monium hydroxide. The analytical sample was prepared by sublimation at 300° (0.05 mm.); $\lambda_{max}^{0.1\,N\ HCl}$ 250, 300 mμ; log ε 4.33, 3.94.

Anal. Calcd. for $C_{10}H_8N_8$: C, 50.0; H, 3.3. Found: C, 50.3; H, 3.4.

2-[5-(4-Amino-2-methylpyrimidyl)]-4-amino-7-methylpyrimido(4,5)pyrimidine (XVII) was prepared in 80% yield from 2-methyl-4-amino-5-cyanopyrimidine as described above and was purified analogously by reprecipitation from dilute acid solution and by vacuum sublimation; m.p. >360°; $\lambda_{max}^{0.1\,N\ HCl}$ 247, 297 mμ; log ε 4.32, 3.93.

Anal. Calcd. for $C_{12}H_{12}N_8$: C, 53.7; H, 4.5. Found: C, 53.7; H, 4.7.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF ILLINOIS INSTITUTE OF TECHNOLOGY]

A Comparison of the Reactions of Some Amines with Nitrosoguanidine, Cyanamide and S-Methylisothiourea Hydrochlorides[1a,1b]

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RECEIVED AUGUST 19, 1957

A comparison of the reaction of *p*-$RC_6H_4NH_2 \cdot HCl$ (R = H, CH_3 and $(CH_3)_2N$) and phenylhydrazine with nitrosoguanidine supports the hypothesis of a prior dearrangement of nitrosoguanidine to cyanamide as advanced by Davis and his students.[3a,b] However, the results of a similar comparison with the series piperidine, 3-methylpiperidine, 2-methylpiperidine and *cis*-2,6-dimethylpiperidine at room temperature strongly favor an addition–elimination mechanism. A similar path is advanced for the behavior of S-methylisothiourea hydrochloride toward the same series of piperidines. Finally, it is demonstrated that the reaction of the corresponding piperidine hydrochlorides with both nitrosoguanidine and S-methylisothiourea proceeds *via* a cyanamide intermediate at reflux temperatures.

Davis and his students have suggested that the formation of guanidine derivatives from the interaction of alkylamines and nitrosoguanidine (eq. 2) is explicable in terms of a prior dearrangement of the substrate to cyanamide.[3a,b]

The isolation of small amounts of urea from the reaction of ammonia with nitrosoguanidine was construed as evidence for an alternate mode of dearrangement (eq. 1b) in which nitrosocyanamide is postulated as the reactive species.[3b]

$$NH_2C(NH)NHNO \begin{cases} \longrightarrow NH_2CN + (NH_2NO) \longrightarrow N_2 + H_2O & (1a) \\ \longrightarrow NH_3 + NONHCN & (1b) \end{cases}$$

$$RNH_2 + NH_2CN \longrightarrow RNHC(=NH)NH_2 \qquad (2)$$

Thiele had earlier considered a similar mechanism (eq. 1a) to explain the formation of aminoguanidine from the action of hydrazine on nitrosoguanidine.[4] However, the fact that the temperature required to cleave nitrosoguanidine is considerably higher than that necessary to initiate this reaction caused Thiele to abandon this hypothesis.

Recently McKay[5] advanced an attractive addition–elimination mechanism[6] to explain the reactions of amines with both nitro- and nitrosonitroguanidine. Furthermore, it appeared to us that the findings of Davis and Rosenquist[3b] could be explained on a similar basis. However, there is at present no direct evidence to vitiate the dearrangement hypothesis.

A preliminary study showed that the course of reaction between phenylhydrazine and nitrosoguanidine is markedly affected by *p*H. Refluxing an aqueous solution of phenylhydrazine hydrochloride and nitrosoguanidine, which is weakly acid, gave a mixture of anilinoguanidine (I) and 1-phenyl-1-aminoguanidine (II) in a ratio of *ca.* 2:1, but when free phenylhydrazine was used in place of its hydrochloride, only dicyandiamide could be isolated. A similar observation on the reaction of free aniline with nitrosoguanidine has been reported by Davis and Rosenquist.[3b]

$$C_6H_5NHNH_3^+ \cdot \xrightarrow[\text{or } NH_2CN]{NONH-C(=NH)-NH_2} C_6H_5NHNH-C(=NH)-NH_3^+ \ (\text{I}) + C_6H_5N(+NH_3)-C(=NH)-NH_2 \ (\text{II})$$

A second series of reactions was carried out under identical conditions with cyanamide. It is evident from Table I that the reactions of phenylhydrazine with nitrosoguanidine and cyanamide in neutral and weakly acidic solution afford identical products in essentially the same yields.

It is pertinent to the succeeding discussion that the data regarding the effect of *p*H on aqueous solutions of cyanamide be summarized.[7] In strongly basic solution (*p*H 12) cyanamide is quantitatively hydrolyzed to urea at a rate which is proportional to the concentration of $(NHCN)^-$. In less basic solutions (*p*H 8–12) cyanamide dimerizes to dicyandiamide at a rate which is proportional to the

(1) (a) Abstracted in part from a dissertation submitted by C. Clinton Rila to the Graduate School of Illinois Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy. (b) This work was supported by U. S. NOTS, Inyokern, China Lake, Calif., Research Contract N 123S-61527, Task Order No. 3.

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(3) (a) T. L. Davis and A. J. Abrams, *Proc. Am. Acad. Arts Sci.*, **61**, 437 (1926); (b) T. L. Davis and E. N. Rosenquist, THIS JOURNAL, **59**, 2112 (1937).

(4) J. Thiele, *Ann.*, **273**, 133 (1893).

(5) A. F. McKay, *Chem. Revs.*, **51**, 312 (1952).

(6) An intermediate may be formed or the addition–elimination reactions occur simultaneously.

(7) For a complete discussion of the effect of *p*H on cyanamide see T. W. J. Taylor and W. Baker, "Sidgwick's Organic Chemistry of Nitrogen," Oxford University Press, London, England, 1937, p. 329.

TABLE I

THE EFFECT OF *p*H ON THE COURSE OF THE REACTION OF PHENYLHYDRAZINE WITH NITROSOGUANIDINE AND CYANAMIDE

Substrate	*p*H	Product	Yield, %	Product	Yield, %
Nitrosoguanidine	7–8	Dicyandiamide	51	.....	..
Cyanamide	7–8	Dicyandiamide	63	.....	..
Nitrosoguanidine	3–5	Anilinoguanidine[a]	35	1-Phenylaminoguanidine[a]	19
Cyanamide	3–5	Anilinoguanidine	35	1-Phenylaminoguanidine	17
Nitrosoguanidine	1	Phenyl azide	46	Guanidine hydrochloride	29

[a] Isolated as a picrate salt.

concentration of both the anion and the undissociated molecule. Apparently both species are present in appreciable concentration from *p*H 8–12, as dimerization occurs easily.

Cyanamide is hydrolyzed to urea in strongly acidic solution at a rate which is proportional to the cation, $(NH_2CNH)^+$. However, in moderately acidic solution (*p*H 3–5) cyanamide is relatively stable with respect to both dimerization and hydrolysis. Under these conditions the ionization and subsequent dimerization is suppressed while, at the same time, protolysis evidently fails to occur to any appreciable extent; that is, the equilibria expressed by equations 3 and 4, are displaced far to the left.

$$NH_2CN + H_2O \rightleftarrows (NHCN)^- + H_3O^+ \quad (3)$$

$$NH_2CN + H_3O^+ \rightleftarrows (NH_2CNH)^+ + H_2O \quad (4)$$

Thus, the formation of dicyandiamide in the weakly basic medium produced by phenylhydrazine is readily explained. Furthermore, the failure to observe any product other than dicyandiamide from the reaction of phenylhydrazine with either cyanamide or nitrosoguanidine in weakly basic media suggests that the cleavage of nitrosoguanidine and the dimerization of cyanamide both occur more rapidly than the attack of phenylhydrazine on either of the two substrates. On the other hand, since cyanamide is relatively stable with respect to dimerization in moderately acidic solution, as is obtained in the solvolysis of the phenylhydrazonium ion, the relatively slow reaction between phenylhydrazine and cyanamide assumes some significance.[8]

The reaction of phenylhydrazine and nitrosoguanidine was observed to pursue still another course in strongly acidic solution. Thus, when an aqueous suspension of the reactants was first adjusted to a *p*H of approximately 1 with 6 *N* hydrochloric acid, and the mixture then refluxed for six hours, it was impossible to detect the presence of any of the guanidine derivatives previously obtained. Instead, phenyl azide and guanidine hydrochloride were isolated in yields of 46 and 29%, respectively (Table I). This observation is consistent with the behavior previously reported for nitrosoguanidine and some of its derivatives in strongly acidic media. Thus, Thiele[4] had earlier observed the formation of nitrous acid and guanidine hydrochloride on warming aqueous hydrochloric acid solutions of nitrosoguanidine. Similarly, Lieber and Parker obtained 2-amino-1-2′-azonaphthalene from the interaction of 2-naphthylamine hydrochloride and 1-methyl-1-nitroso-3-nitroguanidine. These results were ascribed to a partial denitrosation of the nitrosoguanidine derivative, then by diazotization and, finally, a reaction between the coupling agents.[9a,b]

It appeared of interest to extend the scope of this study to include the reactions of a series of arylamines with both nitrosoguanidine and cyanamide. In this connection, Kampf had earlier observed that while the nitrate salts of aniline and *p*-toluidine reacted with cyanamide in an ethanolic medium to form the corresponding arylguanidine nitrate, negatively substituted anilines were unreactive.[10] On the basis of these observations it was decided to limit the study to aniline, *p*-toluidine and *p*-dimethylaminoaniline.

It is evident from Table II that the yield of the individual arylguanidine as obtained from nitrosoguanidine closely approximates that obtained from cyanamide itself. The failure of the data to correspond more closely may, in part, be attributed to a competitive reaction initiated by the easy denitrosation of nitrosoguanidine in acid solution. This is supported by the detection of small amounts of the corresponding phenol. Nevertheless, the results lend additional support to the hypothesis advanced by Davis and Rosenquist.

TABLE II

A COMPARISON OF THE YIELDS OF ARYLGUANIDINES AND *sym*-DIARYLUREAS OBTAINED FROM NITROSOGUANIDINE AND CYANAMIDE IN AQUEOUS SOLUTION

p-$RC_6H_4NH_2$·HCl R =	Yield, % *p*-$RC_6H_4NHC(=NH)NH_2$[a] Nitrosoguanidine	Cyanamide	Ratio	Yield, % of *p*-$RC_6H_4NHC(=O)NHC_6H_4R$ Nitrosoguanidine	Cyanamide
H	42	51	0.82	19	26
CH_3	32	39	.82	17	30
$(CH_3)_2N$	30	37	.81	..[b]	..[b]

[a] Isolated as picrate salt. [b] Isolated only in trace quantities.

An additional side reaction leading to the formation of significant quantities of 1,3-diarylureas (*cf.* Table II) was observed in the reactions of the arylamines with both substrates. That these products could not have been derived from the arylguanidine was evident from the observation that phenylguanidine hydrochloride could be refluxed in aqueous solution for 36 hours without change. Furthermore, the presence of an equimolar quantity of aniline had no effect.

(8) The possibility exists that the reaction may actually involve a protonated form of cyanamide and free phenylhydrazine. While the equilibrium concentration of the conjugate acid of cyanamide is probably quite low, the increased electrophilic character of this species over cyanamide itself should greatly enhance its reactivity toward the free amine.

(9) (a) E. Lieber and K. Parker, THIS JOURNAL, **72**, 5779 (1950); (b) see ref. 5, p. 318.

(10) A. Kampf, *Ber.*, **37**, 1681 (1904).

TABLE III

A COMPARISON OF THE YIELDS OF ARYLGUANIDINES OBTAINED FROM NITROSOGUANIDINE AND CYANAMIDE IN ETHANOL

p-RNH$_2$·HCl R =	Yield, % of RNHC(=NH)NH$_2$,[a] Nitrosoguanidine	Cyanamide
C_6H_5–	23[b]	69
p-$CH_3C_6H_4$–	47	57
C_6H_5NH–	45	49
	20	23

[a] Isolated as picrate salts. [b] Guanidine picrate obtained in 14% yield.

It is well established that *sym*-diarylureas may be obtained by treatment of the appropriate amine salt with an aqueous solution of urea.[11] It would appear, then, that the solvolysis of cyanamide is an important competitive reaction under the conditions imposed in this phase of the study. To test this conclusion, the reaction of the hydrochloride salts of aniline, toluidine and phenylhydrazine were performed an absolute ethanol.[12] This innovation not only increased the yields of the guanidine derivatives (*cf.* Table III), but also eliminated the formation of the *sym*-diarylureas. Furthermore, these findings would seem to obviate the necessity of postulating nitrosocyanamide (eq. 1b) as the direct precursor of urea.[3c]

The use of alcohol as a solvent for nitrosoguanidine was observed to have one serious limitation in that the product frequently is accompanied by the formation of considerable tarry material. These intractable tars presumably arise as a consequence of the variety of paths available to a diazonium salt (*vide supra*) in an alcoholic medium.

In view of the similarity in product composition as obtained in the reactions of both phenylhydrazine and the arylamines with nitrosoguanidine and cyanamide, it appears that, under the conditions employed in the present study, nitrosoguanidine undergoes a prior cleavage to cyanamide. On the other hand it would be difficult to reconcile this conclusion with the observation that aliphatic amines react quite rapidly at room temperature.[3c]

Some consideration was given to the possibility that the relatively basic medium afforded by an aliphatic amine might facilitate the cleavage of nitrosoguanidine to cyanamide. However, it was found that an aqueous solution of triethylamine did not significantly accelerate this cleavage. In view of this observation the possible existence of a duality of mechanism, dependent upon the inherent base strength of the amine employed, was recognized. It was, therefore, decided to extend the product–composition study with nitrosoguanidine and cyanamide to include a series of relatively basic amines.

If the reactions of nitrosoguanidine with the more basic amines should proceed *via* an addition–elimination mechanism, it would be expected, as a first approximation, that an increase in the steric requirements of the amine would be manifested in a corresponding decrease in the relative yields of the guanidine derivatives. On the other hand, should the reaction once again involve a prior cleavage of the substrate, steric effects should be less pronounced and a parallel should exist in the corresponding reactions of cyanamide.

It was desirable that the amines selected for this phase of the study exhibit no sharp deviation among themselves with respect to inherent base strength in order that the results might represent a clear manifestation of only a bulk effect. It appeared that piperidine and suitable methylated derivatives would fulfil these requirements. Hall and Sprinkle[13] had previously reported the base constants for piperidine (pK_b 2.77) and 2-methylpiperidine (pK_b 2.92). Since data were available for only two of these bases, it was decided to redetermine these values in addition to the measurement of the corresponding constants for 3-methylpiperidine and *cis*-2,6-dimethylpiperidine.[14]

Potentiometric titrations were carried out on the piperidine hydrochlorides and the data treated in a manner similar to that employed by Hall and Sprinkle.[13] It should be noted from Table IV that the low value for 2-methylpiperidine, reported by Hall and Sprinkle has been brought into line with the values found for the other piperidines.

TABLE IV

DISSOCIATION CONSTANTS FOR SOME PIPERIDINE DERIVATIVES AT 25°

Base	Observed	Literature
Piperidine	2.82	2.89,[a] 2.77[b]
2-Methyl-	2.85	2.92
3-Methyl-	2.86	..
cis-2,6-Dimethyl-	2.86	..

[a] W. F. K. Wynne-Jones and G. Saloman, *Trans. Faraday Soc.*, 34, 1321 (1938). [b] See ref. 13.

The four piperidines were treated with both nitrosoguanidine and cyanamide at room temperature. The results of this phase of the study are summarized in Table V. The data are, first of all, in agreement with the expected order of steric requirements for the piperidine derivatives with respect to both substrates: piperidine ≅ 3-methylpiperidine < 2-methylpiperidine < *cis*-2,6-dimethylpiperidine. Furthermore, the effect of increasing steric requirements is much more pronounced in the case of nitrosoguanidine and hence precludes

TABLE V

THE REACTION OF SOME PIPERIDINE DERIVATIVES WITH CYANAMIDE, NITROSOGUANIDINE AND S-METHYLISOTHIOUREA HYDROCHLORIDE AT 25°

Amine	Yield of 1-guanylpiperidine derivative,[a] % Nitrosoguanidine	Cyanamide	S-Methylisothiourea hydrochloride
Piperidine	32	50	46
3-Methyl-	31	51	55
2-Methyl-	2	41	15
cis-2,6-Dimethyl-	0	32	0

[a] Isolated as picrate salts.

(11) T. L. Davis and K. C. Blanchard, *Org. Syntheses*, **3**, 95 (1923).

(12) The corresponding study with *p*-dimethylaminoaniline was not undertaken because of the tedious procedure required to purify the corresponding guanidine derivative.

(13) N. F. Hall and M. R. Sprinkle, THIS JOURNAL, **54**, 3469 (1932).

(14) Hydrogenation of 2,6-lutidine hydrochloride (*cf.* Experimental) with either Adams catalyst or Raney nickel afforded only the *cis* isomer.

the possibility of a prior cleavage of the substrate to cyanamide.

The reaction of an amine with a salt of S-methylisothiourea is a classical method for the preparation of guanidine derivatives.[15] However, to our knowledge, the mechanism of this transformation has never been established.

Arndt demonstrated that S-methylisothiourea may be thermally degraded to methyl mercaptan and cyanamide.[16] Similarly, we obtained a 64% yield of dicyandiamide upon refluxing an aqueous solution of this same base.

The recognition of a possible parallel with nitrosoguanidine prompted us to examine the behavior of S-methylisothiourea hydrochloride toward the same series of piperidines at room temperature.

Assuming the establishment of the consecutive equilibria denoted by equations 5 and 6, it is apparent that the formation of an N-guanylpiperidine may involve a transition state composed of either the thiuronium ion, or its conjugate base or possibly cyanamide itself.

$$RNH_2 + (NH_2\overset{SCH_3}{\overset{|}{C}}NH_2)^+ \rightleftharpoons RNH_3^+ + NH_2\overset{SCH_3}{\overset{|}{C}}{=}NH \quad (5)$$

$$NH_2\overset{SCH_3}{\overset{|}{C}}{=}NH \rightleftharpoons CH_3SH + NH_2CN \quad (6)$$

Examination of Table V reveals a trend comparable to that obtained in the corresponding study with nitrosoguanidine under the same conditions and, as such, would seem to preclude the possibility of a cyanamide intermediate at least at room temperature. Obviously, a choice between the thiuronium ion or its conjugate base is not possible without a more detailed investigation, which was beyond the scope of the present work. However, the acid dissociation constant of the thiuronium ion, pK_a 9.88, as determined by potentiometric titration, in conjunction with the pK_b of piperidine did indicate that the conjugate base would comprise approximately 75% of the initial equilibrium mixture (eq. 5). On the other hand, the strongly electrophilic, planar thiuronium ion should afford a transition state (with piperidine) of lower activation energy and hence a greater reaction velocity, which should serve to overcome the apparent equilibrium preponderance of the conjugate base.

The final phase of this study was concerned with the action of the hydrochloride salt of these same piperidines on nitrosoguanidines, cyanamide and S-methylisothiourea at reflux temperatures. On the basis of our previous work with the arylamines, it would be expected that these reactions would be forced to proceed by way of a cyanamide intermediate. If it is assumed that the rate of cleavage of nitrosoguanidine is rapid compared to the rate of formation of the 1-guanylpiperidine, the yields of the latter should closely approximate those obtainable with cyanamide itself. That this actually is the case is evident from the data presented in Table VI. However, it should be noted that, while the yields of 1-guanylpiperidine and 1-guanyl-3-methylpiperidine were essentially unaffected by increasing the temperature of the reaction, the yields of 1-guanyl-2-methylpiperidine and *cis*-1-guanyl-2,6-dimethylpiperidine were actually decreased (*cf.* Tables V–VI). It would appear, in the latter cases, that the cyanamide is being consumed in the formation of dicyanamide and/or urea at a rate which is greater than the reaction with the hindered amine.

TABLE VI

THE REACTIONS OF SOME PIPERIDINE HYDROCHLORIDES WITH CYANAMIDE, NITROSOGUANIDINE AND S-METHYLISOTHIOUREA AT 100°

Amine·HCl	Yield of guanidine derivative, % Nitroso-guanidine	Cyanamide	S-Methyl-isothiourea
Piperidine	46	50	36
3-Methyl-	47	48	31
2-Methyl-	19	22	12
cis-2,6-Dimethyl-	21	21	13

The sharp steric effect noted previously (*cf.* Table V) in the corresponding reactions at room temperature became less pronounced at reflux (*cf.* Table VI). Though the results parallel those obtained with cyanamide itself and hence suggest a prior cleavage of the substrate to cyanamide, the yields of the 1-guanylpiperidines are lower in each case.

A solution of equimolecular quantities of piperidine and S-methylisothiourea hydrochloride, as noted above, affords a relatively high equilibrium concentration of the respective conjugate acid and base. While the formation of the piperidinium ion is assured, without the introduction of additional hydrochloric acid, the resultant medium is distinctly more basic (*p*H 10) than that obtained in the comparable study with the two other substrates. The lower yield with S-methylisothiourea may, then, be attributed to the increased importance of the dimerization of cyanamide as a competitive reaction. Finally, it is pertinent to note that the cleavage of S-methylisothiourea apparently is faster at reflux temperatures than the reaction of the piperidines with the thiuronium ion.

Experimental[17]

2-Methylpiperidine.—The preparation described by McElvain and Adams[18] was slightly altered and hence the modified procedure is described in detail.

A solution of 50 g. (0.54 mole) of 2-methylpyridine in a mixture of 50 ml. of concentrated hydrochloric acid and 100 ml. of water was shaken at room temperature under 3.5 atmospheres of hydrogen in the presence of 0.5 g. of Adams catalyst. After the uptake of hydrogen had ceased, the catalyst was collected and the clear solution saturated with sodium sulfate. The acid solution was then neutralized with 50 g. of sodium hydroxide and extracted with 100 ml. of ether. The ether extract was dried over sodium sulfate and then distilled to give 49 g. (92% yield) of 2-methylpiperidine, b.p. 116–118° (lit.[19] 114–116°); picrate m.p. 136.5–137.5° (lit.[20] 134–135°).

3-Methylpiperidine.—Hydrogenation of 3-methylpyridine in the manner described above for the isomeric compound gave an 82% yield of 3-methylpiperidine, b.p. 122–124° (lit.[21] 124–126°).

(15) See reference 7, p. 297.

(16) F. Arndt, *Ber.*, **37**, 681 (1904).

(17) All melting points are corrected. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(18) S. M. McElvain and R. Adams, THIS JOURNAL, **45**, 2745 (1923).

(19) S. M. McElvain, *ibid.*, **49**, 2835 (1927).

(20) A. Lipp, *Ann.*, **289**, 173 (1896).

(21) A. Ladenburg, *ibid.*, **247**, 1 (1888).

cis-**2,6-Dimethylpiperidine.**—Attempts to prepare this amine by the method of McElvain and Adams[19] were unsuccessful. The reaction ceased after 5% of the theoretical uptake of hydrogen. However, high temperature and pressure smoothly effected the reduction.

A mixture of 40 g. (0.37 mole) of 2,6-lutidine, 35 ml. of concentrated hydrochloric acid and 65 ml. of water was shaken with hydrogen at 100° and 300 atm. in the presence of Adams catalyst. The crude 2,6-dimethylpiperidine was isolated in the same manner as that already described for 2-methylpiperidine; wt. 28.5 g. (70% yield), b.p. 126–129°. The crude base was converted to the hydrochloride and the latter fractionally crystallized from an ethanol–ether mixture. *cis*-2,6-Dimethylpiperidine hydrochloride, m.p. 285–288° (lit.[22] 285°), was obtained in 58% yield (30.7 g.).

The *cis*-2,6-dimethylpiperidine also was obtained by the method of Adkins, *et al.*[23] A solution of 50 g. (0.46 mole) of 2,6-lutidine in 150 cc. of cyclohexane was shaken with hydrogen in the presence of Raney nickel at 175° and 300 atm. Following the completion of the reaction, the catalyst was removed and the reaction mixture distilled to give 34.5 g. (65% yield) of crude 2,6-dimethylpiperidine, b.p. 125–128°.

The hydrochloride was obtained by passing anhydrous HCl into an absolute ethanolic solution of the base (30 g.). Concentration of the solution and precipitation with ether yielded two crops of white needles, m.p. 286–289° (lit.[22] 285°). A portion of this material was converted to a picrate, m.p. 163–165° (lit.[22] 163–165°). The free base was regenerated by treatment of the hydrochloride with aqueous sodium hydroxide, b.p. 126–126.5° (lit.[22] 132–133°).

Dicyanamide Formation (a).—A mixture of 2.00 g. of nitrosoguanidine[24] (0.023 mole) in 100 ml. of water was heated to 60–65° for 13.5 hours. The reaction mixture was then concentrated, the product collected and washed with ethanol to give 0.49 g. (51% yield) of dicyandiamide, m.p. 207–209°; a mixture melting with an authentic sample of dicyandiamide was also 207–209°.

(b).—To a solution of 0.84 g. of cyanamide (0.02 mole) in 100 ml. of water was added 2.16 g. of phenylhydrazine (0.02 mole) and the mixture heated to 60° for 5 hours. The reaction mixture was concentrated to a small volume and the product solidified on standing. The crystals were collected and washed with two 5-ml. portions of absolute ethanol to give 0.53 g. of dicyandiamide (63%), m.p. 205.5–207° alone or with an authentic sample of dicyandiamide.

Determination of Dissociation Constants.—The values for piperidine, 2-methylpiperidine, 3-methylpiperidine, *cis*-2,6-dimethylpiperidine and S-methylisothiourea were determined by potentiometric titration of the respective hydrochloride salt with standard barium hydroxide.

Samples of these salts, *ca.* 0.5 g., were dissolved in redistilled water and diluted to 100 ml. Four 20-ml. aliquots were titrated with 0.1204 *N* barium hydroxide at 25 ± 1° under a stream of nitrogen. After the addition of each increment of base, the *p*H of the solution was measured with a model H Beckman *p*H meter using a glass electrode. The barium hydroxide was added in 1.00-ml. increments in such a manner as to furnish duplicate *p*H readings at intervals of 0.50 ml.

The equation employed by Hall and Sprinkle[13] was modified to give

$$\log X = -p\mathrm{OH} = \log\left[\frac{(N/V) - X}{\frac{S}{V} - \frac{N}{V} + X}\right] - pK_b$$

where S is the number of moles of B·HCl, N the number of equivalents of barium hydroxide, V the total volume of the solution in liter and X the concentration of the hydroxide ion. The concentration of the latter defines the extent of the reaction of the free base with water.

$$B + H_2O \rightleftharpoons BH^+ + OH^-$$

A plot of $\log\left[\frac{(N/V) - X}{\frac{S}{V} - \frac{N}{V} + X}\right]$ *vs.* log X gave a straight line from which the dissociation constant was obtained.

Anilinoguanidine and 1-Phenyl-1-aminoguanidine (a).—To a solution of 2.89 g. of phenylhydrazine hydrochloride (0.02 mole) was added 1.76 g. of nitrosoguanidine (0.02 mole) and the mixture refluxed for 36 hours. The reaction was filtered and the filtrate extracted with ether. The aqueous phase was evaporated to dryness on a steam-bath in a stream of air and the residue fractionally crystallized from absolute ethanol. Two crops of anilinoguanidine hydrochloride, white prisms, m.p. 225–227° dec. (lit.[25] 226° dec.) were obtained in total yield at 0.9 g. (24%). The combined alcoholic filtrates were treated with benzaldehyde, followed by an ether extraction to remove unreacted benzaldehyde. The aqueous phase was then treated with picric acid and the mixture of picrates collected. Recrystallization of the mixture from *ca.* 7 liters of water gave 1.80 g. (19%) of 1-phenyl-1-benzalaminoguanidine picrate, m.p. 246–247° (lit.[26] 242°). Concentration of the filtrate yielded 0.82 g. of anilinoguanidine picrate (total yield 35%), m.p. 191–192.5° (lit.[25] 193°).

(b).—A solution of 2.89 g. of phenylhydrazine hydrochloride (0.02 mole) and 0.84 g. of cyanamide (0.02 mole) in 100 ml. of water was refluxed for 40 hours. The reaction mixture was cooled and extracted with ether. The aqueous phase was then concentrated to *ca.* 50 ml., treated with benzaldehyde and again extracted with ether. Picric acid was added to the aqueous phase, the mixture of salts collected and crystallized from *ca.* 7 liters of water to give 1.63 g. (17% yield) of 1-phenyl-1-benzalaminoguanidine picrate, m.p. 249.5–250°. Concentration of the filtrate gave 2.64 g. (35% yield) of anilinoguanidine picrate, m.p. 192–193°.

Phenyl Azide and Guanidine Hydrochloride.—A suspension of 4.40 g. of nitrosoguanidine (0.05 mole) in 200 ml. of water containing 5.40 g. of phenylhydrazine (0.05 mole) was acidified with 18 ml. of 6 *N* hydrochloric acid and heated at 65–70° for 6 hours. The mixture was then extracted with ether and the extract dried over anhydrous sodium sulfate. Distillation gave 2.71 g. of phenyl azide (46% yield), b.p. 39–41° (1 mm.). This product was identified from infrared absorption measurements. For a further characterization a small sample of the latter material was hydrogenated over Adams catalyst and the product converted to a hydrochloride salt; m.p. 195–196° alone or admixed with an authentic sample of aniline hydrochloride.

The original aqueous layer was evaporated to dryness and the residue crystallized from an ethanol–ethyl acetate mixture to give 1.26 g. of guanidine hydrochloride (29% yield), m.p. 183–184°. A mixed melting point with an authentic sample of guanidine hydrochloride caused no depression.

Reaction of Aniline Hydrochloride with Nitrosoguanidine. (a) **In Water.**—To a solution of 2.59 g. of aniline hydrochloride (0.02 mole) in 100 ml. of water was added 1.76 g. of nitrosoguanidine (0.02 mole). The mixture was refluxed for 40 hours, cooled and the insoluble material (fraction A) collected. Recrystallization of this solid from acetone gave 0.41 g. (19%) of *sym*-diphenylurea, m.p. 241–243° alone or with an authentic sample. The aqueous filtrate was extracted with three 50-ml. portions of ether and the combined extracts (fraction B) were washed with 5% sodium hydroxide. Treatment of the aqueous alkaline layer with chloroacetic acid gave 0.12 g. of phenoxyacetic acid (4% yield), m.p. 98–99° (lit.[27] 99°).

The original aqueous filtrate was treated with a hot saturated solution of picric acid until the deposition of solid was complete. The solid (fraction C) was recrystallized from hot water and gave two crops, 2.69 g., of phenylguanidine picrate (42%), m.p. 226–228° (lit.[28] 218–220°). Concentration of the mother liquor gave 0.80 g. of a yellow solid, m.p. > 300°, which appeared to be guanidine picrate (lit.[29] 333° dec.). The product was not further identified.

The filtrate (fraction D) from the isolation of guanidine picrate was made basic with 5% sodium hydroxide and ex-

(22) J. Pliml, E. Krobloch and M. Protiva, *Chem. Listy*, **46**, 758 (1952).

(23) H. Adkins, L. Kuick, M. Farlow and B. Wojcik, THIS JOURNAL, **56**, 2425 (1934).

(24) V. J. Sabetta, D. Himmelfarb and G. B. L. Smith, *ibid.* **57**, 2478 (1935).

(25) G. Pellizzari, *Gazz. chim. ital.*, **21**, 330 (1891).

(26) G. Pellizzari, *ibid.*, **26**, (II), 179 (1896).

(27) R. L. Shiner and R. C. Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948.

(28) G. B. L. Smith, THIS JOURNAL, **57**, 476 (1929).

(29) H. Lidholm, *Ber.*, **46**, 156 (1913).

tracted with three 50-ml. portions of ether. The ether was then extracted with 2 *N* hydrochloric acid and the acid extract evaporated to dryness on a steam-bath in a stream of air. The residue, 0.26 g. (10%), m.p. 190–194° dec., was identified as aniline hydrochloride.

(b) **In Ethanol.**—A suspension of 1.76 g. of nitrosoguanidine (0.02 mole) in a solution of 2.59 g. of aniline hydrochloride (0.02 mole) in 100 ml. of absolute ethanol was refluxed for 40 hours. The dark red solution was decolorized with Norite, concentrated to a small volume and diluted with *ca.* 25 ml. of water. The reaction mixture was analyzed as described above. Neither diphenylurea nor phenol was obtained. Fraction C yielded 1.50 g. (23%) of phenylguanidine picrate, m.p. 226–227°, together with 0.78 g. (14%) of guanidine picrate. Fraction D yielded 0.12 g. (6%) of aniline hydrochloride, m.p. 190–195° dec.

Reaction of Aniline Hydrochloride with Cyanamide. (a) **In Water.**—A solution of 2.59 g. of aniline hydrochloride (0.02 mole) and 0.84 g. of cyanamide (0.02 mole) in 100 ml. of water was refluxed for 40 hours. The reaction mixture was analyzed in the previously described manner with the exception that fraction B was not obtained in this case.

Fraction A yielded 0.56 g. (26%) of *sym*-diphenylurea, m.p. 238–240°. Fraction C yielded three crops of phenylguanidine picrate, m.p. 226–227°, with a total recovery of 3.28 g. (51%). Fraction D yielded 0.56 g. (22%) of aniline hydrochloride, m.p. 191–193° dec.

(b) **In Ethanol.**—A solution of 2.59 g. of aniline hydrochloride (0.02 mole) and 0.84 g. of cyanamide (0.02 mole) in 100 ml. of absolute ethanol was refluxed for 40 hours. Fractions A and B were not obtained. Fraction C gave 4.39 g. (69%) of phenylguanidine picrate, m.p. 226–227°. Fraction D yielded 0.4 g. (15%) of aniline hydrochloride, m.p. 190–193° dec.

Reaction of *p*-Toluidine Hydrochloride with Nitrosoguanidine. (a) **In Water.**—A suspension of 1.76 g. of nitrosoguanidine (0.02 mole) in a solution of 2.88 g. of *p*-toluidine hydrochloride (0.02 mole) in 100 ml. of water was refluxed for 40 hours. The weakly alkaline reaction mixture, fraction A, was then extracted with three 50-ml. portions of ether. The combined ether extracts were washed with 50 ml. of 2 *N* hydrochloric acid and the aqueous acid phase, fraction B, was evaporated to dryness on a steam-bath in a stream of air. The residue, 1.07 g. (37%), m.p. 237–239°, did not depress the melting point of an authentic sample of *p*-toluidine hydrochloride. The original ether extract was next washed in 25 ml. of 5% sodium hydroxide and the aqueous layer, fraction C, was treated with chloroacetic acid. Acidification and concentration afforded 0.10 g. (3%) of *p*-methylphenoxyacetic acid, m.p. 136–137.5° (lit.[28] 136°). Removal of the ether from the original extract left a residue, fraction D, of 0.4 g. (17%) of *sym*-di-*p*-tolylurea, m.p. 268–269° (lit.[30] 265–266°). A mixture melting point with an authentic sample of *sym*-di-*p*-tolylurea showed no depression.

The original aqueous layer, fraction A, was treated with a hot saturated solution of picric acid until no further precipitation was evident. The product was collected and recrystallized from boiling water to give 2.4 g. (32%) of *p*-tolylguanidine picrate, m.p. 220–221°.

Anal. Calcd. for $C_{14}H_{14}N_6O_7$: C, 44.45; H, 3.73; N, 22.22. Found: C, 44.35; H, 3.84; N, 22.36.

(b) **In Ethanol.**—A suspension of 1.76 g. of nitrosoguanidine (0.02 mole) in a solution of 2.88 g. of *p*-toluidine hydrochloride (0.02 mole) and 100 ml. of absolute ethanol was refluxed for 40 hours. The dark red solution was acidified with dilute hydrochloric acid, decolorized with Norite and evaporated to dryness on a steam-bath in a stream of air. The residue was taken up in 50 ml. of water and a hot, saturated solution of picric acid was added until precipitation was no longer evident. The solid was collected and recrystallized from water to give 3.56 g. (47%) of *p*-tolylguanidine picrate, m.p. 218–219.5°. The original filtrate was made basic with 5% sodium hydroxide and then extracted with ether. The ether layer was extracted with 2 *N* hydrochloric acid and the acid solution evaporated to give 0.83 g. (29%) of *p*-toluidine hydrochloride, m.p. 233–239°.

Reaction of *p*-Toluidine Hydrochloride with Cyanamide. (a) **In Water.**—A solution of 2.88 g. of *p*-toluidine hydrochloride (0.02 mole) and 0.84 g. of cyanamide (0.02 mole) in 100 ml. of water was refluxed for 40 hours. The reaction mixture was analyzed as above with the exception that fraction C was not obtained in this case. *p*-Tolylguanidine picrate, m.p. 221–222°, was isolated from fraction A in 39% yield (2.95 g.). Fraction B contained 0.58 g. (21%) of unreacted *p*-toluidine hydrochloride, m.p. 236–238° dec. Fraction D yielded 0.72 g. of *sym*-di-*p*-tolylurea (30%), m.p. 268–269°.

(b) **In Alcohol.**—A solution of 2.88 g. of *p*-toluidine hydrochloride (0.02 mole) and 0.84 g. of cyanamide (0.02 mole) in 100 ml. of absolute ethanol was refluxed for 40 hours. The reaction mixture was analyzed as above. Unreacted *p*-toludine hydrochloride, 0.60 g. (21%), m.p. 235–240° dec., was recovered in the usual manner, while *p*-tolylguanidine picrate, m.p. 220–221°, was isolated in 57% yield (4.30 g.).

Reaction of *p*-Dimethylaminoaniline. (a) **With Nitrosoguanidine.**—To a suspension of 1.76 g. of nitrosoguanidine (0.02 mole) was added 2.72 g. of *p*-dimethylaminoaniline followed by the addition of 64 ml. of water. The mixture was then refluxed for 40 hours and the blue-black solution filtered. The black tarry material, fraction A, was dissolved in 2 *N* hydrochloric acid and the black solution decolorized twice with Norite. A trace of gray flocculent material separated on addition of 6 *N* ammonium hydroxide, in amount insufficient for positive identification but it was assumed to be *sym*-di-*p*-dimethylaminophenylurea.

The original filtrate, fraction B, was decolorized with Norite and then treated with a saturated aqueous solution of 6.0 g. of ammonium picrate. The purple solid which separated was first dissolved in ethanol, the solution decolorized with Norite and the resulting solid twice recrystallized from ethanol to give 2.45 g. (30%) of *p*-dimethylaminophenylguanidine picrate, red needles, m.p. 228.5–229°.

Anal. Calcd for $C_{15}H_{17}N_7O_7$: C, 44.23; H, 4.21; N, 24.32. Found: C, 44.53; H, 4.31; N, 24.03.

(b) **With Cyanamide.**—A solution of 2.72 g. of *p*-dimethylaminoaniline (0.02 mole), 0.84 g. of cyanamide (0.02 mole) in 36.3 ml. of 0.551 *N* hydrochloric acid (0.02 mole) was diluted with 64 ml. of water and then refluxed for 40 hours. The reaction mixture was analyzed as above. Fraction A yielded only a trace of gray solid which could not be identified but was assumed to be *sym*-*p*-dimethylaminophenylurea. Fraction B yielded 2.97 g. of *p*-dimethylaminophenylguanidine picrate (37%), m.p. 227.5–228.5°.

1-Guanylpiperidines.—The study of the behavior of the four piperidines toward nitrosoguanidine, cyanamide and S-methylisothiourea hydrochloride at 25° (*ca.* room temperature) for 72 hours comprised a series of twelve reactions. In addition, a second series of reactions was carried out at 100° (approximately reflux temperature) for 40 hours in which the behavior of the corresponding piperidine hydrochlorides toward the same group of substrates was examined. In each case, 0.02 mole of either the heterocyclic base or its hydrochloride was treated with 0.02 mole of the substrate in 100 ml. of water. The yields reported in Tables V and VI represent the average of at least two determinations.

Because of the similarity of the experimental method within each series, typical reactions are described for each of the three substrates at two temperatures.

(1) **Piperidine at 25°.** (a) **Nitrosoguanidine.**—A suspension of 1.76 g. (0.02 mole) of nitrosoguanidine in a solution of 1.70 g. of piperidine (0.02 mole) in 100 ml. of water was allowed to react for 72 hours. At the end of this period all of the substrate had disappeared and the reaction mixture was acidified with a saturated, aqueous solution of picric acid. The solid material was collected and fractionally crystallized from water to give 2.30 g. of 1-guanylpiperidine picrate. One recrystallization from water provided an analytical sample, m.p. 254–255°.

Anal. Calcd. for $C_{12}H_{16}N_6O_7$: C, 40.53; H, 4.53; N, 23.59. Found: C, 40.85; H, 4.64; N, 23.32.

The original filtrate, on concentration, yielded 2.82 g. (45%) of piperidine picrate, m.p. 153–156° (lit.[31] 147–149°) alone or when admixed with an authentic sample of this salt.

(b) **Cyanamide.**—A yield of 3.56 g. (50%) of 1-guanylpiperidine picrate, m.p. 255–256°, and a recovery of 2.20 g. (35%) of piperidine picrate were obtained by the substitution of 0.02 mole of cyanamide for the nitrosoguanidine.

(c) **S-Methylisothiourea Hydrochloride.**—A yield of

(30) E. Bamberger and H. Distraz, *Ber.*, **35**, 1874 (1902).

(31) S. Gabriel, *ibid.*, **25**, 415 (1892).

3.26 g. (46%) of 1-guanylpiperidine picrate was obtained using 0.02 mole of S-methylisothiourea hydrochloride. Piperidine picrate could not be conveniently separated from a contaminant which was assumed to be S-methylisothiourea picrate.

(2) **3-Methylpiperidine at 25°.** (a) **Nitrosoguanidine.**—A yield of 2.29 g. (31%) of 1-guanyl-3-methylpiperidine picrate,[32] m.p. 227.5–228.5° was obtained.

Anal. Calcd. for $C_{13}H_{18}N_6O_7$: C, 42.16; H, 4.90; N, 22.70. Found: C, 42.37; H, 4.74; N, 22.73.

(b) **Cyanamide.**—A yield of 3.78 g. (51%) of 1-guanyl-3-methylpiperidine picrate, m.p. 227.5–228.5°, was obtained.

(c) **S-Methylisothiourea Hydrochloride.**—A yield of 4.10 g. (55%) of 1-guanyl-3-methylpiperidine picrate, m.p. 227.5–228.5°, was obtained.

(3) **2-Methylpiperidine at 25°.** (a)-**S-Methylisothiourea Hydrochloride.**—A solution of 2.56 g. (0.02 mole) of S-methylisothiourea hydrochloride and 1.98 g. of 2-methylpiperidine (0.02 mole) in 100 ml. of water was held at room temperature for 72 hours. The addition of 6.0 g. of ammonium picrate gave a yellow precipitate which was collected and fractionally crystallized from water to give 1.10 g. (15% yield) of 1-guanyl-2-methylpiperidine picrate, m.p. 227–229°. A second recrystallization from water provided an analytical sample, m.p. 227.5–229.5°.

Anal. Calcd. for $C_{13}H_{18}N_6O_7$: C, 42.16; H, 4.90; N, 22.70. Found: C, 42.48; H, 4.69; N, 22.62.

Concentration of the original filtrate gave 1.63 g. (25%) of S-methylisothiourea picrate, m.p. 220–221° (lit.[33] 221°) alone or when admixed with an authentic sample.

(b) **Cyanamide.**—A yield of 3.56 g. (41%) of 1-guanyl-2-methylpiperidine picrate, m.p. 227.5–229.5°, was obtained.

(c) **Nitrosoguanidine.**—A yield of 0.13 g. (2%) of 1-guanyl-2-methylpiperidine picrate, m.p. 227.5–229.5°, was obtained. In addition, 0.95 g. of unreacted substrate (54%), was recovered from the reaction mixture.

(4) *cis*-**2,6-Dimethylpiperidine at 25°.** (a) **Cyanamide.**—A solution of 0.84 g. (0.02 mole) of cyanamide and 2.26 g. of *cis*-2,6-dimethylpiperidine (0.02 mole) in 100 ml. of water was allowed to react for 72 hours at room temperature. The reaction mixture was acidified with picric acid and the solid precipitate collected. Crystallization from water gave 2.45 g. of *cis*-1-guanyl-2,6-dimethylpiperidine picrate, m.p. 213.5–216° (32% yield).

Anal. Calcd. for $C_{14}H_{20}N_6O_7$: C, 43.75; H, 5.25; N, 21.87. Found: C, 44.13; H, 5.01; N, 21.89.

(b) **S-Methylisothiourea Hydrochloride.**—No product could be detected from the reaction of this substrate with *cis*-2,6-dimethylpiperidine. Treatment of the reaction mixture with ammonium picrate (6.0 g.) afforded an insoluble mixture of picrate salts of the reagents.

(c) **Nitrosoguanidine.**—The reaction mixture afforded only a recovery of 1.06 g. (60%) of unreacted nitrosoguanidine and 5.64 g. (83%) of impure *cis*-2,6-dimethylpiperidine picrate, m.p. 156–161° (lit.[22] 163–165°).

(5) **Piperidine Hydrochloride at 100°.** (a) **Nitrosoguanidine.**—A suspension of 1.76 g. (0.02 mole) of nitrosoguanidine in a solution of 2.43 g. of piperidine hydrochloride (0.02 mole) and 100 ml. of water was refluxed for 40 hours. The reaction mixture now was neutralized by the dropwise addition of 6 *N* hydrochloric acid and then 4.92 g. of ammonium picrate (0.02 mole). The yellow solid was collected and after a single recrystallization from water it amounted to 3.28 g. (46%) of 1-guanylpiperidine picrate, m.p. 254–255°. The original filtrate, on concentration, yielded 0.53 g. (8%) of piperidine picrate, m.p. 153–155° (lit.[31] 147–149°).

(b) **Cyanamide.**—A yield of 3.50 g. (50%) of 1-guanylpiperidine picrate, m.p. 245.5–255.5°, was obtained. In addition, 0.45 g. (7%) of piperidine picrate was recovered.

(c) **S-Methylisothiourea Hydrochloride.**—A yield of 2.66 g. (36%) of 1-guanylpiperidine picrate, m.p. 255–255.5°, was obtained. From the mother liquors 1.38 g. (22%) of piperidine picrate, m.p. 154–155°, was recovered.

(6) **3-Methylpiperidine Hydrochloride at 100°.** (a) **Nitrosoguanidine.**—A yield of 3.44 g. (47%) of 1-guanyl-3-methylpiperidine picrate, m.p. 227–228.5°, was obtained.

(b) **Cyanamide.**—A yield of 3.55 g. (48%) of 1-guanyl-3-methylpiperidine picrate, m.p. 227.5–228.5°, was obtained.

(c) **S-Methylisothiourea Hydrochloride.**—A yield of 2.30 g. (31% yield) of 1-guanyl-3-methylpiperidine picrate, m.p. 227.5–228.5°, was obtained.

(7) **2-Methylpiperidine Hydrochloride at 100°.** (a) **S-Methylisothiourea hydrochloride.**—A solution of 2.56 g. (0.02 mole) of S-methylisothiourea hydrochloride and 1.98 g. of 2-methylpiperidine (0.02 mole) in 100 ml. of water was refluxed for 40 hours. The solution was acidified with 2 *N* hydrochloric acid and then 6.0 g. of ammonium picrate was introduced. The solid was collected and recrystallized from water to give 0.85 g. (11%) of 1-guanyl-2-methylpiperidine picrate, m.p. 227.5–229.5°.

(b) **Cyanamide.**—A yield of 1.65 g. (22%) of 1-guanyl-2-methylpiperidine picrate, m.p. 227.5–229.5°, was obtained.

(c) **Nitrosoguanidine.**—A yield 1.41 g. (19%) of 1-guanyl-2-methylpiperidine picrate, m.p. 227.5–229.5°, was obtained.

(8) *cis*-**2,6-Dimethylpiperidine Hydrochloride at 100°.** (a) **Cyanamide.**—A solution 0.84 g. (0.02 mole) of cyanamide and 2.99 g. (0.02 mole) of *cis*-2,6-dimethylpiperidine in 100 ml. of water was refluxed for 40 hours. To the clear solution was added 6.0 g. of ammonium picrate and the solid collected. Recrystallization from water gave 1.60 g. (21%) of 1-guanyl-2,6-dimethylpiperidine picrate, m.p. 214–216°.

(b) **Nitrosoguanidine.**—A yield at 1.58 g. (21%) of 1-guanyl-2,6-dimethylpiperidine picrate, m.p. 214–216°, was obtained.

(c) **S-Methylisothiourea.**—A yield of 0.96 g. (13%) of 1-guanyl-2,6-dimethylpiperidine picrate, m.p. 214–216°, was obtained.

(32) In this case, 0.55 g. of nitrosoguanidine (31%) was recovered at the end of 72 hours.

(33) E. A. Warner, *J. Chem. Soc.*, **99**, 1168 (1919).

[CONTRIBUTION FROM THE LABORATORIES OF THE PITTSBURGH PLATE GLASS COMPANY, THE ALDRICH CHEMICAL COMPANY AND HARVARD UNIVERSITY]

Unsaturated Aromatic Amines; A Novel Synthesis of Indoles

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RECEIVED JUNE 14, 1957

Convenient preparations of N-allyl-, N-crotyl- and N-pentenylaniline are described. N-Crotylaniline reacts with polyphosphoric acid to yield 2,3-dimethylindole and a 2,3-dimethylindoline.

Our recent studies of unsaturated phenols[2] prompted a study of the preparations and reactions of simple unsaturated anilines.

N-Allylaniline,[3a-c,d] which had previously been

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(2) A. R. Bader, THIS JOURNAL, **78**, 1709 (1956).

(3) (a) H. Schiff, *Ann. Suppl.*, **3**, 364 (1864); (b) F. B. Davis, R. Q. Brewster, J. S. Blair and W. C. Thompson, THIS JOURNAL, **44**, 2638 (1922); (c) F. L. Carnahan and C. D. Hurd, *ibid.*, **52**, 4586 (1930); (d) *cf.* also the paper by C. D. Hurd and W. W. Jenkins, *J. Org. Chem.*, **22**, 1418 (1957), which appeared while our paper was in press.