108–112° (18 mm.), $n^{30}D$ 1.5665. This was apparently 2-methylamino-3-picoline, which contained none of the azaindole desired, as shown by its complete conversion to the benzoyl derivative. It was dissolved in pyridine and treated with benzoyl chloride by the method of Chichibabin,[12] except that the benzoylation mixture, after heating, was poured into aqueous potassium carbonate and allowed to stand for 40 minutes, after which it was extracted with ether. After removal of ether and pyridine from the dried extracts the product distilled completely at 212° (19 mm.). On cooling the distillate crystallized; m.p. 91.5–96°.

1,7-Dimethyl-1H-pyrrolo[2,3-b]pyridinium Iodide (VII) from Compound III.—To 0.52 g. of compound III, purified by distillation, was added 5 ml. of methyl iodide and the mixture was allowed to stand under nitrogen for 28 hours. At the end of this period the excess alkylating agent was evaporated and the yellow, solid residue was dried in a vacuum desiccator. There was obtained 1.37 g. of product. This yield corresponds to 0.5 mole of extra methyl iodide per mole of monoalkylation product. Recrystallizations from absolute ethanol produced white needles, m.p. 249.5° with sharp decomposition. The melting point depended greatly on the rate of heating.

Anal. Calcd. for $C_9H_{11}N_2I$: C, 39.43; H, 4.05; basic N, 5.11. Found: C, 39.64; H, 4.02; basic N, 4.97.

When compound III, as obtained from the methiodide, was treated in a similar fashion with methyl iodide the same compound was obtained, also in a yield corresponding to 0.5 mole excess alkyl halide. In this case the white needles decomposed at 261°. The ultraviolet spectrum (water solvent) was essentially identical with that of the product obtained by alkylation of the 1-methyl-7-azaindole. Maxima were observed at 227 mμ (log ε 4.522) and at 296 mμ (log ε 3.888). The analytical data, however, again indicated the presence of impurities.

Compound VII by Methylation of 1-Methyl-7-azaindole.—Compound VI (652 mg.) was mixed with 5 ml. of methyl iodide and allowed to stand under nitrogen for a period of 60 hours, during which time a light-yellow solid was slowly deposited. The excess methyl iodide was evaporated in a stream of nitrogen and the residue was washed with cyclohexane. There was thus obtained 597 mg. (44.2%) of alkylation product. From the cyclohexane washings there was obtained, on evaporation, 275 mg. of starting material (42.2%). On recrystallization from absolute alcohol the product melted at 250.5° dec. On admixture with the alkylation product from compound III (obtained from the *p*-toluenesulfonate), a melting point of 251.5° dec. was observed. The ultraviolet spectrum of an aqueous solution had absorption maxima at 227 mμ (log ε 4.506) and at 296 mμ (log ε 3.882).

Anal. Calcd. for $C_9H_{11}N_2I$: C, 39.43; H, 4.05; N, 10.22; I, 46.29. Found: C, 39.65; H, 4.19; N, 10.4; I, 46.0.

Ultraviolet Spectra.—All spectra were measured on a Beckman model DU quartz spectrophotometer at concentrations ranging from 5×10^{-5} to 1.3×10^{-4} *M*. The solvent was in all cases cyclohexane unless otherwise specified.

AMHERST, MASSACHUSETTS

[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

Triazines. XIII. The Ring Cleavage of *s*-Triazine by Primary Amines. A New Method for the Synthesis of Heterocycles[1,2]

BY CHRISTOPH GRUNDMANN AND ALFRED KREUTZBERGER[2a]

RECEIVED MAY 31, 1955

Primary amines cleave *s*-triazine completely under evolution of ammonia and formation of the corresponding N,N′-disubstituted formamidines. Applied to suitable diamines, this reaction which occurs under mild conditions and with high yields provides a valuable method for the synthesis of various heterocycles, such as imidazolines, tetrahydropyrimidines, purines, benzoöxazoles and benzothiazoles.

During our recently reported studies of the halogenation of *s*-triazine[3] we tried to obtain, besides the described 2,4-dichloro-*s*-triazine,[4] the yet unknown monochloro-*s*-triazine by treating an excess of *s*-triazine with chlorine. Working up such reaction mixtures, after treatment with aniline in order to convert the unstable chlorides into the corresponding anilino-*s*-triazines, did not result in the expected 2-anilino-*s*-triazine, which has previously been prepared by a different route.[5a] However, besides 2,4-dianilino-*s*-triazine and 2,4,6-trianilino-*s*-triazine a considerable amount of N,N′-diphenylformamidine (IV) was found which could originate only from unreacted *s*-triazine still present in the chlorination mixture.

This assumption was confirmed by treating aniline with pure *s*-triazine; N,N′-diphenylformamidine was formed almost quantitatively with evolution of ammonia.[5b] The yield of the latter indicates that all three methine groups contained in the *s*-triazine ring participate in this peculiar ring cleavage, the only by-product being three moles of ammonia. The same reaction occurs as well with other aromatic, aliphatic, hydroaromatic and heterocyclic primary amines, under conditions which are given in general in the Experimental part of this paper. Table I lists some of the compounds obtained. These results recommend the reaction of *s*-triazine with primary amines as the best method for the synthesis of N,N′-symmetrical substituted formamidines.

Previously described procedures give often unsatisfactory results and are of limited applicability. Under any circumstances the present method is superior in yield and in ease of carrying out the reaction.

The reaction seems to be strictly limited to pri-

(1) This article is based on work performed under Project 116-B of The Ohio State University Research Foundation, sponsored by the Olin Mathieson Chemical Corporation.

(2) Preceding communication: Ch. Grundmann, H. Schröder and W. Ruske, *Chem. Ber.*, **87**, 1865 (1954).

(2a) Presented before the Division of Organic Chemistry at the 127th Meeting of the American Chemical Society, Cincinnati, Ohio, March 30, 1955.

(3) Ch. Grundmann and A. Kreutzberger, THIS JOURNAL, **77**, 44 (1955).

(4) Ch. Grundmann and E. Beyer, *ibid.*, **76**, 1948 (1954); I. Hechenbleikner, *ibid.*, **76**, 3032 (1954).

(5) (a) R. Hirt, H. Nidecker and R. Berchtold, *Helv. Chim. Acta*, **33**, 1365 (1950). (b) L. E. Hinkel, E E. Ayling and J. H. Beynon (*J. Chem. Soc.*, 678 (1935)), have already described the reaction of their "iminoformylcarbylamine"—which is in fact *s*-triazine—with aniline and some other aromatic amines obtaining aromatic disubstituted formamidines. Of course, on the basis of their false formula they were not able to interpret the mechanism correctly and they did not recognize the wide applicability of this reaction, especially for the synthesis of heterocycles.

TABLE I

PREPARATION OF N,N'-DISUBSTITUTED FORMAMIDINES FROM *s*-TRIAZINE

Amine	Reacn. product RN=CHNHR R =	M.p. or b.p. (mm.), °C.	Yield, %	Empiric formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
n-Butyl-	CH_3-$(CH_2)_3$ (I)[6]	103–104 (4)[a]	96.8	$C_9H_{20}N_2$					17.94	17.96
n-Heptyl-	CH_3-$(CH_2)_6$ (II)	213–214 (4)[b]	94.4	$C_{15}H_{32}N_2$					11.65	11.71
n-Dodecyl-	CH_3-$(CH_2)_{11}$ (III)	72–74	100.0	$C_{25}H_{52}N_2$	78.87	78.28	13.77	13.72	7.36	7.83
Aniline	C_6H_5 (IV)[7]	143	93.0	$C_{13}H_{12}N_2$	79.56	79.65	6.16	6.04	14.28	13.98
Benzyl-	$C_6H_5CH_2$ (V)[8]	79	84.4	$C_{15}H_{16}N_2$	80.32	80.36	7.19	7.20	12.49	12.49
Cyclohexyl-	C_6H_{11} (VI)	106	84.4	$C_{13}H_{24}N_2$	74.94	74.88	11.61	11.48	13.45	13.37

[a] $n^{25}D$ 1.4632. [b] $n^{22}D$ 1.4729.

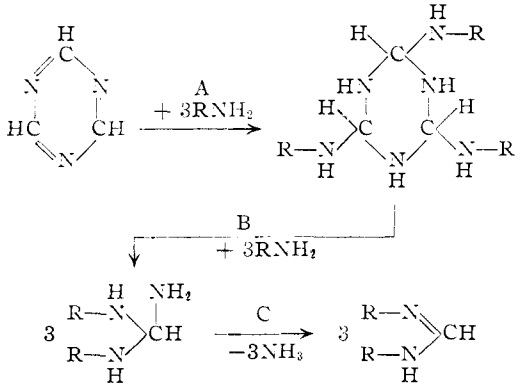
mary amines; secondary and tertiary amines do not react with *s*-triazine. On the other hand, ammonia seems to react with *s*-triazine, but the expected product formamidine—known to be unstable as a free base—undergoes apparently rapid further decomposition resulting in the formation of dark untractable tars.

This type of ring cleavage does not seem applicable to trisubstituted *s*-triazines; the simplest known derivative, 2,4,6-trimethyl-*s*-triazine, does not react with aniline up to 200°. Very few simple mono- or disubstituted *s*-triazines bearing such functional groups which themselves do not react with primary amines are known. The investigation of the behavior of such *s*-triazine derivatives toward amines is in progress.

The ring cleavage of *s*-triazine itself with primary amines, following the general equation

$$C_3H_3N_3 + 6RNH_2 \longrightarrow 3NH_3 + 3R{-}NHCH{=}N{-}R$$

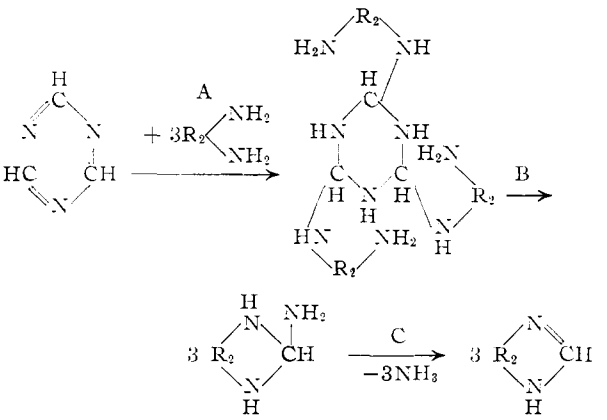
may be explained by the mechanism



In step A, three molecules of a primary amine add to one molecule of *s*-triazine under formation of a hexahydrotriazine derivative, which then in step B, by addition of three further molecules of the primary amine, splits off completely forming thereby three molecules of an N,N'-disubstituted triaminomethane. The latter finally stabilizes by splitting off ammonia (step C), forming an N,N'-disubstituted formamidine.

If *s*-triazine is treated with a diamine having both amino groups in a position relative to each other which makes ring closure possible by connecting them through a methine group, the ring cleavage of *s*-triazine leads to a convenient and simple synthesis of heterocyclic rings. The reaction proceeds analogously to that with monoamines, but just three molecules of the diamine are required instead of the six of a monoamine.

In the first phase (A) three molecules of the diamine add to one molecule of *s*-triazine, forming the hexahydrotriazine ring which then breaks down into three molecules of a cyclic triaminomethane



derivative (step B). The latter finally stabilizes by splitting off NH_3 under formation of a ring containing two N-atoms in 1,3-position (step C). Table II shows experimental results of this type of reaction.

Hitherto the most customary method of synthesizing rings of type VII consisted of the reaction of diamines with formic acid or its derivatives, like alkyl formates, formamide and trialkyl-orthoformates. Thereby, however, the yield is often unsatisfactory, because of contamination of the main product with dark colored by-products; and, in addition, high temperatures and long reaction times are sometimes required. The only by-product of the ring syntheses with *s*-triazine is gaseous ammonia; therefore the yields by this method are often quantitative and the raw products are generally of high purity. Furthermore, in most cases only a few minutes of reaction time are necessary, and also the reaction temperature is usually lower than that required in the previous processes.

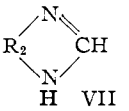
Of the compounds listed in Table II, imidazoline-2 (VIII) has never been prepared, as the well-known general reaction for the synthesis of imidazolines, heating ethylenediamine with a monocar-

(6) L. Davies and W. M. Yelland, THIS JOURNAL, **59**, 1998 (1937).

(7) A. W. Hofmann, *Ann. chim.*, [3] **54**, 197 (1858); G. Heller, *Ber.*, **37**, 3116 (1904).

(8) J. S. H. Davies, W. G. M. Jones and Imperial Chemical Industries, British Patent, 583, 190 (1946).

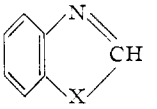
TABLE II

PREPARATION OF HETEROCYCLES OF THE TYPE FROM *s*-TRIAZINE AND DIAMINES  VII

Diamine applied	End product, VII, R_2 =	M.p., °C.	Yield, %	Identification
Ethylenediamine	CH_2–CH_2 (VIII)[a]	Picrate, 201–202	As picrate, 47	Calcd.: N, 23.41. Found: N, 23.03
1,3-Propanediamine	CH_2–CH_2–CH_2 (IX)[b]	Picrate, 279–280	As picrate, 51	Calcd.: N, 22.37. Found: 22.45
o-Phenylenediamine	C_6H_4 (X)[c]	175	100	No depression in m.p. when mixed with an authentic sample
1,8-Naphthalenediamine	$C_{10}H_6$ (XI)[d]	224	100	
1,3-Dimethyl-4,5-diamino-uracil	$C_6H_6N_2O_2$ (XII)[e]	268	99	No depression in m.p. when mixed with an authentic sample
4,5-Diaminopyrimidine	$C_4H_2N_2$ (XIII)[f]	215–217	23	
4,5-Diaminouracil	$C_4H_2N_2O_2$ (XIV)[g]	Dec. >360	29	Conversion into 8-bromocaffeine[15]

[a] VIII = Imidazoline-(2). [b] IX = 3,4,5,6-Tetrahydropyrimidine.[9] [c] X = Benzimidazole.[10] [d] XI = Perimidine.[11] [e] XII = Theophyllin.[12] [f] XIII = Purin.[13,14] [g] XIV = Xanthine.[15]

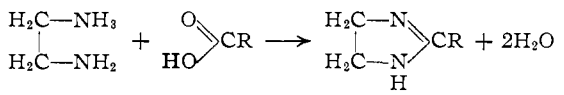
TABLE III

HETEROCYCLES OF TYPE  XV

Starting material	End product	B.p., °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found		Hydrogen, % Calcd.	Hydrogen, % Found		Nitrogen, % Calcd.	Nitrogen, % Found	
N-Methyl-*o*-phenylenediamine	XV, X = NCH_3 (XVI)[a]	60–61[d]	50	Mixed m.p. with an authentic sample								
o-Aminophenol	XV, X = O (XVII)[b]	45 (4 mm.)	89	70.58	70.54	70.38	4.23	4.31	4.29	11.76	11.52	11.68
o-Aminothiophenol	XV, X = S (XVIII)[c]	74.5 (3 mm.)	85	62.20	62.20	62.05	3.73	3.87	3.94	10.37	10.37	10.32

[a] XVI = 1-Methylbenzimidazole.[17] [b] XVII = Benzoxazole.[18] [c] XVIII = Benzthiazole.[19] [d] M.p., °C.

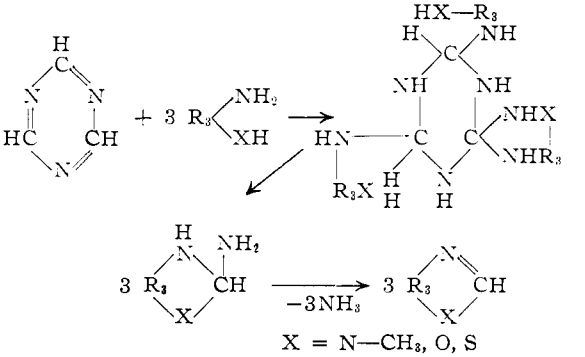
boxylic acid, fails in the case of formic acid (R = H)[16]



VIII was obtained as a semi-solid crystalline mass (m.p. 52–55°, b.p. 68–70° (3 mm.)), apparently extremely hygroscopic and apt to absorb carbon dioxide from the air. Therefore only approximative analytical data could be obtained for the base itself, but its readily-formed picrate is a well-characterized substance. An attempt to characterize VIII as benzoylimidazoline resulted in ring cleavage, N,N′-dibenzoylethylenediamine being the sole isolated product. This kind of ring cleavage is well known with other imidazole derivatives.

3,4,5,6-Tetrahydro-pyrimidine (IX) has been prepared previously in moderate yield by the reaction of 1,3-propanediamine with ethyl orthoformate,[9] but the constants given by the discoverers differ considerably from those of our product (Skinner and Wunz: b.p. 88–89° (1 mm.), $n^{23.5}D$ 1.5143; Grundmann and Kreutzberger: b.p. 71–73° (3 mm.), $n^{23.5}D$ 1.4458). Whether this is due to a shift of the double bond from its original position is still an open question, but it seems to us that the high refractive index reported by the earlier investigators puts some doubt into the assumed structure of their product. Also in the case of IX we had the same difficulties in obtaining correct analytical values for the free base as with VIII; the picrate is best suited to characterize IX.

While *s*-triazine as mentioned before does not react with secondary amines alone, it undergoes cleavage with diamines that contain one primary and one secondary amino group in favored position for ring closure. *s*-Triazine even reacts with *o*-aminophenols and thiophenols analogously under ring formation. These reactions follow the general scheme



Examples of this type of reaction are given in Table III.

It seems possible that generally any primary amino compound having a second functional group X in a position suitable for ring closure will react with *s*-triazine in the manner indicated above, provided that the group X contains at least one mobile hydrogen atom. Work along these lines is under progress.

(9) G. S. Skinner and P. R. Wunz, THIS JOURNAL, **73**, 3814 (1951).
(10) E. Wundt, *Ber.*, 11, 826 (1878).
(11) F. Sachs, *Ann.*, **365**, 83 (1909).
(12) W. Traube, *Ber.*, **33**, 3052 (1900).
(13) E. Fischer, *ibid.*, **31**, 2550 (1898).
(14) I. Isay, *ibid.*, **39**, 257 (1906).
(15) A. Strecker, *Ann.*, **108**, 141 (1858).
(16) K. Hofmann, "Imidazole and Its Derivatives," Interscience Publishers Inc., New York, N. Y., 1953, p. 214.
(17) O. Fischer, *Ber.*, **38**, 321 (1905).
(18) A. Ladenburg, *ibid.*, **10**, 1124 (1877).
(19) A. W. Hofmann, *ibid.*, **11**, 8 (1878).

s-Triazine is resistant to direct substitution[3]; furthermore its great sensitiveness to hydrolytic agents makes it only of limited value as a starting point into the triazine series. On the other hand, its unexpected reactivity might make it a useful tool in many other fields of organic synthesis.

Acknowledgment.—We are very much indebted to the Olin Mathieson Chemical Corporation for their generous support of this work.

Experimental[20]

General Procedure for the Preparation of N,N'-Disubstituted Formamidine and Heterocyclic Compounds.—The reaction can be carried out without any diluent or in a suitable solvent that does not itself react with *s*-triazine; for instance benzene, toluene, tetrahydrofuran, dioxane and dimethylformamide are recommended. Alcohols are suitable if strictly anhydrous.[21] Many amines, especially the lower aliphatic ones, react vigorously with *s*-triazine even at room temperature under evolution of ammonia; generally the reaction starts on warming the components up to about 80°. When working with higher-melting amines, the recommended procedure is to mix the amine intimately with *s*-triazine and to heat the mixture above the melting point of the amine. In such cases it is often more profitable to work in a solvent, especially if the amine or the expected reaction product is sensitive to heat. Working in an inert atmosphere, *e.g.*, nitrogen, was found necessary in the preparation of purine, in order to obtain the optimum yield. Generally 6 moles of the amine (or 3 moles of a diamine or any other bifunctional compound) are applied for one mole of *s*-triazine, but an excess of the latter never had a deleterious effect. A slight excess (about 10%) of *s*-triazine is recommended in cases where temperatures above 80° are necessary to start the reaction, as some triazine might escape the reaction owing to its high volatility. The reaction is usually finished when no more ammonia is evolved; if it is initially carried out below 100°, it is advisable to warm the mixture for 1 or 2 hours more to 100–120°, or to reflux it if working in a solvent. Working up presents no problem as no by-products except of ammonia are formed; an excess of *s*-triazine is easily removed, as it is far more volatile than any possible reaction product; it can also be destroyed by a short treatment of the reaction product with cold water.

COLUMBUS, OHIO

(20) All melting points are corrected; microanalyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(21) Our previous statement (THIS JOURNAL, **76**, 5648 (1954) that *s*-triazine undergoes solvolysis with alcohols is corrected thereby, the former results were obtained with the commercial "absolute" alcohol, which still contains 0.1–0.2% of water.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

1,2,3-Benzotriazines

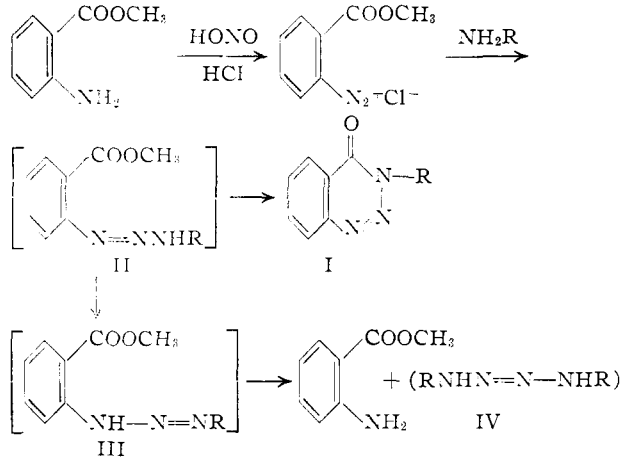
BY EARLE VAN HEYNINGEN

RECEIVED JULY 20, 1955

The synthesis of 3-substituted-3,4-dihydro-4-keto-1,2,3-benzotriazines from diazotized methyl anthranilate is reported.

There are recorded in the literature several methods for the synthesis of 3-substituted-3,4-dihydro-4-keto-1,2,3-benzotriazines. The usual technique has been to cyclize by diazotization an anthranilamide appropriately substituted on the amide nitrogen.[1] An alternative procedure was developed by Mehner[2] for 3-aryl derivatives in which an *o*-carbalkoxylphenylazoarylamine was ring closed in refluxing alcoholic solution. The only synthesis similar to the latter and not involving aryl amines was performed by Zacharias[3] in which an unsubstituted keto-1,2,3-benzotriazine resulted directly from the neutralization of diazotized ethyl anthranilate with ammonium hydroxide.

The latter reaction has now been examined for the extent of its application. It was thought probable that neutralization of diazotized methyl anthranilate with aliphatic amines would give the 3-substituted 4-keto-1,2,3-benzotriazines. This was found to be the case and compounds corresponding to I were obtained in moderate yields with simple aliphatic amines. Primary aliphatic amines with hydroxyl, secondary amino or carboxylate groups substituted on the alkyl group generally furnished the expected products in good yields.



In two cases side reactions predominated over the cyclization. When ethylamine was used, methyl anthranilate was isolated in nearly 60% yield along with a small amount of the anticipated 3-ethyl-3,4-dihydro-4-keto-1,2,3-benzotriazine. This same phenomenon accompanied the formation of a bis-ketobenzotriazinylethylene from ethylenediamine. Evidently, in these reactions the intermediate II tautomerizes to an intermediate such as III and the latter is cleaved by excess amine to methyl anthranilate. The other product of such a cleavage is conjectured to be IV, but no positive evidence was obtained for its existence or that of any of its possible decomposition products.

(1) A. Weddige and H. Finger, *J. prakt. Chem.*, [2] **35**, 263 (1887); H. Finger, *ibid.*, [2] **37**, 435 (1888); **48**, 92 (1893); A. Pictet and A. Gonset, *Chem. Zentr.*, **68**, I, 413 (1897); H. Meyer, *Ann.*, **351**, 278 (1907); K. Kratz, *J. prakt. Chem.*, [2] **53**, 213 (1896); H, King and W. O. Murch, *J. Chem. Soc.*, **125**, 2595 (1924).

(2) H. Mehner, *J. prakt. Chem.*, [2] **63**, 266 (1901).

(3) E. Zacharias, *ibid.*, [2] **43**, 446 (1881).