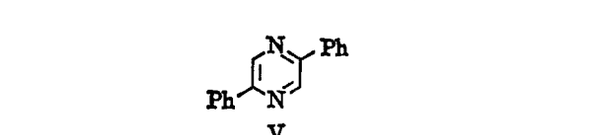
III IV

a, Ar = Ph
b, Ar = *p*-ClPh

diphenylpyrazine (V)[2] and larger quantities of benzanilide VIa and a high-melting substance (215° compound).

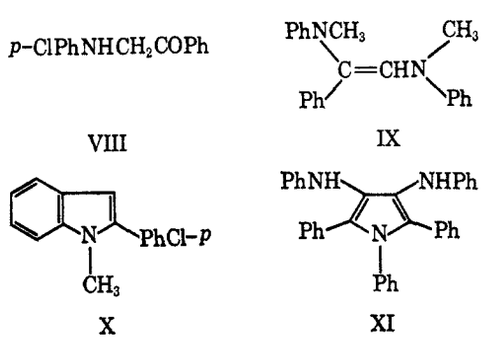
The reaction of IVa with hot *m*-chloroaniline, followed by the usual aqueous acid work-up, formed a small amount of pyrazine V and 25% of phenacyl-*m*-chloroaniline (VIII), but no benz-*m*-chloroanilide (VIb) or derivative of the 215° compound could be found. We were surprised at this apparent change in reaction course, and to test whether the *m*-chloro substituent had some special effect on product formation IVa was heated with *m*-toluidine. As in the original aniline reaction, benztoluidide VIc was obtained. No material corresponding to the 215° compound could be found. However, when *p*-chlorostyryl azide (IIIb) was heated in aniline and the products were isolated in the usual way, a 38% yield of *p*-chlorobenzanilide (VId) was obtained, along with 6% of a high-melting (194°) material with an ultraviolet spectrum almost identical with that of the 215° compound.

Mann and co-workers obtained the same 215° compound by heating phenacylaniline in excess ani-



V VII

VIa, X = Y = H
b, X = H; Y = Cl
c, X = H; Y = CH_3
d, X = Cl; Y = H



VIII IX X XI

line.[3a] They assigned structure VII to this compound on the basis of elemental analysis and ebullioscopic and cryoscopic molecular weight determinations. Although their data appeared compatible with structure VII, the mass spectrum of this material exhibited a parent peak with *m/e* at 477 rather than at 479 as required. Clearly their assignment must be incorrect. This substance is actually 3,4-dianilino-1,2,5-triphenylpyrrole (XI).

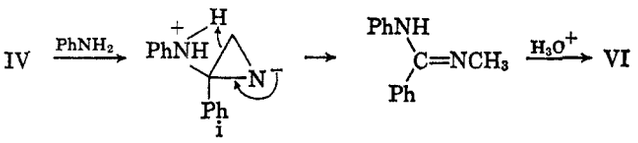
Our assignment of structure XI to the 215° compound is based on the following evidence. The elemental analysis and molecular weight (as determined by mass spectrometry) are compatible with structure XI. The nmr spectrum indicates the absence of aliphatic hydrogen, while the infrared spectrum shows the presence of an N–H group. Furthermore, after recrystallization from O-deuterioethanol, the molecular weight of the 215° compound increases from 477 to 479, indicating the presence of two readily exchangeable hydrogens. In addition, the elemental analysis of the chloro derivative (see above) shows a Cl:N ratio of 2:3 and establishes that the 215° compound contains two azirine and three aniline moieties. Finally,

(1) M. Appl and R. Huisgen, *Ber.*, **92**, 2961 (1959); R. Huisgen and M. Appl, *ibid.*, **91**, 12 (1958); R. Huisgen, D. Vossius, and M. Appl, *ibid.*, **91**, 1 (1958).

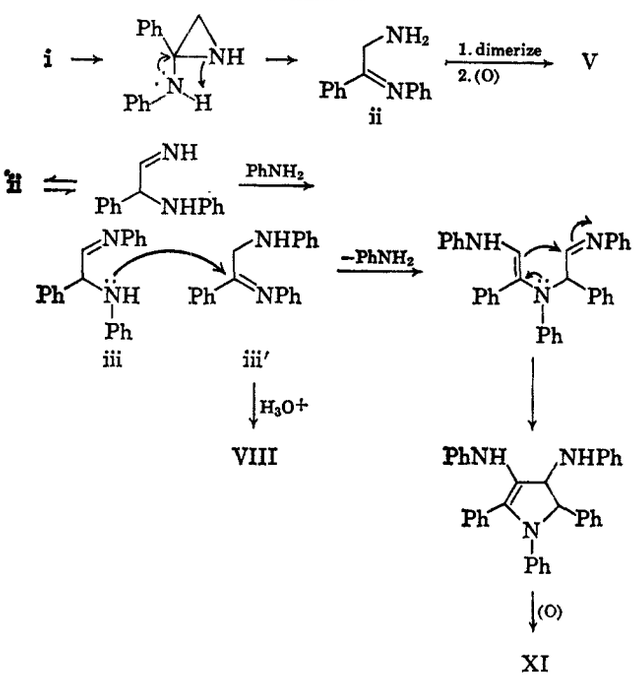
(2) G. Smolinsky, *J. Org. Chem.*, **27**, 3557 (1962).

(3) (a) A. F. Crowther, F. G. Mann, and D. Purdie, *J. Chem. Soc.*, 58 (1943); (b) F. Brown and F. G. Mann, *ibid.*, 847 (1948); (c) *ibid.*, 858 (1948).

SCHEME I



SCHEME II



the mass spectrometric cracking pattern is consistent with this assignment.

Although no single piece of evidence presented above is in itself conclusive, the sum total, in conjunction with reasonable postulated reaction paths for azirines or phenacylanilines with aniline, compels one to the conclusion stated.

Heating azirine IVa with N-methylaniline gave 6% of V and 30% of a $C_{22}H_{22}N_2$ compound. The nmr spectrum of this latter material suggested the presence of two different N–CH_3 groups and the absence of any other aliphatic hydrogen. Its mass spectrometric cracking pattern revealed a parent peak at an *m/e* ratio of 314 along with two major fragments appearing at 196 and 118, as well as fragments having lost components of *m/e* of 15, 29, 77, and/or 106. These data are consistent with a structure such as IX.[3a]

When phenylazirine IVa was heated in cyclohexylamine, only diphenylpyrazine V (14%) could be isolated from the product mixture. Heating IVa in N,N-dimethylaniline resulted in no apparent reaction.

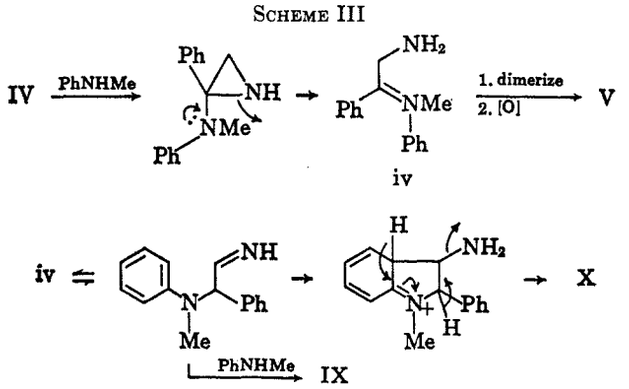
From the pyrolysis of *p*-chlorostyryl azide in N-methylaniline, there was obtained a 66% yield of 1-methyl-2-(*p*-chlorophenyl)indole (X). This was the only isolable product.

The rationale of azirine–aniline reactions appears to be closely related to that of phenacylaniline chemistry.[3] Under the influence of acidic catalysts, phenacylanilines cyclize to 2- and/or 3-arylindoles.[3] When heated with anilines in the absence of acids, products such as IX and XI can form. Azirines react with anilines to give complex product mixtures from which it has been possible to isolate as many as three compounds. However, it is very likely that all of the azirine–aniline reactions discussed above lead to mixtures of the same products, albeit in different ratios. Which compound is actually isolated depends upon a combination of its ease of purification as well as its proportion in the product mixture. All the products can be rationalized as arising from the common intermediate i. For example, benzanilides VI could be formed by hydrolysis of the product obtained when the aziridine ring in i opens by breaking the C–C bond (Scheme I).

Alternatively, i can open in another way to give a second intermediate, ii, which can undergo reactions leading to V, VIII, and XI (Scheme II).

When N-methylaniline rather than aniline is employed as a reactant, then some of the intermediates become trapped because there is now a methyl group rather than a second proton in the aniline. For example, a tautomer of the intermediate corresponding to iii is actually isolated as compound IX (Scheme III).

SCHEME III



One might think that indole X was formed directly from IX by a cyclization process; however, Mann found[3a] that a derivative of IX could not be converted to an indole with a variety of reagents.

The fact that benzanilides VI were obtained from some of these phenylazirine–aniline reactions strikes us as being so unexpected as to require additional comment. As previously mentioned, the reactions of phenylazirine with aniline parallel in many ways the reactions of phenacylamines with aniline. All the compounds obtained from the former system can be gotten from the latter, except for the benzanilides. Obviously the latter came about as a result of opening the ring in aziridine intermediate i in such a way as to break a carbon–carbon bond. This mode of ring opening is especially puzzling in view of the fact that there appears to be no apparent reason for i to undergo such a reaction. We are unable to offer an explanation for this observation but feel that there may be something special about an aziridine ring system which causes the carbon–carbon bond to rupture.[4]

It should be noted that in Huisgen's suggested mechanism for the formation of II from phenyl azide and aniline, the aziridine intermediate must undergo

(4) H. W. Heine and R. Peavy, *Tetrahedron Letters*, 3123 (1965). These workers reported that boiling 1,2,3-triphenylaziridine with diethyl acetylenedicarboxylate in toluene gave 98% 1,2,5-triphenyl-3,4-dicarbethoxy-3-pyrroline.

carbon–carbon bond rupture. We feel our results lend support to this proposal of Huisgen, *et al.*[1]

Experimental Section[5]

α-Azidostyrene (IIIa).—This compound was prepared as described elsewhere.[2]

α-Azido-*p*-chlorostyrene (IIIb).—Commercially available *p*-chlorostyrene was dissolved in carbon tetrachloride and treated dropwise with a slight excess of bromine. The reaction solution was then washed with dilute sulfurous acid, followed by water, and finally with saturated potassium bicarbonate solution. After drying the solution over anhydrous sodium sulfate, the carbon tetrachloride was removed at reduced pressure. The yield of solid dibromide was approximately quantitative.

This material was converted to the styryl azide by the method described previously.[3] The infrared spectrum exhibited the characteristic absorption of styryl azides[2] at 4.5–4.75 μ.

3-Phenyl-2H-azirine (IVa).—This compound was prepared as previously described[2] and was found to be stable over long periods if stored at liquid nitrogen temperature. *Care should be exercised in handling this compound in that it is very irritating to the skin and prolonged or repeated contact can cause sensitization which may lead to an allergic reaction.*

Pyrolysis of 3-Phenyl-2H-azirine (IVa).—Either 3-phenyl-1H-azirine (IVa) of α-azidostyrene (IIIa), which is converted to IVa under the reaction conditions, was heated with a number of primary and secondary amines. The following standardized procedure was used. A large excess of amine was maintained at the boiling point or 175–180°, whichever was lower, and the azirine IV or azidostyrene III was added dropwise. Heating was continued for 5–10 min after the addition was completed. If gas was evolved, the reaction temperature was maintained for 5–10 min after bubbling ceased. The reaction mixture was distilled under reduced pressure (water aspirator) almost to dryness. The residue was dissolved in methylene chloride, washed well with dilute hydrochloric acid, followed by water, and 1 *N* carbonate, and dried over anhydrous potassium carbonate; the methylene chloride was removed under reduced pressure. The residue was treated as described under the individual reactions listed below.

A. In Cyclohexylamine.—Azirine IVa (6 g, 51 mmoles) was added to 150 ml of boiling cyclohexylamine and the reaction was carried out as described above. The residue was treated with ether. The ether-insoluble material (820 mg, 14%) had a melting point of 193–196° and was shown to be 2,5-diphenylpyrazine (V) by comparison with an authentic sample.[6] The ether-soluble material was intractable.

Styryl azide IIIa (4.6 g, 32 mmoles) in 125 ml of cyclohexylamine treated as above yielded 464 mg (13%) of 2,5-diphenylpyrazine (V).

B. In Aniline.—Azirine IVa (9.5 g, 81 mmoles) was added to 200 ml of aniline at ~175°. The work-up is outlined in Chart I. The total crude residue (R_a) was treated with about 50–60 ml of hot ethanol. Crystals (C_a) appeared upon cooling, and additional C_a was obtained when the solution was concentrated to about half the original volume. C_a was collected (200 mg, 2%) and recrystallized from benzene–ethanol, mp 197–199°, and identified as 2,5-diphenylpyrazine (V).[6]

The residue (R_b) from the above mother liquors was transferred to a sublimation apparatus and heated at 100° (0.001 mm) overnight. The crystalline sublimate (C_b), which weighed approximately 2.8 g, was washed with ether and recrystallized from benzene–hexane (mp 163–164°). C_b was found to be identical with authentic benzanilide (VIa).

The residue (R_c) from the sublimation was treated with hot ethanol (~40 ml); the ethanol-insoluble material, C_c was collected. The ethanol solution was evaporated to dryness, and the crystalline residue was washed with ether and identified as additional benzanilide (VIa), C_b, 1.7 g (total yield 22%).

Crystals, C_c (1.61 g, 9%) had a melting point, taken in an evacuated capillary, of 215–217° and could be recrystallized from benzene–ethanol. The ultraviolet spectrum of C_c in ethanol exhibited a shoulder (ϵ_{280} 24,200), a maximum (ϵ_{250} 36,400), and a minimum (ϵ_{227} 22,400). C_c, compound XI, had an identical melting point, mixture melting point, and infrared spectrum (chloroform solution) with a sample prepared from the reaction of aniline and phenacyl aniline by the procedure of Mann and co-workers.[3a]

Anal. Calcd for $C_{34}H_{27}N_3$: C, 85.50; H, 5.70; N, 8.80; mol wt, 477. Found: C, 85.3; H, 6.1; N, 8.7; mol wt, 477.

The mass spectrometric cracking pattern of this material showed a parent peak at an *m/e* ratio of 477 along with several major fragments appearing at 386, 385, 282, 280, 197, 193, 180, 165, 105, 93, and 77.

When styryl azide IIIa was pyrolyzed in aniline as described above, 8% benzanilide (VIa) and 24% XI were isolated from the reaction mixture.

C. In *m*-Chloroaniline.—Phenylazirine IVa (6.2 g, 55 mmoles) was added to 150 ml of *m*-chloroaniline maintained at ~175°. The crude residue obtained was warmed with ether. The ether-insoluble material weighed 300 mg (9%) and was identified as 2,5-diphenylpyrazine (V).[6] The ether-soluble material proved to be intractable.

Styryl azide IIIa (3.9 g, 27 mmoles) was added to hot (~175°) *m*-chloroaniline. The total crude product was transferred with the aid of methylene chloride to a sublimation apparatus and heated at 120° (0.001 mm) for 48 hr. The crystalline sublimate (1.6 g, 25%) was recrystallized from ethanol (mp 134–136°) and shown to be N-phenacyl-3-chloroaniline (VIII) by comparison with an authentic sample.[7]

D. In N-Methylaniline.—Phenylazirine IVa (6.2 g, 55 mmoles) was added to 120 ml of hot (~175°) N-methylaniline. The crude product was stirred with ether (50 ml), leaving undissolved 440 mg (6%) of 2,5-diphenylpyrazine (V)[6] (mp 193–197°). The ether-soluble material was transferred to a sublimation apparatus and heated at 120° (0.001 mm) overnight. The crystalline sublimate (5.3 g, 30%) was recrystallized from benzene–hexane: mp 144–145°; the ultraviolet spectrum in ethanol exhibited three maxima (ϵ_{314} 15,700, ϵ_{237} 14,800, ϵ_{241} 12,500), and a shoulder (ϵ_{231} 14,300). The nmr spectrum exhibited two sharp peaks at δ 2.94 and 3.06 with an integrated area of three protons each, and a multiplet in the region δ 6.3–7.3 of 16 protons. This material was designated as IX.

Anal. Calcd for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N, 8.91; mol wt, 314.41. Found: C, 83.7; H, 6.5; N, 9.1; mol wt 314 (mass spectrum).

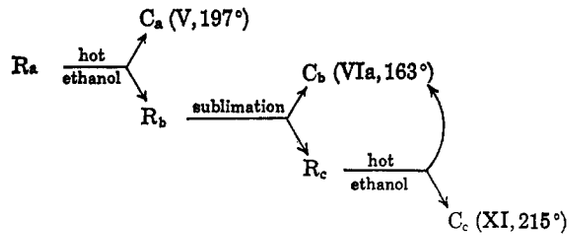
The residue from the sublimation proved to be intractable.

When the reaction was carried out using styryl azide IIIa instead of phenylazirine IVa only IX (mp 144–145°) was identified among the reaction products, in 25% yield.

E. In *m*-Toluidine.—Styryl azide IIIa (2.4 g, 17 mmoles) was added to 200 ml of *m*-toluidine maintained at ~175°. The crude material was heated in a sublimation apparatus at 150° (0.001 mm) for 2 days. The sublimate (3 g), in benzene, was passed through a 60-g column of Merck acid-washed alumina. The compound, after chromatography, was recrystallized from cyclohexane containing a few drops of benzene and had a melting point of 123–124°. This material was identified as benz-*m*-toluidide (Vc) by comparison of its properties with those of an authentic sample.

F. Pyrolysis of *p*-Chlorostyryl Azide IIIb in Aniline.—*p*-Chlorostyryl azide IIIb (5.6 g, 31 mmoles) was added to 100 ml of hot (~175°), stirred aniline. The crude product was heated in a sublimation apparatus at 120° (0.001 mm) overnight. The sublimate was (2.7 g, 38%) recrystallized from ethanol (mp 195–197°) and was identified as *p*-chlorobenzanilide (VId) by comparison with an authentic sample.

CHART I
FLOW DIAGRAM OF AZIRINE IVa–ANILINE WORK-UP



(5) Boiling and melting points are uncorrected. Ultraviolet spectra were determined with a Cary 15 recording spectrophotometer, and infrared spectra on an Infracord. The nmr spectra were determined in carbon tetrachloride on a Varian A-60 instrument with tetramethylsilane used as an external standard.

(6) L. Wolff, *Ber.*, **20**, 432 (1887).

(7) A. Bischler, *ibid.*, **25**, 2867 (1892).

The residue from the sublimation was recrystallized several times from benzene–ethanol (500 mg, 6%) and had a melting point of 191–194° (evac. cap.). The ultraviolet spectrum in ethanol showed two maxima (ϵ_{286} 26,400, ϵ_{250} 31,700) and two minima (ϵ_{289} 25,000, ϵ_{232} 24,700).

Anal. Calcd for $C_{34}H_{25}Cl_2N_3$: C, 74.72; H, 4.57; Cl, 12.98; N, 7.69. Found: C, 74.3; H, 4.9; Cl, 13.1; N, 7.6.

G. Pyrolysis of *p*-Chlorostyryl Azide IIIb in N-Methylaniline.—*p*-Chlorostyryl azide IIIb (6.1 g, 34 mmoles) was added to 150 ml of N-methylaniline maintained at ~175°. The total crude product was taken up in benzene and passed through two columns of 120 g of Merck alumina each. The material eluted from the columns was crystallized from cyclohexane: mp 123–123.5°. The ultraviolet spectrum in ethanol exhibited two maxima (ϵ_{303} 19,500, ϵ_{242} 18,500) and two minima (ϵ_{265} 5200, ϵ_{237} 18,200). This material was identified as 1-methyl-2-(*p*-chlorophenyl)indole (X) by comparison of its properties with those of an authentic sample.[3o] The yield of X was about 60%.

Synthesis and Azidolysis of 2-Chlorotetramethylguanidine. Synthetic Utility of Hexa- and Tetramethylguanidinium Azide

ANTHONY J. PAPA

The Fabrics and Finishes Department, E. I. Du Pont De Nemours and Company, Wilmington, Delaware

Received October 15, 1965

2-Chloro- and 2-bromotetramethylguanidine were synthesized by the direct halogenation of 1,1,3,3-tetramethylguanidine. (*Caution:* These compounds are explosive and should not be heated above 50° at atmospheric pressure.) An investigation of halide replacement with sodium azide was undertaken. In acetonitrile, the reaction afforded β-dimethylaminoacrylonitrile in 66% yield. Bis(dimethylamino)carbene and 3,3-bis(dimethylamino)propionitrile are proposed as intermediates in the reaction mechanism. When dimethylformamide was employed in place of acetonitrile, hexamethylguanidinium azide was obtained in 16% yield. This azide is representative of a class of organic azides which possess the property of being both thermally stable and a highly reactive source of azide ion. A synthesis of tetramethylguanidinium azide and its use in an improved synthesis of alkyl azides and 5-substituted tetrazoles is also described.

Although a few N-halo guanidines substituted on the imino nitrogen have been reported,[1] tetrasubstituted guanidine derivatives have not hitherto been described. The present work was undertaken in an effort to synthesize a 2-halotetrasubstituted guanidine and to study the chemistry of this new class of compounds.

2-Chloro- and 2-bromotetramethylguanidine have been obtained by direct liquid-phase halogenation with chlorine and bromine in carbon tetrachloride solution in 76 and 59% yield, respectively. The reaction proceeds readily at 0–10°, and the insoluble tetramethylguanidine hydrohalide by-product separates from solution during the addition of halogen. Initial attempts to apply the preparative procedures to tetramethylguanidine using sodium hypohalite were unsuccessful. It was subsequently shown that 2-halotetramethylguanidine derivatives are sensitive to hydrolysis and must be prepared in nonaqueous systems.

$$2[(CH_3)_2N]_2C{=}NH + X_2 \longrightarrow [(CH_3)_2N]_2C{=}NX + [(CH_3)_2N]_2C{=}\overset{+}{N}H_2X^-$$

I, X = Cl
II, X = Br

Compounds I and II are pale yellow liquids which possess a strong ozonelike odor and rapidly oxidize iodide ion to iodine in acetone solution. The N-halo derivatives are quite unstable, each decomposing to some extent on standing at 0° for several weeks. The least stable was II, which turned orange on standing in air at room temperature for 30 min with the separation of a substantial quantity of tetramethylguanidine hydrobromide. Samples of I have been stored for months under refrigeration and protection from light with slight decomposition. The decomposition products of I include the hydrochlorides of a mixture of self-chlorinated products. *Caution must be exercised when working with these compounds since explosion results when heated at a temperature above 50° at atmospheric pressure.*

The instability of I and II precluded an accurate elemental analysis. The characterization and the location of the halogen on the imino nitrogen were evident from infrared spectral studies. The spectra exhibited an absorption band at 6.48 μ attributable to stretching frequency of the >C=NX group and showed the disappearance of N–H stretching at 3.1 μ. A proton nmr spectrum of I consists of two singlets of equal intensities at 2.68 and 2.81 ppm. Starting tetramethylguanidine shows two singlets at 5.26 and 2.60 ppm in a ratio of 1:12.

The observed singlets in I could be due to interaction between the chlorine group and one of the dimethylamino groups. Interestingly, the spectrum of dimethyl N-chloroiminocarbonate[2] has been found to consist of a singlet peak at 3.89 ppm as low as −60°. This difference is attributed to the failure of the methyl protons and the =NCl group of the iminocarbonate to come into intramolecular proximity to produce a chemical shift.

Further support for the assigned structures of I and II was obtained by treating them with triphenylphosphine to give the 1,1,2,2-tetramethyl-3-(triphenylphosphoranylidene)guanidinium halide (III).

$$\text{I (II)} + (C_6H_5)_3P \longrightarrow \underset{\text{III}}{\{[(CH_3)_2N]_2C{=}N{=}P(C_6H_5)_3\}^+X^-}$$

The structure of the salt III obtained from II was confirmed by carbon and hydrogen analysis, infrared spectra, and the formation of the corresponding tetramethylguanidine hydrohalide and triphenylphosphine

(1) (a) J. Goerdeler and K. Doerk, *Ber.*, **95**, 154 (1962); (b) J. Goerdeler and M. Willig, *ibid.*, **88**, 1071 (1955); (c) C. K. Morehouse and R. Glicksman, *J. Electrochem. Soc.*, **104**, 467 (1957); (d) G. F. Wright, *Can. J. Chem.*, **30**, 62 (1952); (e) I. Kamenski, *Ber.*, **11**, 1600 (1878).

(2) Synthesized according to the procedure of J. Houben and E. Schmidt, *ibid.*, **46**, 2447 (1913).