and was found to have the following composition (mole %): *sym*-triazine, 7; 2-ethyl-*sym*-triazine, 42; 2,4-diethyl-*sym*-triazine, 42; 2,4,6-triethyl-*sym*-triazine,[19] 9. Attempted fractional distillation failed to give analytically pure samples of these products.

Cotrimerization of Formamidine Hydrochloride with Benzamidine Hydrochloride.—A mixture of 8.05 g. of formamidine hydrochloride (0.10 mole) and 15.65 g. (0.10 mole) of benzamidine hydrochloride was heated to 250° at 10–20 mm. pressure in a distilling apparatus. Some solid sublimed into the condenser and 1.0 g. of liquid was collected in the receiver which was immersed in a Dry Ice-acetone-bath. The residue in the distilling flask (14.0 g.) was extracted with water and the remaining 8.0 g. of solid was recrystallized from methanol whereby 4.5 g. of 2,4-diphenyl-*sym*-triazine was obtained, m.p. 87–88° (lit.[31] 88.5°). The sublimate from the condenser was united with the mother liquor. Steam distillation of the mixture gave an oil which crystallized as the distillate cooled. This was **2-phenyl-*sym*-triazine**, m.p. 60–62° (63–65° from methanol; lit.[30] 63.5°). An additional 2 g. of crude 2,4-diphenyl-*sym*-triazine crystallized from the steam distillation residue. The yield of this product was 56% based on benzamidine hydrochloride used, and the yield of 2-phenyl-*sym*-triazine was 20% based on formamidine hydrochloride used. The liquid distillate obtained was chiefly benzonitrile (10% yield).

Anal. (2-phenyl-*sym*-triazine) Calcd. for $C_9H_7N_3$: C, 68.77; H, 4.49; N, 26.74. Found: C, 68.36; H, 4.79; N, 26.71.

Anal. (2,4-diphenyl-*sym*-triazine) Calcd. for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.02. Found: C, 76.99; H, 4.88; N, 17.90.

Cotrimerization of N-(Trichloroacetimidyl)-trichloroacetamidine (VIII) with Benzamidine Hydrochloride.—A mixture of 1.5 g. (0.010 mole) of benzamidine hydrochloride and 3.0 g. (0.010 mole) of VIII was fused in a test-tube. At about 120° a homogeneous melt was obtained and ammonia evolution was evident. Heating was continued for 15 minutes at about the same temperature. The reaction mixture was then cooled and the solid obtained was recrystallized from wet ethanol. The product (1.9 g.) melted at 76–79°. Further recrystallization from aqueous acetone and other solvents failed to raise this melting point. The product, nevertheless, was virtually identical, according to infrared comparison, with authentic 2-phenyl-4,6-bis-(trichloromethyl)-*sym*-triazine (XI), m.p. 96–8°, prepared by the cotrimerization of benzonitrile and trichloroacetonitrile.[32] Analysis of the low-melting product gave the following fairly satisfactory results.

Anal. Calcd. for $C_{11}H_5N_3Cl_6$: N, 10.72; Cl, 54.40. Found: N, 11.21; Cl, 54.32.

Cotrimerization of VIII with Benzamidine.—A solution of benzamidine in ethanol was prepared by treating 7.8 g. (0.050 mole) of benzamidine hydrochloride with a solution of 2.7 g. (0.050 mole) of sodium methoxide in 25 cc. of ethanol. The precipitated sodium chloride was filtered after 15 minutes, and 15.3 g. (0.050 mole) of VIII was added to the filtrate. The reaction mixture was heated for 1.5 hours 50–60° and then was allowed to stand at room temperature. Slow crystallization gave 6.75 g., m.p. *ca.* 130°. This material melted at 135–136° after recrystallization from aqueous alcohol. It appears to be an open chain compound rather than a *sym*-triazine but remains unidentified. The filtrate from this product was concentrated to crystallize 3.4 g. of 2-amino-4-phenyl-6-trichloromethyl-*sym*-triazine (XII), m.p. 172–174° (from wet ethanol; lit.[12] 175–176° cor.), yield 23%. Infrared comparison showed this compound to be identical with an authentic sample prepared by reaction of XI with ammonia as described by Kreutzberger.[12]

Cotrimerization of VIII with Acetamidine.—A solution of 0.033 mole of acetamidine was prepared by reaction of equimolar amounts of acetamidine hydrochloride and sodium methoxide in 10 cc. of ethanol. To this was added 10 g. of VIII. The mixture was allowed to stand overnight at room temperature. It was then evaporated at reduced pressure to remove the solvent, and the residue was heated to 180° during one hour. The dark reaction product was extracted with hot ethanol. From the extract was isolated 1.8 g., m.p. 146–150°. This was found to be crude **2-amino-4-methyl-6-trichloromethyl-*sym*-triazine (XIII)**. Recrystallization from ethanol raised the m.p. to 156–158° (lit.[12] 158–159° cor.). Infrared examination of by-product fractions from the reaction mixtures indicated that no other *sym*-triazine compound was present in significant amount.

Anal. Calcd. for $C_5H_3N_4Cl_3$: C, 26.40; H, 2.22. Found: C, 26.68; H, 2.43.

(31) G. Grundmann, H. Ulrich and A. Kreutzberger, *Chem. Ber.*, **86**, 181 (1953).

(32) K. Dachlauer, German Patent 682,391 (1939).

STAMFORD, CONN.

[CONTRIBUTION FROM THE STAMFORD LABORATORIES, CENTRAL RESEARCH DIVISION, AMERICAN CYANAMID CO.]

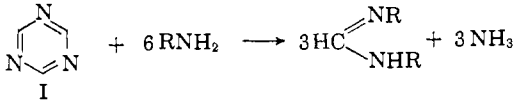
Synthesis of the *sym*-Triazine System. II.[1] Preparation of Monosubstituted *sym*-Triazines by Reaction of *sym*-Triazine with Amidines

BY FRED C. SCHAEFER AND GRACE A. PETERS

RECEIVED AUGUST 21, 1958

The reaction of amidino compounds with *sym*-triazine is reported as an efficient and broadly applicable method for the preparation of monosubstituted *sym*-triazines.

The dominant characteristic of the chemistry of *sym*-triazine (I) is the suceptibility of the ring system to cleavage and destruction by nucleophilic



I

reagents. Among such reagents amino compounds have received most attention. The literature[2] on "hydrocyanic acid dimer," as it was then called, discloses the reaction of I with aniline which produces N,N'-diphenylformamidine. Grundmann and Rätz[3] and, independently, Dr. Hechenbleikner in our laboratory have also shown the reaction of *sym*-triazine with ammonium chloride to be very clean and to lead to formamidine hydrochloride in essentially quantitative yield. Application of this degradation reaction for the preparation of such heterocyclic formamidines as benzimidazole and 3-aminotriazole has also been reported.[4] Undoubtedly such reactions proceed in a stepwise manner, and it occurred to us that if the reagent used was an

(1) Paper I, F. C. Schaefer, I. Hechenbleikner, G. A. Peters and V. P. Wystrach, THIS JOURNAL, **81**, 1466 (1959).

(2) L. E. Hinkel and E. F. Ayling and J. H. Beynon, *J. Chem. Soc.*, 678 (1935).

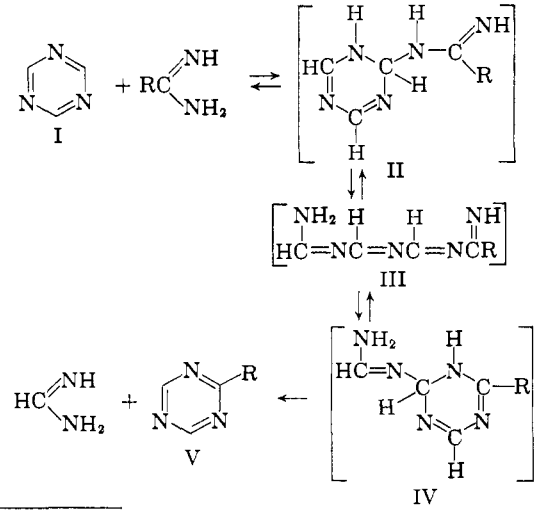
(3) C. Grundmann and R. Rätz, *J. Org. Chem.*, **21**, 1037 (1956).

(4) C. Grundmann and A. Kreutzberger, THIS JOURNAL, **77**, 6559 (1955).

amidine an intermediate would be formed which might recyclize to give a substituted *sym*-triazine compound. In this paper are presented the results of our investigation of the reaction of I with amidines and amidine salts. This has proved to be a useful synthetic method applicable to a very wide variety of amidino compounds and has made available to us classes of *sym*-triazine compounds which have hitherto been unknown or only difficultly accessible.

Previously available methods for the preparation of monosubstituted *sym*-triazines (V) are quite limited in scope or in practicality. The procedure of Hirt, Nidecker and Berchtold,[5] who prepared 2-phenoxy-*sym*-triazine and a variety of 2-amino-*sym*-triazines by catalytic reduction of the corresponding dichloro-*sym*-triazines, appears to have been quite inefficient although the intermediates are readily available. Although it was described as more useful, yields were not stated for their alternative process for the preparation of 2-amino-*sym*-triazines by reaction of 2-phenoxy-*sym*-triazine with amines. The preparation of 2-phenyl-*sym*-triazine by Grundmann, Ulrich and Kreutzberger[6] by degradation of 2,4-dichloro-6-phenyl-*sym*-triazine or 2,4-bis-(trichloromethyl)-6-phenyl-*sym*-triazine while a notable achievement does not make this monosubstituted *sym*-triazine available in useful amounts, and the procedures may not be applicable for interesting related compounds. The same deficiencies are apparent in the recently successful preparation of 2-methyl-*sym*-triazine by Grundmann and Kober.[7] Our preparation[1] of 2-alkyl- and aryl-*sym*-triazines by cotrimerization of formamidine hydrochloride with other amidines is relatively simple but also is unsatisfactory because of inadequate yields.

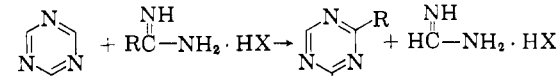
As a preface and an aid in the presentation of the experimental results, our working hypothesis regarding the broad features of the general reaction is given at this point. It is convenient to consider the reaction of an amidine with *sym*-triazine as proceeding in the manner shown below.



The reaction is considered to be initiated by nucleophilic attack of the amidine molecule at one of the electron-deficient carbon atoms of the triazine ring. The resultant transient adduct II would be in tautomeric ring-chain equilibrium with III. This is a symmetrical structure in a sense and would be able to recyclize to form either II or IV. Structure IV could then form a substituted *sym*-triazine (V) by elimination of formamidine. The success of the reaction depends on the fact that V in all cases is much more stable than I in this environment.

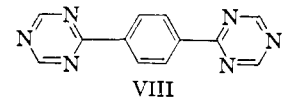
It has been found that either the free amidines or their acid salts can be used in the reaction with I. The net result is essentially the same in either case, and it is not clear what influence the added acid may have in the over-all process. In the mechanistic scheme outlined above the acid might, for example, have a retarding effect by reducing the nucleophilic character of the amidine, it might catalyze the reaction by forming the *sym*-triazinium ion which would have greater electrophilic character, or it might have an influence on the recyclization rate.

The reaction of I with aromatic amidine hydrochlorides has been found to be very clean-cut and the process very simple. Yields of 2-phenyl-



VI, R = C_6H_5
VII, R = *m*-$NO_2C_6H_4$

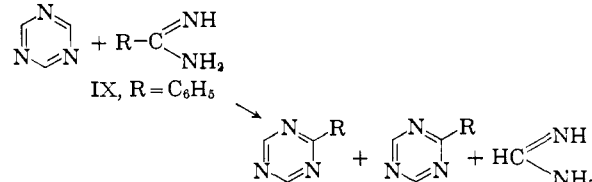
sym-triazine (VI) and 2-*m*-nitrophenyl-*sym*-triazine (VII) of 87 and 77%, respectively, were obtained by mixing equimolar amounts of the corresponding amidine hydrochloride with I in methanol at room temperature. Boiling methanol was used with terephthalamidine dihydrochloride to increase its solubility. The product in this case was the interesting compound, 2,2′-*p*-phenylenedi-*sym*-triazine (VIII). N-Methylbenzamidine



VIII

hydrochloride was also tried, and it was found that the N-substituent markedly retarded the reaction although VI was obtained in 33% yield after 1.5 hours in boiling ethanol.

The reaction of I with free aromatic amidines proceeds equally easily. It was observed, however, that under some conditions, as for example in a fusion process or in boiling acetonitrile, reaction of free benzamidine (IX) with *sym*-triazine produced both VI and 2,4-diphenyl-*sym*-triazine (X).



VI, R = C_6H_5 X, R = C_6H_5
XI, R = CH_3 XII, R = CH_3

The formation of this by-product presumably is due to attack by the amidine on one of the tran-

(5) R. Hirt, H. Nidecker and R. Berchtold, *Helv. Chim. Acta*, **33**, 1365 (1950).

(6) C. Grundmann, H. Ulrich and A. Kreutzberger, *Ber.*, **86**, 181 (1953).

(7) C. Grundmann and E. Kober, *J. Org. Chem.*, **21**, 641 (1956).

sient intermediates in the desired reaction before the recyclization to VI has occurred. We have demonstrated that VI itself does not react with benzamidine even on long heating in boiling ethanol. In an experiment designed to minimize formation of X by keeping the amidine concentration low, a relatively dilute solution of the amidine in methanol was added gradually to I in methanol at 25°. The 2-phenyl-*sym*-triazine which was obtained in 94% yield did not contain a detectable amount of the diphenyl derivative.

The reaction is also applicable but somewhat less satisfactory with the aliphatic amidines. The reaction of acetamidine hydrochloride with *sym*-triazine was tried in methanol at 25° and in ethanol and acetonitrile at their boiling points. In all cases mixtures of 2-methyl-*sym*-triazine (XI) and 2,4-dimethyl-*sym*-triazine (XII) were obtained and in some cases small amounts of 2,4,6-trimethyl-*sym*-triazine were also found.[8] The total yields were only of the order of 50%, however, and about 20% of the *sym*-triazine was recovered unchanged. Acetonitrile seemed to be the best medium for the reaction. Because of its relatively low solvent power for acetamidine hydrochloride, the solution in this solvent contained a favorable ratio of the reactants for minimizing the formation of XII. As a result the molar ratio of mono- to dimethyl-*sym*-triazine obtained was approximately 4:1. An additional advantage in the use of acetonitrile is that by-product formamidine hydrochloride crystallizes from it as formed and may be recovered practically quantitatively by filtration before the solution is distilled.

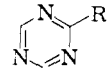
Somewhat better results were obtained with free acetamidine. Slow addition at room temperature of a dilute solution of acetamidine in methanol to *sym*-triazine in methanol and subsequent distillation of the reaction mixture gave a fraction which contained about 80% XI. Small amounts of both I and XII were also present. The 2-methyl-*sym*-triazine content of this fraction indicated a yield of approximately 70%. It is probably impossible to avoid the formation of some XII in such reactions because we find that unlike 2-phenyl-*sym*-triazine, XI is itself attacked fairly readily by the amidine and converted to the disubstituted derivative. In fact, it is possible through the use of a large excess of acetamidine to convert I fairly completely to XII under essentially the same conditions as used to prepare XI. Such a reaction gave yields of XI and XII of about 8 and 84%, respectively. These figures are based on conversion of one mole of starting *sym*-triazine to one mole of the substituted derivative.

Substituted aliphatic amidine hydrochlorides which were investigated were 2-phenylacetamidine hydrochloride (XIII) and 2,2,2-trichloroacetamidine hydrochloride (XIV). Reaction of XIII with *sym*-triazine in boiling acetonitrile gave a mixture from which 2-benzyl-*sym*-triazine (XV) and 2,4-dibenzyl-*sym*-triazine were recovered by distillation in 34 and 35% yields, respectively. Under the same conditions XIV gave a 65% yield of 2-trichloromethyl-*sym*-triazine (XVI). It is interesting, however, that 2,2,2-trichloroacetamidine base (XVII) reacted with *sym*-triazine to give 2-amino-*sym*-triazine (XVIII) in 53% yield, chloroform being formed as a by-product. Such dual reactivity has been found in other work with this amidine.[1]

Compounds in which an amidino group is attached to an element other than carbon can also be used in the manner of the typical aromatic and aliphatic amidines to prepare substituted *sym*-triazines. 2-Methylpseudothiourea hydriodide (XIX) reacted very smoothly at room temperature in acetonitrile. Approximately 66% of the theoretical formamidine hydriodide crystallized as the reaction proceeded. Fractional distillation of the mother liquor gave 2-methylthio-*sym*-triazine (XX) in 90% yield. The yield of 2-methoxy-*sym*-triazine (XXI) from 2-methylpseudourea hydrochloride (XXII) was 81%. Guanidine hydrochloride (XXIII) gave a 50% yield of 2-amino-*sym*-triazine (XVIII) and phenylguanidine carbonate (XXIV) gave a 74% yield of 2-anilino-*sym*-triazine (XXV). It was rather surprising that dodecylguanidine acetate was almost unreactive toward *sym*-triazine in boiling ethanol. The free base XXVI reacted fairly readily, however, to give 2-dodecylamino-*sym*-triazine (XXVII) in 46% yield.

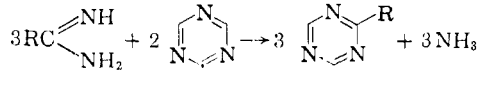
TABLE I

2-SUBSTITUTED *sym*-TRIAZINES.



Amidine compound used, $R'CNHNH_2 \cdot HCl$			Product, R	
	R′	X		
XIII	$C_6H_5CH_2$	Cl^-	XV	$C_6H_5CH_2$
XIV	CCl_3	Cl^-	XVI	CCl_3
XVII	CCl_3	(Free base)	XVIII	NH_2
XIX	CH_3S	I^-	XX	CH_3S
XXII	CH_3O	Cl^-	XXI	CH_3O
XXIII	NH_2	Cl^-	XVIII	NH_2
XXIV	C_6H_5NH	$^1/_2CO_3^=$	XXV	C_6H_5NH
XXVI	$C_{12}H_{25}NH$	(Free base)	XXVII	$C_{12}H_{25}NH$

In all of the reactions reported yields mentioned were based on the reaction of one mole of *sym*-triazine with one mole of the amidine compound to form one mole each of the substituted *sym*-triazine and formamidine or formamidine salt. It is clear that this is the correct stoichiometry when the amidine hydrochlorides are used because in several cases the formamidine hydrochloride by-product was recovered nearly quantitatively. However, in the reactions in which the free amidines were used there is less basis for calculating the yields in this way. We had hoped to find that under these conditions the free formamidine which was expected to be a by-product of the reaction would spontaneously trimerize to regenerate *sym*-triazine with evolution of ammonia. If this took place the equation for the over-all reaction would be



(8) Pure samples of the methyl-*sym*-triazines were not isolated in this work. Yield data are based on mass spectroscopic analyses of mixtures and infrared analyses calibrated by mass spectroscopy.

The potential 50% increase in the yield based on starting *sym*-triazine which might thus be achieved was very attractive, of course. Unfortunately, this recycling reaction does not appear to take place in our experiments. Reactions of free benzamidine and free acetamidine with *sym*-triazine were run at molar ratios of 3:2, but the yields on this basis were low. They did, however, approach 100% on a 1:1 basis. The 94% yield obtained in the very clean reaction of benzamidine particularly suggests that the correct stoichiometry is 1:1.

Experimental Section[9]

2-Phenyl-*sym*-triazine (VI).—A mixture of 7 g. (0.050 mole) of benzamidine hydrochloride, 4.05 g. (0.050 mole) of *sym*-triazine[10] and 5 cc. of methanol was allowed to stand at room temperature for 18 hours. Crystallization of by-product formamidine hydrochloride began in about one hour. The amount of solid present did not appear to increase after 1.5 hours, indicating that the reaction was substantially complete in this time. Dilution of the reaction mixture with 100 cc. of water caused separation of 6.8 g. (86.7%) of 2-phenyl-*sym*-triazine, m.p. 63–65°.[1,6] Infrared examination of the product indicated that 2,4-diphenyl-*sym*-triazine was absent.

Compound VI was also obtained by heating an equimolar mixture of N-methylbenzamidine hydrochloride,[11] and I in ethanol at reflux for 1.5 hours. The yield was 33%.

Reaction of I with benzamidine base (IX) was carried out as follows: Sodium methoxide (2.05 g., 0.038 mole) was added to a solution of 5.95 g. (0.038 mole) of benzamidine hydrochloride in 20 cc. of methanol. The precipitated sodium chloride was removed by filtration after about 15 minutes, and the filtrate was added gradually (one hour) to a stirred mixture of 2.0 g. (0.025 mole) of I in 5 cc. of methanol at 25°. The reaction mixture was allowed to stand for one day during which partial crystallization of the product occurred. After the usual work-up procedure, 3.7 g. of VI was obtained, m.p. 64–65°. The yield was 94%, based on conversion of one mole of I to one mole of VI.

In another experiment equimolar amounts of IX and I were heated together in refluxing acetonitrile. Both VI and 2,4-diphenyl-*sym*-triazine were obtained. These products were separated by steam distillation[1] and recovered in yields of 20%, m.p. 61–62°, and 10%, m.p. 87–88°, respectively.

Fusion of free benzamidine[12] (0.10 mole) with I (0.033 mole) at 150° gave VI in 92% yield based on I used. In addition, 2,4-diphenyl-*sym*-triazine was recovered in about 3% yield.

2-*m*-Nitrophenyl-*sym*-triazine (VII) was prepared from *m*-nitrobenzamidine hydrochloride[13] in 77% yield by the procedure used for VI; m.p. 120–122° (from aqueous methanol).

Anal. Calcd. for $C_9H_6N_4O_2$: C, 53.46; H, 2.99; N, 27.72. Found: C, 53.46; H, 3.09; N, 27.71.

2,2′-*p*-Phenylenedi-*sym*-triazine (VIII).—A mixture of 4.0 g. (0.017 mole) of terephthalamidine dihydrochloride,[14] 2.75 g. (0.034 mole) of *sym*-triazine and 20 cc. of methanol was boiled for 2.5 hours. After dilution of the reaction mixture with water, the crude product was filtered and washed with water and with methanol; yield 2.8 g. (70%), m.p. 293–295° (298–299° from benzene).

Anal. Calcd. for $C_{12}H_8N_6$: C, 61.01; H, 3.41; N, 35.58. Found: C, 61.16; H, 3.54; N, 35.80.

2-Methyl-*sym*-triazine (XI). A. Reaction of Acetamidine Hydrochloride with I.—A mixture of 23.8 g. (0.25 mole) of acetamidine hydrochloride,[15] 16.2 g. (0.20 mole) of I and 20 cc. of acetonitrile was boiled under reflux for 4 hours. Two liquid phases were present throughout most of this time. The lower phase crystallized as the reaction mixture cooled and was shown to be chiefly formamidine hydrochloride (approx. 90% yield). The liquid portion of the reaction mixture was distilled to obtain a 13.5 g. fraction boiling at 120–130° which contained the product methyl-*sym*-triazines and most of the recovered I. Mass spectroscopic analysis of the mixture showed the yield of XI to be approximately 40% and that of **2,4-dimethyl-*sym*-triazine (XII)** to be 10%.

B. Reaction of Acetamidine with I.—Sodium metal (3.2 g., 0.14 g. at.) was dissolved in 40 cc. of methanol and to the solution was added 14.2 g. (0.15 mole) of acetamidine hydrochloride. After filtration, the resultant solution of acetamidine was added gradually at 25° (40 minutes) to a stirred mixture of 8.1 g. (0.10 mole) of I and 5 cc. of methanol. The reaction mixture was then distilled, yielding 8.3 g., b.p. 120–135°. This was shown by infrared analysis to be approximately 80% XI with small amounts of I and XII present.

2,4-Dimethyl-*sym*-triazine (XII)[16].—A solution of acetamidine was prepared by reaction of 28.4 g. (0.30 mole) of acetamidine hydrochloride and 16.2 g. (0.30 mole) of sodium methoxide in 40 cc. of methanol. To this was added 4.05 g. (0.050 mole) of I at room temperature. The mixture was allowed to stand for 18 hours. It was then freed and distilled at low pressure. The distillate was stripped of methanol at atmospheric pressure, and the residue (5.7 g., f.p. 36°) was analyzed by mass spectroscopy. It was found to have the composition (mole %): XII, 82; XI, 8; I, 0; **2,4,6-trimethyl-*sym*-triazine,**[1] 11. From this it was calculated that the yield of XII was 84% and of XI 8%.

Reaction of 2-Phenylacetamidine Hydrochloride (XIII)[17] with I.—A mixture of 4.25 g. (0.025 mole) of XIII, 2.0 g. (0.025 mole) of I and 15 cc. of acetonitrile was heated at reflux for 2 hours. After cooling, the acetonitrile solution was decanted from insoluble formamidine hydrochloride and evaporated to remove the solvent. Distillation of the residue (3.2 g.) yielded a small forerun of recovered I followed by 1.4 g. of **2-benzyl-*sym*-triazine (XV)**, b.p. 100–105° at 2 mm., yield 34%.

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.15; H, 5.30; N, 24.55. Found: C, 70.38; H, 5.55; N, 24.59.

The residue from the distillation (1.1 g.) solidified on cooling. Infrared comparison showed it to be quite pure **2,4-dibenzyl-*sym*-triazine** (yield 35%). Recrystallization from wet methanol gave material melting at 80–82°.

Anal. Calcd. for $C_{17}H_{15}N_3$: C, 78.13; H, 5.78; N, 16.09. Found: C, 78.13; H, 5.98; N, 16.27.

2-Trichloromethyl-*sym*-triazine (XVI).—Trichloroacetamidine hydrochloride (XIV), m.p. 217–220°, was prepared by treatment of the free amidine in acetone with hydrogen chloride.[18]

A mixture of 10.2 g. (0.0515 mole) of XIV, 4.17 g. (0.0515 mole) of I and 20 cc. of acetonitrile was heated at reflux for 30 minutes. The product solution was cooled and decanted from crystallized by-product formamidine hydrochloride. Distillation gave 6.65 g. of XVI, b.p. approximately 110° at 20 mm., yield 65%. Redistilled material had b.p. 109° at 19 mm., $n^{25}D$ 1.5392.

Anal. Calcd. for $C_4H_2N_3Cl_3$: C, 24.21; H, 1.02; Cl, 53.60; N, 21.17. Found: C, 24.68; H, 1.36; Cl, 53.40; N, 21.12.

Reaction of 2,2,2-Trichloroacetamidine Base with I.—A mixture of 0.11 mole each of 2,2,2-trichloroacetamidine (XVII)[1,19] and I in 15 cc. of acetonitrile was allowed to stand at 25° for 18 hours. Gradual crystallization gave 5.1 g. of **2-amino-*sym*-triazine (XVIII)**, m.p. 208–210° (53% yield). Recrystallization from wet ethanol gave material melting at 220–222°. Infrared comparison showed the

(9) Melting points are uncorrected. Microanalyses were carried out in these laboratories under the direction of Dr. J. A. Kuck. Infrared spectra were obtained and interpreted by Dr. J. E. Lancaster. Mass spectroscopic analyses were carried out under the supervision of Mr. A. H. Struck.

(10) L. E. Hinkel and R. T. Dunn, *J. Chem. Soc.*, 1834 (1930).

(11) H. L. Wheeler, *Am. Chem. J.*, **20**, 481 (1898).

(12) A. Pinner, "Die Imidoäther und ihre Derivate," Robert Oppenheim (Gustav Schmidt), Berlin, Germany, 1892, p. 154.

(13) A. Pinner, *Ber.*, **28**, 473 (1895).

(14) Reference 12, p. 196.

(15) Reference 12, p. 107.

(16) H. Schroeder and C. Grundmann, THIS JOURNAL, **78**, 2447 (1956).

(17) Reference 12, p. 187.

(18) This is similar to work reported by H. J. Backer and W. L. Wanmaker, *Rec. trav. chim.*, **70**, 638 (1951).

(19) K. Dachlauer, German Patent 671,785 (1939).

product to be identical with that prepared from formylguanidine and formamidine.[20]

2-Methylthio-*sym*-triazine (XX).—A mixture of 37.8 g. (0.17 mole) of 2-methylpseudothiourea hydriodide (XIX),[21] 14.0 g. (0.17 mole) of I and 40 cc. of acetonitrile produced a clear solution after shaking for 10 minutes at about room temperature. Shortly thereafter, crystallization of formamidine hydriodide began, and the mixture warmed appreciably. After 20 hours the mixture was filtered. The solid collected (19.4 g.) was formamidine hydriodide, m.p. 235–240° dec. (66% of theory). The filtrate was stripped of acetonitrile at reduced pressure, and the partly crystalline residue was then distilled as completely as possible. The distillate weighed 19.4 g. and had a freezing point of 31° (yield 90%). Upon redistillation a boiling point of 91° at 19 mm. was observed and a center cut taken for analysis had f.p. 32.5°.

Anal. Calcd. for $C_4H_5N_3S$: C, 37.78; H, 3.96; N, 33.05; S, 25.21. Found: C, 37.78; H, 4.08; N, 33.20; S, 25.27.

2-Methoxy-*sym*-triazine (XXI).—A mixture of 109 g. (0.98 mole) of 2-methylpseudourea hydrochloride (XXII),[22] 69 g. (0.85 mole) of I and 150 cc. of absolute ethanol was boiled for 3 hours. The solution was then distilled as completely as possible from the residue of formamidine hydrochloride and any unreacted XXII. The distillate was fractionated at reduced pressure, yielding 73.6 g., b.p. 71–73° at 21° mm., $n^{22.5}D$ 1.4936. A center-cut had a freezing point of 11°, yield 78%.

Anal. Calcd. for $C_4H_5N_3O$: C, 43.24; H, 4.54; N, 37.82. Found: C, 43.39; H, 4.75; N, 37.61.

Reaction of 2-methylpseudourea base with I under the same conditions as described for XXII gave a 10% yield of 2-amino-*sym*-triazine and no XXI was found.

Reaction of Guanidine Hydrochloride (XXIII) with I.—As a solution of 0.050 mole of I and 0.075 mole of XXIII in 10 cc. of ethanol was boiled under reflux crystallization of **2-amino-*sym*-triazine (XVIII)** occurred. The crude product (2.45 g., 50% yield) melted at approximately 200°. Recrystallization from water gave material melting at 224–227°.

2-Anilino-*sym*-triazine (XXV)[5].—Phenylguanidine carbonate[23] (8.3 g., 0.025 mole) was heated with 2.75 g. (0.034 mole) of I in 15 cc. of ethanol. A clear solution was obtained in a few minutes at reflux. Solid began to separate shortly after. The mixture was boiled under reflux for 1.5 hours, cooled and filtered. The recovered solid weighed 4.7 g., m.p. 164–167°, yield 74%. After recrystallization from ethanol the product melted at 171–173°.[24]

Anal. Calcd. for $C_9H_8N_4$: C, 62.78; H, 4.68; N, 32.54. Found: C, 62.44; H, 4.88; N, 32.57.

2-Dodecylamino-*sym*-triazine (XXVII).—Dodecylguanidine acetate[25] (9.40 g., 0.0327 mole) was treated with a solution of 1.77 g. (0.0327 mole) of sodium methoxide in 20 cc. of anhydrous ethanol to prepare the free guanidine XXVI. *sym*-Triazine (2.65 g., 0.0327 mole) was then added and the mixture was boiled under reflux for 2 hours. Filtration after cooling gave 9.0 g. of solid. Extraction of this material with 40 cc. of hot ethyl acetate left 3.0 g. This appeared to be a mixture of sodium acetate and unchanged dodecylguanidine acetate. More of the latter was also recovered from the alcoholic filtrate from the reaction mixture. From the ethyl acetate solution was recovered 4.15 g. of XXVII, m.p. 80–81° (46% yield). Recrystallization from ethyl acetate raised the m.p. to 83–84°.

Anal. Calcd. for $C_{15}H_{28}N_4$: C, 68.14; H, 10.69; N, 21.19. Found: C, 68.42; H, 10.51; N, 20.91.

When a mixture of dodecylguanidine acetate was heated with an equimolar amount of I in boiling anhydrous ethanol for 1.5 hours, little or no reaction occurred.

(20) J. P. English and J. H. Paden, U. S. Patent 2,334,162 (1943). C. Grundmann, L. Schwennicke and E. Beyer, *Chem. Ber.*, **87**, 19 (1954), also used this reaction and obtained XVIII in a maximum yield of 15%, m.p. 225–226°.

(21) H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, **29**, 478 (1903).

(22) F. Kurzer and A. Lawson, *Org. Syntheses*, **34**, 67 (1954). This procedure was modified in that commercial sodium acid cyanamide was treated directly with hydrogen chloride in methanol. The yield of XXII was 79%, m.p. 116–118°.

(23) R. Walther and W. Grieshammer, *J. prakt. Chem.*, [2] **92**, 247 (1915).

(24) Reference 5 gives m.p. 148–150° for XXV prepared by reaction of 2-phenoxy-*sym*-triazine with aniline. However, there can be no doubt of the identity of our higher-melting product in view of confirmatory infrared comparison with related products.

(25) Dodecylguanidine acetate was prepared by the procedure of J. H. Paden and A. F. McLean, U. S. Patent 2,425,341; m.p. 135–136°.

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A Stereochemical Interpretation of the Biosynthesis of Indole Alkaloids[1]

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The conversion of yohimbine and 3-epi-α-yohimbine, ajmalicine and corynantheine, cinchonamine and corynantheine to common intermediates is illustrated. The stereochemistry of all conversion products is discussed. The discovery of a unique C-15 configuration for the indole alkaloids is incorporated in a novel theory of biosynthesis of these natural products.

The study of the structure and synthesis of naturally occurring substances and their mode of biosynthesis has aroused much interest in recent years. While theories of biogenesis for whole classes of natural products, *e.g.*, for terpenoids and steroids,[2] and for alkaloids,[3] have been proposed, relatively little experimental verification has followed so far. With the advent of radiotracer techniques much headway has been made in the realm of terpenoids and steroids[4–7] and natural phenolic and enolic substances.[8,9] However, only a bare beginning has been made in the experimental determination of the biogenesis of alkaloids.[10]

Present concepts of alkaloid biogenesis are based primarily on inspection of alkaloid skeleta and their state of oxidation and represent attempts at unification of structural patterns among substances

(1) For preliminary communications of this work see (a) E. Wenkert, E. W. Robb and N. V. Bringi, THIS JOURNAL, **79**, 6570 (1957); (b) E. Wenkert and N. V. Bringi, *ibid.*, **80**, 3484 (958).

(2) *Cf.* L. Ruzicka, *Experientia*, **10**, 357 (1953).

(3) *Cf.* R. Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955.

(4) *Cf.* H. Rilling, T. T. Tchen and K. Bloch, *Proc. Natl. Acad. Sci.*, **44**, 167 (1958).

(5) *Cf.* J. W. Cornforth, R. H. Cornforth, G. Popják and I. Y. Gore, *Biochem. J.*, **69**, 146 (1958).

(6) *Cf.* A. J. Birch, R. W. Rickards and H. Smith, *Proc. Chem. Soc.*, 192 (1958).

(7) *Cf.* D. Arigoni, *Experientia*, **14**, 153 (1958).

(8) *Cf.* A. J. Birch, "Biosynthetic Relations of Some Natural Phenolic and Enolic Compounds," in L. Zechmeister, "Progress in the Chemistry of Organic Natural Products," Springer–Verlag, Vienna, 1957.

(9) *Cf.* A. J. Birch, Massy-Westropp, R. W. Rickards and H. Smith, *J. Chem. Soc.*, 360 (1958).

(10) *Cf.* L. Marion, *Bull. soc. chim. France*, 109 (1958).