tained by Servis[7] for the trinitro complex **1** (R = $OCH_3$) give $\Delta\delta$ 0.25 ppm for H-3,5; a quantitative comparison of the magnitude of this value with that obtained for H-3 in this study is not meaningful because of the difference in solvent employed. The large $\Delta\delta$ observed for H-6 is consistent with expectation; conventional canonical structures for the ions would localize charge at H-2,4,6 at the expense of H-3,5. The difference in $\Delta\delta$ values for H-3 and H-5 may reflect a difference in charge density at the two positions resulting from the presence of the nitro substituents. However, it is unlikely that these $\Delta\delta$ values are representative solely of charge density differences. The anisotropy of the substituent groups may well change on the transition from aromatic substrate to complex[35] and any nonqualitative charge density determinations based on $\Delta\delta$ values would have to provide an anisotropy correction term.

The results of this study demonstrate that the alkoxyl complexes of dinitro-substituted aromatic ethers are structurally similar to those of the more stable trinitro-substituted Meisenheimer complexes[5] and are best represented by the covalent, rather than the charge-transfer complex, structures. The isolation of the methoxyl complex of 2,4-dinitroanisole provides further evidence for the previously suggested mechanism of symmetrical methoxyl exchange reactions in methanol in which the formation of an intermediate between methoxide ion and 2,4-dinitroanisole was proposed to be rate determining.[10]

**Registry No.**—**5**, 119-27-7; **6**, 610-54-8.

# A Novel Synthesis of N,N',N''-Trisubstituted Guanidines

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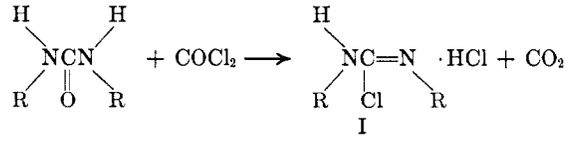
The action of phosgene on N,N'-disubstituted ureas is described in literature as giving a variety of products depending upon the reaction conditions. However, in no instance has the formation of N,N',N''-trisubstituted guanidines been reported from the above reaction. A novel synthesis is now presented in which these aforementioned guanidines are obtained. This reaction involves the phosgenation of N,N'-dialkyl- or N-alkyl-N'-arylureas at temperatures between 110 and 120° in an inert solvent such as monochlorobenzene. In the case of symmetrically disubstituted alkylureas, the N,N',N''-trialkylguanidines in the form of their hydrochloride salts are obtained. Unsymmetrically substituted ureas upon phosgenation also give guanidines, the type of which, in terms of their substituents, is dependent upon the ability of the urea nitrogen to act as a nucleophile as well as the steric nature of the substituent itself. Thus, phosgenation of N-cyclohexyl-N'-phenylurea gives N,N'-dicyclohexyl-N''-phenylguanidine exclusively. In cases where the substituents on nitrogen atoms of the urea molecule are alike in electron-donating abilities, product distributions are obtained, as with N-cyclohexyl-N'-isopropylurea. Where one urea nitrogen is strongly deactivated, as with N-cyclohexyl-N'-trifluoroethylurea, there is no indication of guanadine formation. Different types of compounds are isolated from these reactions. A mechanism is proposed to account for these observed patterns.

The preparation of symmetrically trisubstituted guanidines was described in 1869 by Hofmann,[1] who prepared the triphenyl derivative from the reaction of diphenylthiourea with iodine in the presence of excess aniline. Twenty-five years later, Nef[2] uncovered a new method which encompassed the reactions of isocyanide dichlorides with substituted primary amines. This valuable reaction can also be adapted to the synthesis of pentasubstituted guanidines by reaction with secondary amines. Preparation of guanidines in which the substituents are not identical was reported by Schenck and Kirchhof,[3] who accomplished the synthesis of N,N'-dimethyl-N''-ethylguanidine through the reaction of trimethylpseudothiourea with ethylamine. Other experimenters devised methods of synthesizing trisubstituted guanidines which involve alkylation of thioureas. Cronshaw and Naughton[4] employed diphenylthiourea and aniline hydrochloride in the presence of lead carbonate while Heuser[5] obtained tritolylguanidine from ditolylthiourea and *o*-toluidine in the presence of lead oxide. The formation of trimethylguanidine by the successive methylamination of iodocyanogen was described by Schenck.[6]

Snedker[7] reported that the reaction of aniline hydrochloride with diphenylcarbodiimide formed the hydrochloride salt of symmetrical triphenylguanidine.

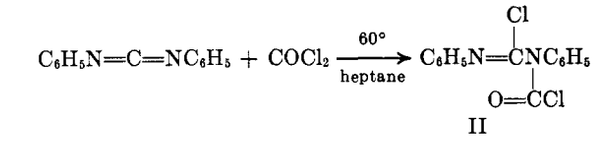
Reactions of phosgene with ureas have been extensively investigated only in the last 10 years. Reaction conditions such as temperature, steric effects, and solvent play an important part in determining the final products. As late as 1957, Shinqu[8] reported that phosgene does not react with symmetrical diphenylurea below 110° but readily forms phenylisocyanate and hydrogen chloride above 120°. In 1960, a review was published by Eilingsfeld[9] which related to various types of imido chlorides. It was stated that disubstituted ureas react with phosgene to form chloroformamidine hydrochlorides (I). The reactions



are run at 0–60°, thus negating, in part, the conclusion of Shinqu. Upon heating, the chloroformamidine hydrochloride is transformed into a disubstituted

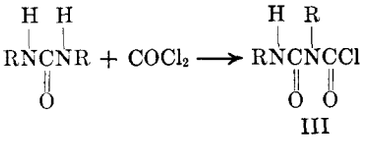
(1) A. W. Hofmann, *Ber.*, **2**, 453 (1869).
(2) J. U. Nef, *Ann.*, **270**, 282 (1892).
(3) M. Schenck and H. Kirchhof, *Z. Physiol. Chem.*, **154**, 292 (1926).
(4) J. Cronshaw and W. Naughton, British Patent 224,376 (1923).
(5) R. Heuser, U. S. Patent 1,437,419 (1923).
(6) M. Schenck, *Z. Physiol. Chem.*, **150**, 121 (1925).
(7) S. J. C. Snedker, *J. Soc. Chem Ind.*, (London), **46**, 353T (1927).
(8) H. Shinqu, T. Nishimura, and T. Takeqomi, *Yuki Gosei Ragaku Kyoknai Shi*, **15**, 140 (1957).
(9) H. Elingsfeld, H. Seefelder, and H. Weidinger, *Angew. Chem.*, **73**, 836 (1960).

carbodiimide accompanied by the loss of hydrogen chloride. Fisher,[10] in 1963, described the reaction of phosgene with carbodiimides to give symmetrical disubstituted N-chloroformylchloroformamidines (II).



II

Ulrich and Sayigh[11] demonstrated that the above reaction succeeds with diphenylthiourea and with dibutylurea in the presence of triethylamine and excess phosgene. However, in no instance did these experimenters report on the formation of guanidines from the reactions of ureas and phosgene. Ulrich[12] reported, in addition, that the reaction of phosgene with symmetrically disubstituted alkylureas resulted in the formation of symmetrical dialkylallophonyl chlorides (III). He indicated that this product and chloroamidine hydrochlorides both form from this reaction sequence, the distribution of which is dependent upon the nature of the substituent and the polarity of the solvent.



III

In the work presented herein, the formation of guanidines, both symmetrical and unsymmetrical, is reported as resulting from the reaction of disubstituted ureas with phosgene at 115°. Further, the distribution of guanidine types is directly related to the electronic nature of the substituent groups on the reacting urea. Finally, a mechanism is proposed to account for the formation of the various guanidines.

## Experimental Section

**Preparation of N,N′-Disubstituted Ureas.**—The substituted ureas were prepared by a well-established reaction sequence. A 10% solution of the appropriate isocyanate in hexane was added at room temperature with stirring to a 10% hexane solution of the required primary amine. The addition rate was such that the temperature did not rise above 30° and a 10% molar excess of the amine was used in all cases. The white precipitates that formed were filtered, washed three times with hexane, and dried *in vacuo*. Yields were nearly quantitative in all cases. The following N,N′-disubstituted ureas, identified by melting points and infrared spectra, were prepared in this manner: dicyclohexyl-, cyclohexylisopropyl-, cyclohexyltrifluoroethyl-, cyclohexylethyl-, isopropylphenyl-, cyclohexylphenyl-, and diphenylurea.

**Reactions of Phosgene with N,N′-Disubstituted Ureas. Reaction of Dicyclohexylurea with Phosgene.**—To a solution of 19.1 g (0.085 mole) of N,N′-dicyclohexylurea in 250 ml of monochlorobenzene, a solution of 10.1 g (0.102 mole) of phosgene (a 20% molar excess) in 96 g of monochlorobenzene was added dropwise with stirring over a period of 1.5 hr. The addition temperature was held at 115°. The appearance of a white solid was noted. The temperature was then raised to 120–130° and the system was purged with nitrogen for 15 min to remove excess phosgene. The solution was cooled; the precipitate was filtered, washed with low-boiling petroleum ether (bp 35–60°), and dried *in vacuo*. N,N′,N″-Tricyclohexylguanidine hydrochloride (11.9 g) was isolated, mp 291–292°. *Anal.* Calcd for $C_{19}H_{36}N_3Cl$: C, 66.73; H, 10.61; N, 12.29; Cl, 10.37. Found: C, 66.5; H, 10.8; N, 12.5; Cl, 10.5.

A similar procedure was conducted, but in the presence of a large excess of phosgene. It consisted of the addition of phosgene gas into a stirred solution of dicyclohexylurea (25.0 g, 0.104 mole) in 250 ml of monochlorobenzene at a rate of 1.0 g/min for 2 hr. The temperature was maintained at 115°. A white crystalline solid formed as before. After the addition of phosgene was completed, the reaction mixture was purged with nitrogen for 15 min at 125–130° to remove the excess phosgene. The solution was cooled; the white crystals were filtered, washed with hexane, and dried *in vacuo*. This resulted in isolation of 11.2 g of a white solid which, by mixture melting point and infrared spectra, was shown to be identical with 1,2,3-tricyclohexylguanidine hydrochloride isolated in the preceding experiment. This amount corresponds to a 64% yield.

**Reaction of N-Cyclohexyl-N′-isopropylurea with Phosgene.**—Using a procedure analogous to that described for the tricyclohexylguanidine derivative and employing N-cyclohexyl-N′-isopropylurea (25.0 g, 0.136 mole) and a large excess of phosgene, 10.6 g of a white, solid reaction product was isolated. Elemental analyses indicated that this solid was a mixture of the two possible N,N′,N″-trisubstituted guanidines, N-cyclohexyl-N′,N″-diisopropyl- and N,N′-dicyclohexyl-N″-isopropylguanidine hydrochloride. The two materials were separated by fractional crystallization from water. The less soluble of the two, N,N′-dicyclohexyl-N″-isopropylguanidine hydrochloride, was isolated as a white crystalline solid, mp 282–283°. *Anal.* Calcd for $C_{16}H_{32}N_3Cl$: C, 63.7; H, 10.6; N, 13.9. Found: C, 63.2; H, 10.7; N, 13.9. The water-soluble filtrate was reduced in volume and a white crystalline solid was isolated. It was dried *in vacuo* and analyzed. It was N-cyclohexyl-N′,N″-diisopropylguanidine hydrochloride, mp 287–289. *Anal.* Calcd for $C_{13}H_{28}N_3Cl$: C, 59.7; H, 10.7; N, 16.0. Found: C, 60.6; H, 10.8; N, 15.2. The isolated material corresponded to an approximate product distribution of two to one of the dicyclohexylmonoisopropylguanidine hydrochloride to the monocyclohexyldiisopropylguanidine hydrochloride, with yields of 41 and 18%, respectively, based on the starting ureas.

**Reaction of N-Cyclohexyl-N′-ethylurea.**—Using the same procedure as previously described and employing N-cyclohexyl-N′-ethylurea (17.0 g, 0.10 mole) and 13.0 g of phosgene (0.13 mole), 7.3 g of N-cyclohexyl-N′,N″-diethylguanidine hydrochloride was isolated, mp 237–241°. This corresponds to a 31.4% yield. *Anal.* Calcd for $C_{11}H_{24}N_3Cl$: C, 56.7; H, 10.3; N, 18.0; Cl, 15.1. Found: C, 57.6; H, 10.3; N, 17.8; Cl, 14.9.

**Reaction of N-Cyclohexyl-N′-trifluoroethylurea.**—Employing 19.6 g (0.087 mole) of N-cyclohexyl-N′-trifluoroethylurea and an excess of phosgene, the reaction was conducted in the aforementioned manner. However, the reaction did not yield solid material as in previous cases. Removal of the solvent resulted in the isolation of 19.8 g of an amber oil, the distillation of which yielded 16.4 g of N-cyclohexyl-N′-trifluoroethylchloroformylchloroformamidine, bp 100° (0.3 mm), $n^{30}D$ 1.4605. *Anal.* Calcd for $C_{10}H_{13}N_2OCl_2F_3$: C, 39.4; H, 4.3; N, 9.2; Cl, 23.3; F, 18.7. Found: C, 39.6; H, 4.3; N, 9.0; Cl, 24.0; F, 18.8. The mass spectrum of this compound also corroborates this structural formula with a mass peak at 206, corresponding to the molecular weight of the carbodiimide, and peaks which would be associated with phosgene. The yield, based on 1 mole of urea giving 1 mole of chloroformylchloroformamidine, is 62%.

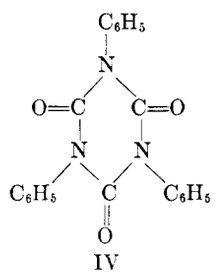
**Reaction of N-Cyclohexyl-N′-phenylurea with Phosgene.**—No crystalline product resulted from the reaction of N-cyclohexyl-N′-phenylurea with a 20% molar excess of phosgene by the aforementioned procedure. Consequently, the volatiles were removed by vacuum distillation at 60°. Analysis of distillate by vapor phase chromatography showed that the liquid contained approximately equimolar amounts of phenylisocyanate and cyclohexylisocyanate. The oily residue was washed with heptane, dissolved in 50 ml of ethanol, and then 150 ml of water was added. The aqueous phase was then extracted with ether. To the aqueous portion was added 2 ml of 2 *N* $Na_2CO_3$. This gave a white precipitate which was washed with water, recrystallized from acetone, and dried, giving 2.4 g of N,N′-dicyclohexyl-N″-phenylguanidine, mp 167–168°. *Anal.* Calcd for $C_{19}H_{29}N_3$: C, 76.4; H, 9.8; N, 14.1. Found: C, 76.5; H, 9.6; N, 14.5. The yield was 17.4%. The structure was confirmed by nuclear magnetic resonance spectroscopy.

**Reaction of N-Isopropyl-N′-phenylurea with Phosgene.**—Employment of the aforementioned procedure and utilizing 16.4

(10) P. Fisher, German Patent 1,131,661 (1963).
(11) H. Ulrich and A. Sayigh, *J. Org. Chem.*, **28**, 1427 (1963).
(12) H. Ulrich, J. Tilley, and A. Sayigh, *J. Org. Chem.*, **29**, 2401 (1964).

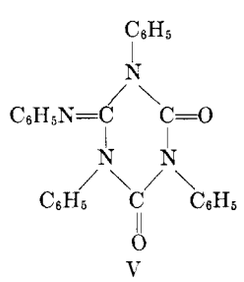
g (0.092 mole) of N-isopropyl-N′-phenylurea and a 20% excess of phosgene produced no solid material in the reaction mixture. The solvent was removed by vacuum distillation and found, by vapor phase chromatography, to contain isopropylisocyanate and phenylisocyanate in an approximate 1:3 *M* ratio. The residue was washed with heptane, resulting in the formation of 7.0 g of white solid. The solid was extracted with water, the water-soluble portion neutralized with aqueous caustic, and the resulting solid recrystallized from heptane. This yielded 2.0 g of N,N′-diisopropyl-N″-diphenylguanidine, mp 131–132°. *Anal.* Calcd for $C_{13}H_{21}N_3$: C, 71.3; H, 9.6; N, 19.2. Found: C, 71.3; H, 10.0; N, 19.1. The structure was confirmed by nuclear magnetic resonance spectroscopy. The yield was 20.8%.

**Reaction of N,N′-Diphenylurea with Phosgene.**—Utilization of the standard procedure with the employment of diphenylurea (25.0 g, 0.118 mole) and a large excess of phosgene did not result in the precipitation of a white solid. Consequently, the solvent was removed by vacuum distillation, leaving behind 20.3 g of an amber oil. Further distillation of this residue (140°, 0.2 mm) yielded fractions corresponding to phenylisocyanate (1.0 g), diphenylcarbodiimide (6.8 g), and a white solid residue (8.2 g). It was noted that phosgene was evolved during this procedure. Extraction of the latter solid with acetone resulted in a separation into two products. The acetone-soluble portion (3.0 g) was isolated by evaporation of the solvent, recrystallized twice from toluene, and dried *in vacuo*. This compound was shown, by melting point (280–281°) and infrared spectral analysis, to be triphenylisocyanurate (IV). The portion exhibiting



IV

limited acetone solubility was collected (4.5 g), recrystallized twice from acetone, and dried *in vacuo*. The resulting white crystalline product (mp 294–295°) was postulated, based on elemental analysis and infrared spectral identification, to be a substituted triazene analog (V). *Anal.* Calcd for $C_{27}H_{20}N_4O_2$: C, 75.0; H, 4.6; N, 13.0. Found: C, 75.1; H, 4.8; N, 12.7.



V

**Reactions with Substituted Chloroformamidine Hydrochlorides. Preparation of N,N′-Dicyclohexylchloroformamidine Hydrochloride.**—This compound was synthesized by the method of Ulrich.[12]

**Reaction of N,N′-Dicyclohexylchloroformamidine Hydrochloride and N,N′-Dicyclohexylurea.**—A solution of 3.06 g (0.11 mole) of N,N′-dicyclohexylchloroformamidine hydrochloride and 2.46 g (0.01 mole) of N,N′-dicyclohexylurea in 70 ml of monochlorobenzene was heated to 155° and held at this temperature until the evolution of hydrogen chloride ceased. About 1.5 hr was required. During the course of the reaction, white crystals formed. The mixture was purged with nitrogen for 15 min at 125° to remove excess gas, cooled, and filtered. This resulted in the isolation of 3.60 g (0.0106 mole) of symmetrical tricyclohexylguanidine hydrochloride, which was identified by mixture melting point and its infrared spectrum. This corresponds to a 97% yield.

**Preparation of N,N′-Diphenylchloroformamidine Hydrochloride.**—This compound was prepared by the method of Lengfeld and Stieglitz.[13]

(13) F. Lengfeld and J. Stieglitz, *Am. Chem. J.*, **17**, 108 (1895).

**Reaction of N,N′-Diphenylchloroformamidine Hydrochloride with N,N′-Dicyclohexylurea.**—A solution of 0.66 g (0.0025 mole) of N,N′-diphenylchloroformamidine hydrochloride and 0.6 g (0.0025 mole) of N,N′-dicyclohexylurea in 10 ml of monochlorobenzene was held at 115–120° for 2 hr and then purged with nitrogen for 10 min. Upon cooling, 0.26 g of white crystals separated, which were identified by infrared analysis as the starting dicyclohexylurea. Addition of 25 ml of heptane to the filtrate resulted in the precipitation of a white solid (0.22 g) which was identified by its infrared spectrum and mixture melting point as symmetrical diphenylurea. Concentration of the heptane filtrate resulted in the isolation of 0.3 g of an oily mass, which, upon recrystallization from heptane, gave the diphenylcarbodiimide trimer, mp 191–192° (lit.[14] 196°). *Anal.* Calcd for $C_{39}H_{30}N_6$: C, 80.4; H, 5.2; N, 14.4. Found: C, 80.2; H, 5.4; N, 14.6.

**Infrared Spectra.**—The spectra in the 2.5–15-μ range were obtained with a Perkin-Elmer Model 137 Infracord recording spectrophotometer. Samples were contained between sodium chloride plates in all cases.

**Vapor Phase Chromatography.**—Chromatographic analyses were carried out with a F & M Scientific Corp. Model 720 vapor phase chromatograph, employing Model W filaments, with 30% G.E. 30 (General Electric Corp.) silicon oil dispersed on 60–80 mesh Chromosorb W packing (Johns-Manville Corp.). The column dimensions were 6 ft × 0.25 in. o.d. aluminum "Utilatube" (Alcoa "Alclad"). The carrier gas was helium at a rate of 50 cc/min as measured at exit port. The program rate was 15°/min, with an injection port temperature of 225° and an indicator temperature of 215°. The indicator current was 200 ma and the components were estimated by internal normalization of peaks areas.

**Mass Spectral Data.**—This information was obtained by use of a Consolidated Electrodynamics Corp. Type 21-103-C mass spectrometer.

**Nuclear Magnetic Resonance Data.**—Nuclear magnetic resonance spectra were obtained in a Varian A-60 nuclear magnetic resonance spectrophotometer.

**Melting Points.**—These are uncorrected and were obtained on a Mel-Temp metal block apparatus.

## Discussion

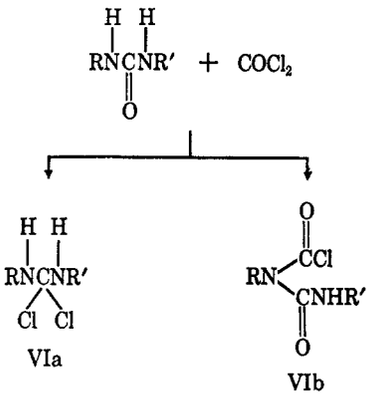
The phosgenation of disubstituted ureas offers a facile approach to the syntheses of N,N′,N″-trisubstituted alkyl- and mixed alkylarylguanidines. By this new method, symmetrically trisubstituted alkylguanadines as the hydrochloride salt can be obtained in essentially a pure state. A list of the guanidines that were prepared, together with the ureas from which they were derived, are presented in Table I.

TABLE I
GUANIDINES FROM N,N′-DISUBSTITUTED UREAS AND PHOSGENE

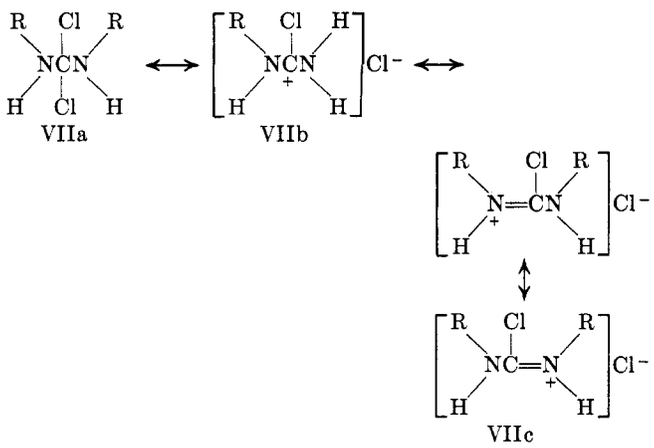
| Substituted urea | Guanidine(s) formed | Yield, % of theoretical |
|---|---|---|
| N,N′-Dicyclohexyl- | N,N′,N″-Tricyclohexyl- | 64 |
| N-Cyclohexyl-, N′-isopropyl- | N,N′-Dicyclohexyl-, N″-isopropyl- | 18 } 59 |
| | N,N′-Diisopropyl-, N″-cyclohexyl- | 41 } |
| N-Cyclohexyl-, N′-ethyl- | N-Cyclohexyl-, N′,N″-diethyl- | 31 |
| N-Isopropyl-, N′-phenyl- | N,N′-Diisopropyl-, N″-phenyl- | 21 |
| N-Cyclohexyl-, N′-phenyl | N,N′-Dicyclohexyl-, N″-phenyl- | 17 |
| N-Cyclohexyl-, N′-trifluoroethyl- | None | |
| N,N′-Diphenyl- | None | |

(14) M. Busch, G. Blume, and E. Pungs, *J. Prakt. Chem.*, **79** (2), 519 (1910).

Before discussing the reaction mechanism, it is appropriate to allude to some prior chemistry pertaining to the phosgenation of substituted ureas. The reaction of phosgene with symmetrically disubstituted alkylureas is reported to result in the formation of two products, N,N′-disubstituted chloroformamidines (VIa) and N,N′-disubstituted allophanoyl chlorides[12] (VIb).




The distribution of these products is mainly determined by steric effects, the allophanoyl compound forming from primary substituents, whereas chloroformamidine formation is facilitated by branched substituents.[12] The chloroformamidines have been postulated as resulting from an attack by phosgene on the oxygen atom rather than nitrogen atom of the urea.[15] The disubstituted chloroformamidine may be represented as a resonance hybrid involving several canonical forms (VII). To account for the formation of guanidines, a mechanism is proposed which involves a nucleophilic attack by the nitrogen atom of the urea on the positively charged carbon atom of the chloroformamidine (VIIb). The loss of a proton accompanied by

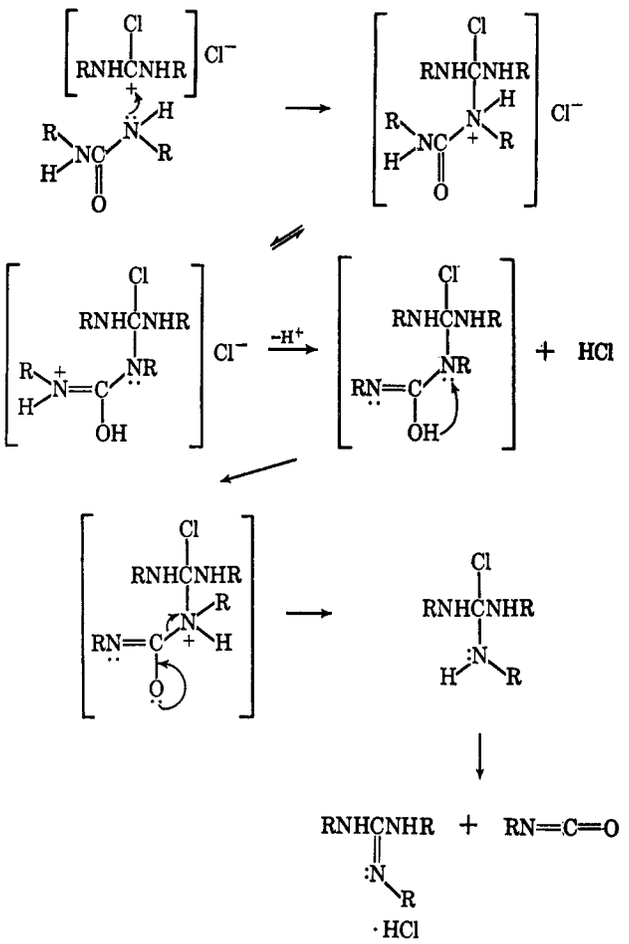



electronic redistribution results in the formation of the guanidine and appropriate isocyanate (Scheme I). If this is valid, then one should be able to obtain guanidines by the direct action of the substituted urea on the chloroformamidine. Further, it is to be expected that, with N,N′,N″-trisubstituted guanidines containing more than one type of substituent, the distribution of products should be dependent upon the inductive effect of the groups attached to the nitrogen atoms of the attacking urea.

With regard to the first of these tests, independent syntheses of dicyclohexylchloroformamidine, subsequent reaction with N,N′-dicyclohexylurea in equimolar proportions and isolation of N,N′,N″-tricyclohexylguanidine hydrochloride in near quantitative yields is in agreement with the postulated mechanism. The formation of cyclohexylisocyanate was also realized.

Concerning the second point, in cases of N,N′-disubstituted ureas in which the two groups are dissimilar, it is possible to obtain two different guanidines. If the proposed mechanism is correct, the distribution of guanidines should be dependent upon the inductive nature of the substituent groups on the attacking urea. Since the attack is by the electron pair of one of the urea nitrogens on the nucleophilic carbon of the chloroformamidine, the presence of an electron-donating group would enhance the ability of that nitrogen to act as a nucleophile. Consequently, an even distribution of guanidines would not be expected. This is,

SCHEME I




in fact, borne out by the results listed in Table I. A typical case in point is the reaction of N-cyclohexyl-N′-phenylurea with phosgene. The electron-donating nature of the cyclohexyl group makes the electron pair on the adjacent nitrogen atom more available for nucleophilic attack. On the other hand, the phenyl group, being electron withdrawing, decreases the electron density on its nitrogen. Consequently, the expectation is solely for the formation of N,N′-dicyclohexyl-N″-phenylguanidine. This is what has been observed. Similar results were also obtained with N-isopropyl-N′-phenylurea.

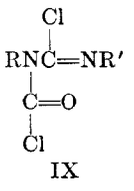
(15) I. Ugi, F. Beck, and U. Fetzer, *Ber.*, **95**, 126 (1962).

In the case where both groups are electron donating, two guanidines were obtained, the distribution of which depends on subtle differences in induction effects. Thus, the phosgenation of N-cyclohexyl-N′-isopropylurea results in a 41% yield of N,N′-diisopropyl-N″-cyclohexylguanidine hydrochloride and an 18% yield of N,N′-dicyclohexyl-N″-isopropylguanidine hydrochloride. Similar results should have been expected from the action of phosgene on N-cyclohexyl-N′-ethylurea. However, this was not realized. Elemental analyses demonstrate that the major component and perhaps the only component is N-cyclohexyl-N′,N″-diethylguanidine hydrochloride. However, the variance in analyses could be interpreted as indicating that 10% of the product could be N,N′-dicyclohexyl-N″-ethylguanidine hydrochloride. Owing to the similarity in properties of the two components, successful separation was not accomplished. A possible explanation for the negligible yield or complete absence of N,N-dicyclohexyl-N″-ethylguanidine hydrochloride could reside in the steric requirements of the two substituent groups. Whereas the size relationships between an isopropyl and a cyclohexyl group do not differ greatly, the contrast between an ethyl and a cyclohexyl group is appreciable. Consequently, this could facilitate an attack by the less bulky ethyl group.

One additional point need be considered. As the electron-donating substituent groups are altered from secondary to primary, the over-all yield decreases (Table I). This is in agreement with the findings of Ulrich,[12] who indicated that the yields of the chloroformamidines (precursors of the guanidines) decrease when primary substituent groups are present.

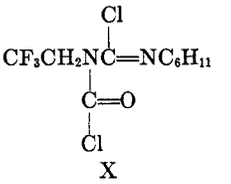
The final class of compounds to be considered involve ureas, of the general formula RNHC(=O)NHR′, in which one or both substituent groups are electron withdrawing. Three types of molecules need be considered: (1) R is electron donating and R′ is weakly electron withdrawing; (2) R is electron donating and R′ is strongly electron withdrawing; and (3) R and R′ are both electron withdrawing.

The first type of compound is exemplified by N-isopropy-N′-phenylurea, which upon phosgenation resulted in the formation of N,N′-diisopropyl-N″-phenylguanidine in a 21% yield. A further example involved N-cyclohexyl-N′-phenylurea, which gave N,N′-dicyclohexyl-N″-phenylguanidine in a 17% yield. Both of these reactions have been discussed earlier. One additional point should be noted. Infrared analysis of the products of the reaction prior to separation of the guanidine indicates the presence of substantial amounts of chloroformylchloroformamidines (IX). The



IX

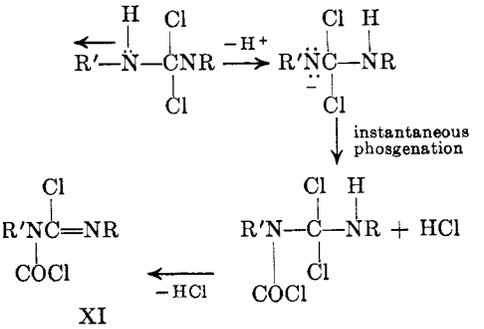
significance of this compound will shortly become obvious. The second grouping, that in which one of the substituents is strongly electron withdrawing, is typified by N-cyclohexyl-N′-trifluoroethylurea. Reaction of this compound with an excess of phosgene followed by distillation resulted in a 62% yield of N-cyclohexyl-N′-chloroformyl-N′-trifluoroethylchloroformamidine (X).



X

N,N′-Diphenylurea, the third type of compound, also forms the chloroformylchloroformamidine from this reaction as evidenced by infrared spectroscopy. This compound was found to be unstable at distillation temperatures which is in agreement with the observation reported by Fisher.[10]

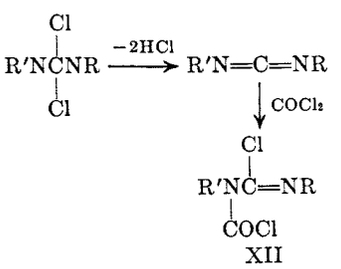
A mechanism consistent with these observations involves the attack by phosgene on one of the nitrogen sites of the chloroformamidine (VIIc) rather than the carbon atom, as was the case in the formation of guanidines. Why should an electron-withdrawing group promote this type of attack? A withdrawing group would decrease the electron density on the adjacent nitrogen site, enhance the acidity of the proton attached to that nitrogen, and thus facilitate its removal. This would then be accompanied, or immediately followed, by an attack of phosgene. Dehydrochlorination would then lead to the chloroformylchloroformamidine (XI), a compound which has been observed in each of the cases where a deactivating group was present.




XI

where R′ is electron withdrawing

An equally acceptable mechanism involves the formation of a carbodiimide by removal of 2 moles of hydrogen chloride from the chloroformamidine. This is followed by reaction with phosgene to form the chloroformylchloroformamidine (XII) in a reaction previously described by Fisher.[10] It is inherent in




XII

where R′ is a electronegative group

both of these mechanisms that there will be a preference in the nitrogen to which the phosgene will attach itself and this, in turn, will depend on the electron-wit h-

drawing nature of the substituent group. The nitrogen adjacent to the electron-withdrawing group will be the site of attack. The final product will be the same by either mechanism. The latter mechanism is similar to that postulated by Ulrich[12] to account for the formation of N,N′-di-*n*-butyl-N′-chloroformylchloroformamidine by phosgenation of N,N′-di-*n*-butylurea in the presence of triethylamine. Further, the addition of phosgene to carbodiimides at room temperature is well established.[11]

A related series involves the reactions of N,N′-dicyclohexylurea with N,N′-dicyclohexyl- and N,N′-diphenylchloroformamidine hydrochloride at 115° in the absence of phosgene. The expected guanidine was isolated from the former reaction. In the latter, there was no indication of the formation of trisubstituted guanidines. This establishes that the nature of the chloroformamidine and not the urea is the overriding factor in determining the extent of guanidine formations.

In summary, a novel method for the synthesis of N,N′,N″-substituted guanidines is presented. This type of compound results from the phosgenation of ureas containing electron-donating groups. In contrast, the complete absence of guanidine formation is observed in cases where all the substituent groups on the ureas are electron withdrawing or one of the substituents is strongly electron withdrawing. Reaction mechanisms are postulated to explain these observations.

**Registry No.**—IV, 498-63-5; V, 13134-13-9; N,N′,N″-tricyclohexylguanidine hydrochloride, 13134-14 0; N,N′-dicyclohexyl-N″-isopropylguanidine hydrochloride, 13134-15-1; N-cyclohexyl-N′,N″-diisopropylguanidine hydrochloride, 13134-16-2; N-cyclohexyl-N′,N″-diethylguanidine hydrochloride, 13134-17-3; N,N′-dicyclohexyl-N″-phenylguanidine, 13134-18-4; N,N′-diisopropyl-N″-diphenylguanidine, 13134-19-5; diphenylcarbodiimide trimer, 13136-42-0.

# Studies on the Baudisch Reaction. I. The Synthesis of *o*-Nitrosophenols

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The reaction mechanism of the Baudisch reaction, which is the synthetic reaction of *o*-nitrosophenols from benzene or substituted benzenes, hydroxylamine hydrochloride, and hydrogen peroxide in the presence of copper(II) ion, has been reinvestigated. The phenolic hydroxyl group plays an important role in this reaction and the marked steric influence of a methyl group at the position *meta* to the phenolic hydroxyl group was observed on nitrosation at the position *ortho* to both the methyl and the hydroxyl groups. These results support the hypothesis that a bulky copper–hydroxylamine comlpex is involved in this specific *o*-nitroso hydroxylation. It was found also that nitrous acid, which had been proposed previously as the true nitrosation agent in this reaction, was unable to give the product ratio of *o*- to *p*-nitrosophenol which is observed in the Baudisch reaction.

In the presence of copper(II) ion, a solution containing aqueous hydroxylamine hydrochloride and hydrogen peroxide reacts with benzene or phenol to give *o*-nitrosophenol. This reaction was discovered by Baudisch[2] about 25 years ago. Cronheim[3] has further developed the Baudisch reaction to prepare a variety of *o*-nitrosophenols from the corresponding substituted benzenes.

Concerning the mechanism of this reaction, Baudisch[4] and Cronheim[3] postulated that the copper(I) nitrosyl ion, $CuNO^+$, attacks the aromatic ring leading to nitrosation and that hydroxylation adjacent to the position attacked follows this nitrosation. They made the tentative hypothesis that the copper(I) nitrosyl ion was formed from Cu(I) and nitrosyl radicals which had been generated *via* prior oxidation–reduction reactions among the various reagents. Moreover, they suggested that by forming a complex with the resultant *o*-nitrosophenol, the Cu(II) ion plays a role in preventing further oxidation to *o*-nitrophenol and rearrangement to *p*-nitrosophenol. More recently, Konecny[5] has proposed a mechanism in which nitrous acid produced by the reaction of hydroxylamine and hydrogen peroxide is postulated to act as a nitrosation agent for the phenol which had been produced by the hydroxylation of benzene. This hypothesis was supported by the fact that hydroxyl radicals could be produced from hydrogen peroxide through the catalytic action of Cu(II) ion.[6] However, no systematic investigation of this reaction has ever been reported.

Since this unusual exclusive *o*-nitroso hydroxylation of aromatics was of considerable interest and since the mechanism by which the reaction occurs was in doubt, we reinvestigated the reaction and have come to the conclusion that this reaction does not follow the mechanisms proposed by former investigators.

## Results and Discussion

**Rate of Formation of *o*-Nitrosophenols.**—As *o*-nitrosophenols are extremely volatile and readily oxidized in air, it is difficult in general to isolate them and determine their concentrations. Fortunately, these *o*-nitrosophenols form stable copper(II) complexes which have an intense red color in aqueous solution. The spectra of the copper complexes in water showed characteristic absorption maxima at *ca.* 420 and *ca.* 530 mμ in the visible region and at about 340 mμ in the ultraviolet region. The absorption band at *ca.* 340 mμ was the most intense and could be used alone for the determination of the concentration of *o*-nitrosophenols. We followed the rates of formation of

(1) (a) Kyoto University; (b) Kyoto Women's University.

(2) O. Baudisch, *Naturwissenschaften*, **27**, 768 (1939); O. Baudisch and S. H. Smith, *ibid.*, **27**, 769 (1939).

(3) G. Cronheim, *J. Org. Chem.*, **12**, 1 (1947).

(4) O. Baudisch, *Science*, **92**, 336 (1940); *Arch. Biochem.*, **5**, 301 (1944).

(5) J. O. Konecny, *J. Am. Chem. Soc.*, **77**, 5748 (1955).

(6) J. O. Konecny, *ibid.*, **76**, 4993 (1954).