[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

Triazines. XXIII. The Reaction of s-Triazine with Active Methylene Compounds[1,2a]

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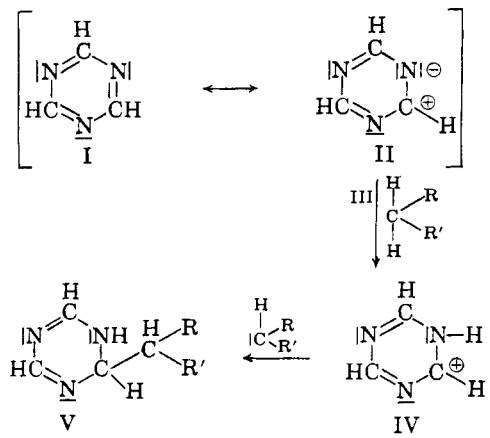
The behavior of *s*-triazine (I) towards active methylene compounds has been investigated. I reacts with ethyl acetoacetate (IIIa) to give 2,6-dimethyl-3,5-dicarbethoxypyridine (IX). The reaction of I with 2,4-pentanedione (IIIb) and ethyl cyanoacetate (IIIc) leads to the formation of 3-aminomethylene-2,4-pentanedione (Xa) and ethyl 2-aminomethylenecyanoacetate (Xb), respectively. Malononitrile (IIId) cleaves the *s*-triazine ring with formation of a mixture of aminomethylenemalononitrile (Xc) and 4-amino-5-cyanopyrimidine (XIVa). In the reaction of I with diethyl malonate (IIIe), 4-hydroxy-5-carbethoxypyrimidine (XIVb) is formed exclusively, the structure of which has been proved by an independent synthesis starting with formamidine hydrochloride (XV) and diethyl ethoxymethylenemalonate (XVI). 4-Phenyl-5-carbethoxypyrimidine (XIVc) results from the reaction of I with ethyl benzoylacetate (IIIf). I does not react with fluorene, triphenylmethane, acetic and benzoic acid.

Several investigations following the identification of the polymerization product of hydrocyanic acid under acidic conditions as *s*-triazine,[3,4] allow the conclusion that this heterocycle is to be considered a resonance hybrid receiving major contributions from structures I and II. In consequence, all C atoms in *s*-triazine are expected to be amenable to nucleophilic reagents. This expectation is fulfilled in the readily occurring ring cleavage of *s*-triazine under the influence of amines[5] and hydrazines.[6]

The electromeric displacement in II becomes a particularly important factor in the neighborhood of an organic compound from which a hydrogen atom attached to a carbon atom is removable as a proton. This effect creates especially electron-rich nitrogen atoms in II which are expected to attract the proton, thus forming IV. This step, in the case of organic active methylene compounds (III), would result in the occurrence of a carbanion which subsequently could add to an adjacent electron-deficient carbon atom with the formation of V.



RESULTS AND DISCUSSION

As a matter of fact, *s*-triazine does react with a great variety of active methylene compounds (III). Representatives of III selected for investigations are given in Table I.

TABLE I

ACTIVE METHYLENE COMPOUNDS $H_2C(R)(R')$ (III) USED

Name	R	R′	Designation
Ethyl acetoacetate	$CO_2C_2H_5$	Ac	IIIa
2,4-Pentanedione	Ac	Ac	IIIb
Ethyl cyanoacetate	C≡N	$CO_2C_2H_5$	IIIc
Malononitrile	C≡N	C≡N	IIId
Diethyl malonate	$CO_2C_2H_5$	$CO_2C_2H_5$	IIIe
Ethyl benzoylacetate	Bz	$CO_2C_2H_5$	IIIf

The reaction between *s*-triazine and III proceeds smoothly upon heating a mixture of the components either without solvent or dissolved in an inert sufficiently high boiling solvent. Within two to four hours at a bath temperature between 140–160°, in exceptional cases at room temperature, the reaction is usually completed. A significant difference from the reaction of *s*-triazine with amines is that with III no evolution of ammonia takes place, indicating that in this type reaction

(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, New York, N. Y.

(2)(a) Preceding communication: E. Kober and Ch. Grundmann, *J. Am. Chem. Soc.*, **81**, 3769 (1959). (b) Present Address: Ford Motor Company, Scientific Laboratory, Dearborn, Mich. (c) Present Address: General Cigar Co., Research Laboratory, Lancaster, Pa.

(3) Ch. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.*, **76**, 632 (1954).

(4) Ch. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.*, **76**, 5646 (1954).

(5) (a) Ch. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.*, **77**, 6559 (1955). (b) Ch. Grundmann and A. Kreutzberger, *J. Polymer Sci.*, **38**, 425 (1959).

(6) Ch. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.*, **79**, 2839 (1957).

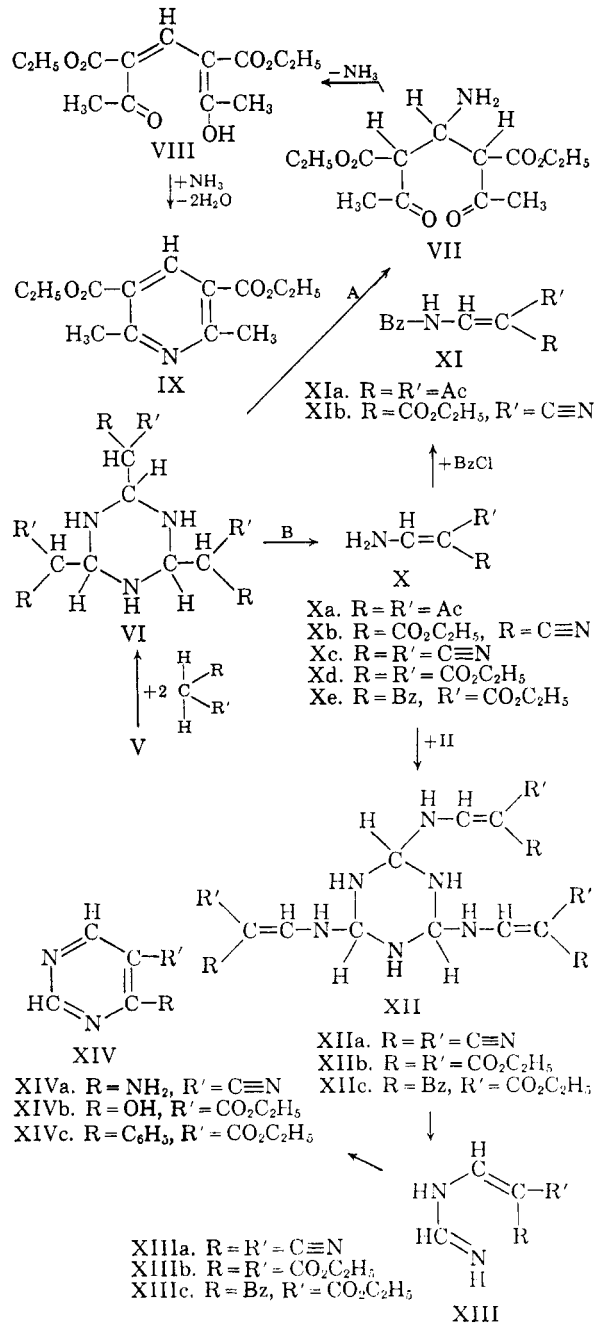
all of the ring atoms of *s*-triazine are used to build a new molecule.

Largely depending on the nature of the substituents R and R′ in III, the reaction of *s*-triazine with III follows one of two different courses ending up with either a pyridine (course A) or pyrimidine derivative (course B). The last joint hypothetical intermediate of these two courses is presented by structure VI which is formed by repetition of the reaction sequence II → IV → V on the remaining four C and N centers in V.

Course A is realized with ethyl acetoacetate (IIIa), three molecules of which add to VI and concomitantly cleave the ring to form three molecules of the aminomethane derivative VII. Ammonia is eliminated in the subsequent step to form the glutaconic derivative VIII, the very species which, as in the glutaconic type pyridine synthesis,[7] gives rise to the formation of 2,6-dimethyl-3,5-dicarbethoxypyridine (IX), the end product in this course.[7b] The preparative advantage of this one-step-synthesis of IX as compared with the known two-step-process starting with IIIa, formaldehyde, and ammonia and proceeding *via* 1,4-dihydro-IX[8a] is obvious, the yield being approximately equal in both cases.

All of the other active methylene compounds listed above (IIIb, IIIc, IIId, IIIe, and IIIf) enter the reaction course B, *i.e.*, the hexahydrotriazine derivative VI breaks down into three molecules of an aminomethylene derivative X.[8b] This in some cases is so stable that it does not undergo any further reaction and thus represents then the end of course B. Examples of this reaction type are IIIb and IIIc in which cases two compounds could be isolated which proved to be identical with 3-aminomethylene-2,4-pentanedione (Xa)[9] and ethyl 2-aminomethylenecyanoacetate (Xb)[10] respectively. The aminomethylene compounds or their tautomeric forms, the aldimines, call to mind Stephen's aldehyde synthesis[11] in which they are used as intermediates and in the simplest case may be prepared according to the sequence III → III-halide → III-nitrile → X. Also, there is a procedure for preparing Xa from IIIb and liquid hydrogen cyanide in the presence of aluminum chloride and hydrochloric acid as catalysts.[12] Upon comparing the previous processes with the new one-step procedure III → X requiring no catalyst, the simplicity of the latter becomes clearly apparent.

Whereas the attempt failed to characterize X through acetylation with acetic anhydride as the corresponding *N*-acetyl-X, successful structure characterization of X could be had by benzoylation with benzoyl chloride in pyridine leading to 3-benzamidomethylene-2,4-pentanedione (XIa) and ethyl 2-benzamidomethylenecyanoacetate (XIb), respectively.



(7)(a) L. Claisen, *Ann.*, **297**, 71 (1897); P. Baumgarten, *Ber.*, **57**, 1622 (1924). (b) The alternative path by which IX may have been formed *via* ethyl aminomethyleneacetoacetate (X. R = $CO_2C_2H_5$, R′ = Ac) must tentatively be ruled out, because there is no reaction known to convert this intermediate into IX, whereas the cleavage of VI into VIII *via* VII parallels a known path (see footnote 5) followed by the well established step VIII → IX.

(8)(a) H. Meyer and H. Tropsch, *Monatsh.*, **35**, 208 (1914); A. Singer and S. M. McElvain, *Org. Syntheses*, Coll. Vol. II, 214 (1943). (b) In the formula scheme, X is given as the aminomethylene form with the understanding that it may be in a tautomeric equilibrium with its iminomethyl form.

(9) L. Claisen, *Ann.*, **297**, 65 (1897).

(10) E. G. DeBollemont, *Bull. soc. chim. France*, [3] **25**, 41 (1901).

(11) H. Stephen, *J. Chem. Soc.*, 1874 (1925); L. N. Ferguson, *Chem. Revs.*, **38**, 243 (1946).

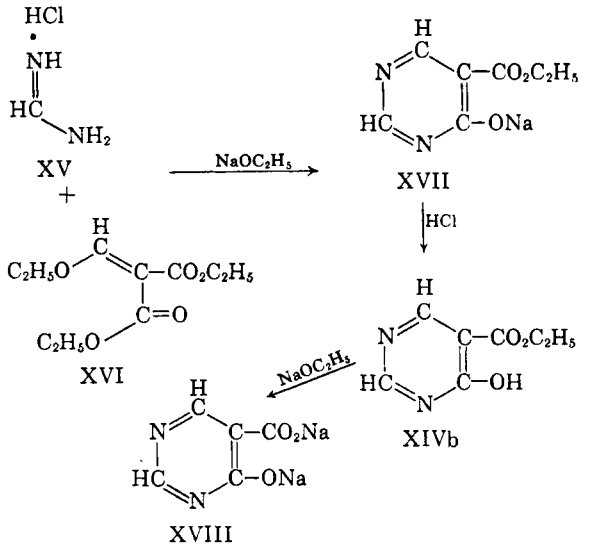
(12) H. Wieland and E. Dorrer, *Ber.*, **58**, 819 (1925).

Also with IIId the corresponding aminomethylene compound X is formed, *i.e.*, aminomethylenemalononitrile (Xc).[13] This, however, is not so stable as to represent the only final product in this reaction, but rather belongs to that category of X which, once formed, undergoes further reaction with *s*-triazine. In the case of IIId at least part of Xc originally formed reacts further with *s*-triazine to end up with 4-amino-5-cyanopyrimidine (XIVa).[14] The mixture of Xc and IVa obtained from IIId is readily separable, Xc being easily soluble and IVa sparingly so in ethanol. Application of an inert solvent like ethanol or xylene was found inevitable for the reaction between IIId and *s*-triazine because these two components without solvent react violently upon heating to give a dark red tarry product from which only trimeric IIId[15] could be isolated.

To explain the formation of XIVa, it may be assumed that first three molecules of Xc add to one still unchanged *s*-triazine ring to give the hexahydro-*s*-triazine intermediate XIIa which subsequently breaks down into three molecules of an *N*-vinylformamidine derivative (XIII). The latter finally stabilizes by cyclization to XIV.

Contrary to Xa and Xb, diethyl aminomethylenemalonate (Xd), which is to be expected of the reaction of *s*-triazine with IIIe, is so prone to further reaction with *s*-triazine that it could not be isolated at all. The only detectable end product in this case was a white substance $C_7H_8N_4O_3$ which, if it had been formed through an analogous reaction sequence—*i.e.*, Xd → XIIb → XIIIb → XIVb—should be 4 - hydroxy - 5 - carbethoxypyrimidine (XIVb).

This compound has been mentioned briefly[16] in connection with desulfurization attempts of 2 - mercapto - 4 - hydroxy - 5 - carbethoxypyrimidine, when 5-carbethoxyuracil was obtained as chief product which "was contaminated with a small quantity" of XIVb. Aside from an elemental analysis, no further structure proof for this compound was given. As XIVb is, however, a critical structure in the formulation of the mechanism of these reactions with *s*-triazine, its preparation by an independent route was most desirable. Such a synthesis was found in the reaction of formamidine hydrochloride (XV) with diethyl ethoxymethylenemalonate (XVI) which, in the presence of sodium ethoxide, led to the sodium compound of 4-hydroxy-5-carbethoxypyrimidine (XVII). Liberation of free XIVb from XVII by means of hydrochloric acid met, however, with considerable difficulties, mainly because of the solubility in water, dilute hydrochloric acid and dilute sodium hydroxide of XIVb as well as of XVII and sodium chloride. The attempt to circumvent this situation by ethylating XVII with ethyl bromide in a pressure vessel failed. Also the attempt to substitute piperidine for sodium ethoxide in the condensation of XV with XVI was unsuccessful. Consequently it was tried to treat XIVb with sodium ethoxide to identify possibly the reaction product with XVII, but this reaction took a different course and yielded the disodium compound of 4-hydroxy-5-carboxypyrimidine (XVIII). Finally the clue for liberating the free XIVb was found in treating XVII with hydrochloric acid and subsequently subjecting the obtained mixture to vacuum-sublimation when only XIVb sublimed, the latter establishing its identity with the reaction product from *s*-triazine and IIIe.



The successful synthesis of XIVb from XV and XVI is particularly noteworthy in view of the fact that urea which may be commonly used for the synthesis of the pyrimidine nucleus has been found not to react with XVI.[17]

The same course as with IIIe is taken if *s*-triazine is caused to react with IIIf. The reaction sequence proceeds through the intermediates Xe → XIIc → XIIIc to yield a compound $C_{18}H_{12}N_2O_2$ to which, in analogy to XIVb, the structure of 4-phenyl-5-carbethoxypyrimidine (XIVc) has been ascribed.

Supporting the postulate that the aminomethylene compounds X are intermediates and not side products in the reaction of *s*-triazine with IIId, IIIe and IIIf leading to pyrimidine derivatives, are the facts that XV reacts with both IIId[14] and Xc[18] to give the same end product, namely XIVa, and that Xd also reacts with certain other agents

(13) T. Passalacqua, *Gazz. chim. ital.*, **43**, II, 566 (1913); O. Diels, H. Gärtner, and R. Kaack, *Ber.*, **55**, 3443 (1922).

(14) J. Baddiley, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 386 (1943).

(15) R. Schenck and H. Finken, *Ann.*, **462**, 274 (1928).

(16) E. Ballard and T. B. Johnson, *J. Am. Chem. Soc.*, **64**, 796 (1942).

(17) H. L. Wheeler, T. B. Johnson, and C. O. Johns, *Am. Chem. J.*, **37**, 394 (1907).

(18) G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 388 (1943).

with formation of cyclic α-hydroxycarboxylic esters.[19]

Pyrimidine unsubstituted in position 2 have generally been prepared by reduction of 2-halopyrimidines,[20] desulfurization of 2-mercaptopyrimidines,[21] or decarboxylation of 2-carboxypyrimidines.[22] *s*-Triazine offers now another interesting possibility, aside from XV, for a direct synthesis of 2-unsubstituted pyrimidines.

Theoretically the production of IX and X requires a molar ratio of *s*-triazine: III = 1:6 and 1:3 respectively, while the formation of pyrimidines XIV calls for a molar ratio of *s*-triazine: III = 2:3. However, in several cases, it was found expedient to have one of the components in excess in order to arrive at a better yield of end product.

So far, of active methylene compounds investigated fluorene has been found not to undergo reaction with *s*-triazine. This failure is most probably to be attributed to too small a permanent polarization in fluorene due to the lack of any activating substituents. Likewise, triphenylmethane could not be caused to react with *s*-triazine.

As another class of compounds containing removable hydrogen, organic acids were included in these investigations. The reaction of *s*-triazine with glacial acetic acid yielded a main fraction of the composition $C_{17}H_{31}N_3O_{14}$. By the ring cleavage reaction with aniline,[5] the presence of unchanged *s*-triazine in this fraction was established. The product $C_{17}H_{31}N_3O_{14}$ is thus to be considered an azeotropic mixture $7CH_3COOH.C_3H_3N_3$. A clear-cut answer on the question concerning the behavior of organic acids towards *s*-triazine was obtained from the reaction with benzoic acid, in which case both components could be recovered unchanged.

EXPERIMENTAL[23]

2,6-Dimethyl-3,5-dicarbethoxypyridine (IX). *s*-Triazine (5 g.) was dissolved at room temperature in 24 g. of IIIa and the mixture immersed into an oil bath preheated to 140° and kept there for 2 hr. After cooling, the reaction contents were subjected to vacuum-distillation at 6 mm. As main fraction a yellowish viscous oil of b.p.$_6$ 167–169° was obtained, which crystallized mostly in the receiving flasks. By vacuum-filtration, 11.5 g. of colorless needles was obtained. These were recrystallized from ethanol and showed then a melting point of 72–73°.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.58. Found: C, 62.18; H, 6.60; N, 5.49.

The identity of this product with structure IX was established by a mixed melting point with an authentic sample.[8] Based on IIIa, the yield of 11.5 g. of IX corresponds to 49.7%. Furthermore, the compound obtained could be characterized by a picrate. Upon the addition of a saturated ethanolic picric acid solution to a solution of the needles referred to above in ethanol, crystallization of clusters of yellow needles set in. These were filtered and dried, melted at 118–119°, and showed no depression in melting point when mixed with authentic IX-picrate.[24]

3-Aminomethylene-2,4-pentanedione (Xa). A mixture containing 5 g. of *s*-triazine and 37 g. of IIIb was heated to gentle boiling (155° bath temperature) for 0.5 hr., when it turned slightly orange in color. Extending the reaction period does not increase the yield of end product, but causes a reddish-brown discoloration of the reaction contents and merely renders the work-up more difficult. Upon cooling, a beige crystalline mass deposited, which was suction-filtered and amounted to 8.1 g. An additional amount of 6.8 g. of this substance could be obtained by concentrating the mother liquor in vacuum until b.p. 100° (16 mm.) was reached and then allowing the residue to crystallize. The crude crystalline material could be recrystallized best from methanol; beige scales, m.p. 145–146°. The mixed melting point with an authentic sample of Xa[9] was not depressed; total yield: 14.9 g., or 63% based on *s*-triazine.

Anal. Calcd. for $C_6H_9NO_2$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.62; H, 7.15; N, 10.94.

3-Benzamidomethylene-2,4-pentanedione (XIa). Benzoyl chloride (5.6 g., 0.04 mole) was added dropwise to a suspension of Xa (5.1 g., 0.04 mole), obtained as described in the preceding paragraph, in absolute pyridine (6.4 g., 0.08 mole) with intermittent shaking at a rate not to exceed 50° reaction temperature. The reaction contents became gradually viscous and finally solidified largely. After two successive treatments with 40-ml. portions of water at room temperature, 7.3 g. of a white solid could be collected. Repeated crystallizations from ethanol furnished faintly yellowish fine needles, the melting point of which (101–102°) was not depressed when mixed with an authentic sample[25]; yield: 7.3 g., 78.8%.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.45; H, 5.60; N, 6.00.

Ethyl 2-aminomethylenecyanoacetate (Xb). It was found advisable to conduct this experiment in an inert solvent; without this, it was rather difficult to extricate a pure material from the viscous reaction contents.

An absolute ethanolic solution of 4 g. of *s*-triazine and 17 g. of IIIc was kept at gentle boiling (140° bath temperature) for 7 hr., when the originally colorless solution turned gradually bright brown. On cooling, a slightly yellowish material crystallized which was filtered after standing for 3 weeks; weight: 14.2 g. This substance was insoluble in ether, soluble in water, dil. hydrochloric acid, dil. sodium hydroxide, ethanol, methanol and acetone and could best be recrystallized from ethanol, from which solvent it crystallized as fine white needles, m.p. 134–135°. Authentic Xb[10] is reported to melt at 130°, but was found in this laboratory to have a melting point of 134–135°. A mixed melting point showed no depression. The amount of 14.2 g. equals 68.0% based on IIIc.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.43; H, 5.76; N, 20.00. Found: C, 51.50; H, 5.66; N, 20.01.

Ethyl 2-benzamidomethylenecyanoacetate (XIb). To 4.2 g. (0.03 mole) of Xb obtained as described above and dispersed in 4.8 g. (0.06 mole) of dry pyridine was added dropwise 4.2 g. (0.03 mole) of benzoyl chloride with periodic shaking at a rate such as not to exceed 50°. The reaction contents turned orange, assumed first a honey-like consistency and then gradually crystallized upon standing for 3 hr. Pyridine hydrochloride formed during the reaction was removed by trituration with two 100-ml. portions of water. By vacuum-filtration, 6.8 g. (92.6%) of a yellowish product was obtained which was insoluble in water and dilute hydrochloric acid and soluble in methanol, ethanol, butanol, acetone, acetic acid, dioxane, benzene, acetic anhydride,

(19) S. Ruhemann and R. W. Morrell, *Ber.*, **27**, 2742, 2747 (1894).

(20) S. Angerstein, *Ber.*, **34**, 3957 (1901).

(21) H. Andersag and K. Westphahl, *Ber.*, **70**, 2035 (1937).

(22) S. Gabriel and J. Colman, *Ber.*, **32**, 1531 (1899).

(23) All melting points are corrected. Microanalyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(24) E. Knoevenagel and J. Fuchs, *Ber.*, **35**, 1793 (1902).

(25) L. Claisen, *Ann.*, **297**, 31, 67 (1897).

and dil. sodium hydroxide. Recrystallization from ethanol furnished white needles, m.p. 121–122°.

As no authentic XIb was known, Xb as prepared according to DeBollemont[10] was treated with benzoyl chloride in pyridine suspension and worked up as described above. Again white needles were obtained which melted at 121–122°. A mixed melting point of the two specimen of XIb was undepressed.

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.87; H, 4.74; N, 11.57.

4-Amino-5-cyanopyrimidine (XIVa). When 4 g. of *s*-triazine (0.05 mole) and 9.9 g. of IIId were dissolved in 50 ml. of absolute ethanol, the colorless solution within a few minutes turned yellow, became warm and started precipitating a yellow solid. The reaction mixture was shaken from time to time, allowed to stand overnight, and then vacuum-filtered (filtrate A). The filter-cake consisted of 3.8 g. of a yellow substance which was insoluble in ether, petroleum ether, carbon tetrachloride, acetone, ethyl acetate, benzene, chlorobenzene, toluene, and cyclohexane, scarcely soluble in ethanol, 1-pentanol, and dioxane and soluble in the following boiling solvents: methanol, water, glacial acetic acid, butyl alcohol, nitrobenzene, tetrahydrofuran, acetic anhydride, diethyl malonate, aniline, and dil. sodium hydroxide. By repeated recrystallization from methanol, the substance was obtained as fine beige needles, m.p. and mixed m.p. with authentic XIVa[14] 255–256°. The yield of 3.8 g., 21.3%, remained essentially unaltered if a batch of the same size was refluxed for 6 hr.

Anal. Calcd. for $C_6H_4N_4$: C, 49.99; H, 3.36; N, 46.65. Found: C, 50.15; H, 3.40; N, 46.67.

While the attempt to obtain a picrate of XIVa in ethanolic solution failed, the addition of aqueous picric acid solution saturated at room temperature to a hot aqueous solution of XIVa caused precipitation of yellow needles, m.p. 189°, which were identical in all aspects with authentic XIVa-picrate.[14]

Aminomethylenemalononitrile (Xc). Filtrate A obtained in the isolation of XIVa as described above was stripped of solvent and the remaining bright yellow powder recrystallized from a concentrated aqueous solution. Thereby 11.1 g. (78.7%) of slightly yellowish crystals was obtained, which melted at 145–146° and proved to be identical with authentic Xc.[13]

4-Hydroxy-5-carbethoxypyrimidine (XIVb). A. *From s-triazine and* IIIe. A solution of 6 g. of *s*-triazine in 35.6 g. of IIIe was heated for 4 hr. at a bath temperature of 160°. Any *s*-triazine that sublimed during the reaction period was caught in the reflux condenser and from time to time pushed back into the reaction flask. Upon cooling a yellowish substance precipitated which was vacuum-filtered after standing for several days. An additional amount of the same substance was obtained by stripping the filtrate of any solvent *in vacuo*, thus bringing the total amount of crude material to 16.5 g. This was triturated with ether and then repeatedly recrystallized from ethanol to give fine white needles, m.p. and mixed m.p. with XIVb as obtained by an independent route (see below under B) 194–195°. The total amount of 16.5 g. of XIVb corresponds to a yield of 88.6% based on *s*-triazine. XIVb is insoluble in ether, scarcely soluble in acetone and ethyl acetate, and soluble in methanol, ethanol, dioxane, water, dil. sodium hydroxide, and dil. hydrochloric acid.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 49.98; H, 4.80; N, 16.66. Found: C, 49.90; H, 4.72; N, 16.67.

This compound could be further characterized by its picrate, which was obtained by adding a cold saturated ethanolic solution of picric acid to a hot ethanolic solution of XIVb. Upon cooling, stout yellow needles crystallized which, after recrystallization from methanol, melted at 164–165°. This melting point was not depressed when mixed with XIVb-picrate as obtained from an independent synthesis (see following chapter).

Anal. Calcd. for $C_7H_8N_2O_3 \cdot C_6H_3N_3O_7$: N, 17.63. Found: N, 17.56.

B. *From* XVII. The sodium compound of 4-hydroxy-5-carbethoxypyrimidine (8.9 g.) (see next paragraph) was dissolved in 100 ml. of warm water and filtered. An amount of 4.6 ml. of 37.5% hydrochloric acid was added and the whole mixture taken to dryness *in vacuo* resulting in 10.6 g. of a beige crystalline substance. Divided into four individual portions, this material was subjected to fractional sublimation at 2 mm. The white crystals condensing at the cold finger were collected and amounted to 2.6 g. (33.0%) of XIVb. The analytical sample was thrice vacuum-sublimed and exhibited then a melting point of 194–195°.

The reported[16] melting point of "185° with sintering" is probably due to an insufficient amount of XIVb isolated, not enabling the previous investigators to further purify this substance.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 49.98; H, 4.80; N, 16.66. Found: C, 49.84; H, 4.66; N, 16.63.

The *picrate*, prepared in ethanol and recrystallized from the same solvent, melted at 164–165°.

Anal. Calcd. for $C_7H_8N_2O_3 \cdot C_6H_3N_3O_7$: N, 17.63. Found: N, 17.42.

Sodium compound of 4-hydroxy-5-carbethoxypyrimidine (XVII). Sodium (1.5 g.) was dissolved in absolute ethanol (30 ml.) and XV (4.4 g.) added. When XVI (12.0 g.) was added in small portions, the reaction mixture warmed up and turned yellow. After heating for 2 hr. on the steam bath, the suspension was allowed to cool and the white solids suction-filtered, wt. 10.6 g. (100%). Purification could be achieved by digestion with acetone, which rendered the solid as a white powder. On heating, it turned brown at 210–220° and decomposed at 262–264°.

Anal. Calcd. for $C_7H_7N_2NaO_3$: C, 44.21; H, 3.71; N, 14.74. Found: C, 44.31; H, 3.92; N, 15.15.

Disodium compound of 4-hydroxy-5-carboxypyrimidine (XVIII). To a solution of 0.74 g. of sodium in 20 ml. of absolute ethanol was added 2.7 g. of XIVb and the suspension well agitated at room temperature. No heat evolution was noticeable, but within 10 min. the contents assumed a lard-like consistency. An additional amount of 20 ml. of ethanol had to be added to make stirring still possible. After stirring for a total of 2 hr., the reaction contents were allowed to stand overnight and then were vacuum-filtered, washed with ethanol and dried in a vacuum-desiccator. Thereby 2.3 g. of a beige solid was obtained. For analysis, the substance was digested successively with ethanol and acetone and then exhibited a melting point of 414–416°.

Anal. Calcd. for $C_5H_2N_2Na_2O_3 \cdot H_2O$: C, 29.71; H, 2.00; N, 13.87; Na, 22.76. Found: C, 29.97; H, 2.02; N, 14.05; Na, 22.53.

4-Phenyl-5-carbethoxypyrimidine (XIVc). Upon heating a clear solution of 5 g. of *s*-triazine in 30 g. of IIIf for 2 hr. at 140°, a reddish brown viscous oil resulted which was allowed to stand at room temperature overnight. The contents were concentrated under reduced pressure, whereupon a brown somewhat tacky solid remained. Repeated triturations of this material with ether afforded 6.4 g. of a dry brown powder which was insoluble in water, dil. hydrochloric acid, dil. sodium hydroxide, ether, ethyl acetate, toluene, and cyclohexane and soluble in methanol, acetone, dioxane, acetic acid, acetic anhydride, pyridine, and concd. hydrochloric acid. Further purification of the material could best be achieved by digestion with boiling ether. In this manner XIVc was obtained as a yellow powder, m.p. 159–161°. The yield of 6.4 g. equals 30.4% based on *s*-triazine.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.30; N, 12.28. Found: C, 68.52; H, 5.49; N, 12.09.

s-Triazine and glacial acetic acid. s-Triazine (8 g.) dissolved in glacial acetic acid (60 g.) without any noticeable change in temperature or color. This solution was heated for 3 hr. at 135–140°, allowed to stand overnight, and then vacuum-distilled. The main fraction consisted of 51 g. of a colorless liquid which was three more times fractionated,

whereupon refractive index and boiling point remained constant; b.p.$_{30}$ 43–44°, n_D^{30} 1.3912.

This fraction was shown to react with aniline under evolution of heat. If this reaction were carried out at 60°, a white solid was formed. Next it could be shown that this solid was not acetanilide, despite the literature statement that a mixture of aniline and acetic acid at room temperature within four months had formed acetanilide.[26]

Finally, by recrystallization from benzene, white needles were obtained which, through m.p. and mixed m.p. (143°) with authentic material, were identified as *N,N*-diphenylformamidine.[5] This result, along with the analytical data, suggests the conclusion that the fraction of n_D^{30} 1.3912 is an azeotropic mixture of the composition $7CH_3COOH.C_7H_9N_3$.

Anal. Calcd. for $7CH_3COOH.C_7H_9N_3$: C, 40.73; H, 6.23; N, 8.38. Found: C, 40.68; H, 6.25; N, 8.04.

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[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH DEPARTMENT OF THE SCHERING CORPORATION]

3-Azaphenothiazine and Dialkylaminoalkyl Derivatives

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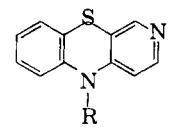
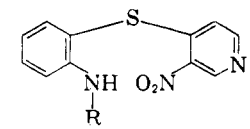
3-Azaphenothiazine has been synthesized and converted to 10-(3-dimethylaminopropyl)-3-azaphenothiazine. When 3-azaphenothiazine is alkylated with methyl iodide, or with the salts of aminoalkyl halides it forms novel quaternary salts which, upon treatment with aqueous alkali, liberate the corresponding anhydronium bases. The structures of these 3-alkyl derivatives of 3-azaphenothiazine are supported by their infrared and ultraviolet spectra as well as by *p*Ka measurements. The dipole moments of 3-azaphenothiazine and of 3-methyl-3-azaphenothiazine anhydronium base have been measured in dioxane solution. The pharmacology of the aminoalkyl derivatives of 3-azaphenothiazine is discussed.

The possibility that 10-(3-dimethylaminopropyl)-3-azaphenothiazine (I) might possess tranquilizing properties similar to those of the corresponding phenothiazine derivatives[1] led us to prepare and alkylate 3-azaphenothiazine (II).[2] Although in recent years many azaphenothiazines[3] and diazaphenothiazines[4] have been synthesized, the unsubstituted 3-azaphenothiazine[5] has not been described. We found that the Smiles rearrangement[6] of 2-acetamidophenyl 3-nitro-4-pyridyl sulfide (III) proceeded smoothly in acetone solution by the addition of powdered potassium hydroxide[7] to give a 62% yield of 3-azaphenothiazine (II). The preparation of the intermediate 2-aminophenyl 3-nitro-4-pyridyl sulfide (IV) in a number of steps starting from pyridine has been described.[3e]



I. R = $CH_2CH_2CH_2N(CH_3)_2$
II. R = H



III. R = $COCH_3$
IV. R = H

3-Azaphenothiazine (II) was alkylated with 3-dimethylaminopropyl chloride using sodium amide in refluxing toluene to give 10-(3-dimethylaminopropyl)-3-azaphenothiazine (I). The dihydrochloride of I was nearly inactive as a tranquilizing agent when injected intraperitoneally in mice and, in marked contrast to the corresponding 10-dialkylaminoalkyl-1-azaphenothiazines[8] had only slight sedative and antihistamine properties.

On the other hand, alkylation of 3-azaphenothiazine (II) with 3-dimethylaminopropyl chloride in the absence of a stronger base gave the novel 3-(3-dimethylaminopropyl)-3-azaphenothiazinium chloride (V chloride) which on treatment with

(1) For a review see D. G. Friend, *Clin. Pharmacol. Therap.*, 1, Adv. p. 5 (1960).

(2) For numbering of the phenothiazine nucleus see v. J. P. Bourguin *et al.*, *Helv. Chim. Acta*, 42, 2541 (1959).

(3) (a) V. A. Petrow and E. L. Rewald, *J. Chem. Soc.*, 591 (1945); (b) H. L. Yale and F. Sowinski, *J. Am. Chem. Soc.*, 80, 1651 (1958); (c) A. R. Gennaro, *J. Org. Chem.*, 24, 1156 (1959); (d) Y. Maki, *Chem. Abstr.*, 52, 1174 (1958); (e) A. J. Saggiomo, P. N. Craig, and M. Gordon, *J. Org. Chem.*, 23, 1906 (1958); (f) T. Takahashi and E. Yoshii, *Pharm. Bull.*, 2, 382 (1954).

(4) (a) J. Druey, *Angew. Chem.*, 70, 5 (1958); (b) T. Takahashi and Y. Maki, *Chem. Abstr.*, 52, 14622 (1958); (c) Y. Maki, *Chem. Abstr.*, 51, 14738 (1957); (d) T. Takahasi and Y. Maki, *Chem. Pharm. Bull.*, 6, 369 (1958).

(5) 1-Nitro- and 1-amino-3-azaphenothiazines have been synthesized, and treatment of the latter compound with nitrous acid led to the formation of 3-azaphenothiazine-1,10-diazole.[3a] Attempts to prepare 3-azaphenothiazine by the fusion of 4-anilinopyridine with sulfur[3a] or by the Smiles rearrangement[6] of 2-formàmidophenyl 3-nitro-4-pyridyl sulfide[3e] were unsuccessful.

(6) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 151, 1263 (1935).

(7) The use of anhydrous potassium hydroxide in acetone as a medium for condensation reactions has been described, see K. A. Latif, M. M. Hossain, and M. A. Salam, *J. Ind. Chem. Soc.*, 35, 619 (1958). We found that when the alkali was added in alcoholic solution by the usual procedure the product was more difficult to isolate and the yield was lower.

(8) (a) Report of the Committee on New and Unused Therapeutics, *Ann. Allergy*, 16, 237 (1958); (b) A. Von Schlichtegroll, *Arz. Forsch.*, 7, 237 (1957); (c) *Arz. Forsch.*, 8, 489 (1958).