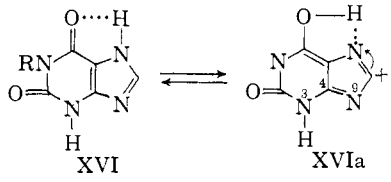
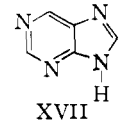
Applying similar considerations to the xanthine series, we observe that only the 1-methyl derivative serves as substrate of XO (see Table II). Oxidation at C-8 thus requires free NH-groups in position 3 and in the imidazole ring. The first condition again suggests participation of the partial structure $HN^{3}—C^{4}=N^{9}$ in chelation with an appropriate part of the active surface. In addition, intramolecular hydrogen bonding as in hypoxanthine involves a free 7-NH group (XVI). Therefore, we propose formula XVIa as the active form of xanthine to explain all experimental observations in this series.



XVI XVIa

Finally, there remains the problem of oxidation of purine, where neither a 7- nor a 9-methyl group prevents enzymatic attack at C-6, although the rate is greatly reduced. Purine may assume the form XVII, in which again the grouping $N^{3}=C^{4}—NH^{9}$ is present.[20] This would probably lead to attack at C-2. Therefore, we may assume that XVII does not become stabilized in the absence of a carbonyl group. Further discussion of this problem will be deferred in view of recent results, obtained in the pteridine series.



XVII

In summarizing this discussion, it appears that attachment of purines to the active surface of XO may involve structures, which differ from the form prevailing in free solution. It is not so much the intrinsic polarity of a given purine derivative that decides its interaction with the enzyme; of much greater importance is the structure of the ES complex which depends on specific binding groups both in the enzyme and substrate and therefore may involve mesomeric or tautomeric forms, which represent only a small percentage of all molecules present. This view is supported by the observation that the same purine derivative can be oxidized along a different pathway by another xanthine oxidase, present in certain bacterial strains.[21] Thus, the fact that 3-methylxanthine is oxidized by the bacterial enzyme[22] indicates that here the type of chelation, assumed for the structures III, VI, XIb, XIIa and XVIa, is absent.

(20) A. Bendich, P. S. Russell, Jr., and J. J. Fox, THIS JOURNAL, **76**, 6073 (1954), place the mobile hydrogen atom in purine at N-9, because of the similarity of the absorption spectra of the cationic form of purine and its 9-methyl derivative.

(21) F. Bergmann, H. Kwietny, G. Levin and H. Engelberg, *Biochim. Biophys. Acta*, in press.

(22) S. Dikstein, F. Bergmann and Y. Henis, *J. Biol. Chem.*, **224**, 67 (1957).

[CONTRIBUTION FROM THE PHOTO PRODUCTS DEPARTMENT, RESEARCH DIVISION, E. I. DU PONT DE NEMOURS AND CO.]

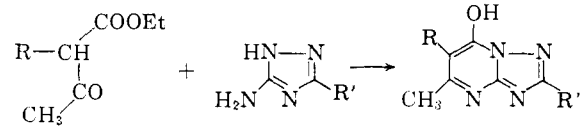
The Structure and Reactivity of 5-Hydroxy-7-methyl-*s*-triazolo[2,3-a]pyrimidine

BY V. C. CHAMBERS

RECEIVED JUNE 11, 1959

Physical and chemical evidence has been presented for the tautomeric equilibrium between an enol and three keto forms of 5-hydroxy-7-methyl-*s*-triazolo[2,3-a]pyrimidine (I). The structures of two products obtained by reaction of the silver salt of I with ethyl iodide were investigated. One of these was established by synthesis.

The product of the reaction of ethyl acetoacetate and 3-amino-1,2,4-triazole was first prepared by Bülow,[1] who ascribed to it the structure of 5-hydroxy-7-methyl-*s*-triazolo[2,3-a]pyrimidine (I). Since 1936, various triazolopyrimidines have been suggested as additions to photographic emulsions to inhibit the development of fog.[2] The structure was originally questioned by Birr, who later presented evidence favoring the structure of 5-hydroxy-7-methyl-*s*-triazolo[4,3-a]-pyrimidine.



I, R, R = H
II, R = C_2H_5, R′ = H
III, R = H, R′ = C_2H_5

The acidic character of this substance was demonstrated by Bülow.[1]

Recently Allen *et al.*,[3] showed that Birr's conclusions were incorrect and established the structure originally proposed by Bülow.

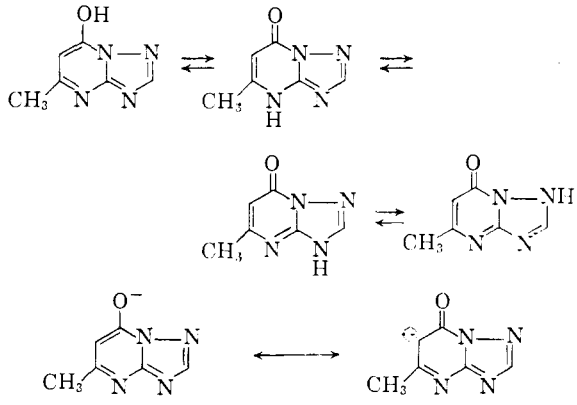
In the present research, the structure and reactivity of I were investigated in order to interpret its photographic behavior. As in the case of the hydroxypurines, tautomeric forms of I may be written in which the acidic proton is attached to nitrogen or oxygen.

Similar forms also contribute to the anion derived from I and this resonance stabilization probably accounts for the acidic character. In the case of the anion, an additional form may be written in which the negative charge is ascribed to carbon. That such a structure does not make an important contribution to the stabilization of the anion is

(1) C. Bülow and K. Haas, *Ber.*, **42**, 4642 (1909).

(2) (a) E. J. Birr, *Z. wiss. Phot.*, **47**, 2 (1952); (b) N. Heimbach and W. Kelly, Jr., U. S. Patent 2,444,605 (July 6, 1948) (assigned to General Aniline and Film Corp.).

(3) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker and J. A. VanAllan, *J. Org. Chem.*, **24**, 787 (1959).



indicated by the small changes in the apparent dissociation constants K_A reported in Table I.

TABLE I

APPARENT IONIZATION CONSTANTS K_A IN WATER AT 25° OF SUBSTITUTED *s*-TRIAZOLO[2,3-a]PYRIMIDINES

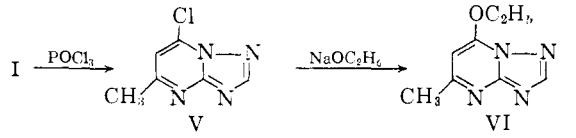
Substituents	Half-point scale reading[a]	$K_A \times 10^7$[b]
I, 5-OH, 7-CH_3	6.34	4.57
II, 5-OH, 6-C_2H_5, 7-CH_3	7.01	0.98
III, 5-OH, 2-C_2H_5, 7-CH_3	6.63	2.35

[a] Readings on *p*H scale of *p*H meter at half-neutralization point using glass and saturated calomel electrodes. [b] Calculated assuming the activity coefficients of the acid and its anion were unity and that the reading of the *p*H meter scale at the half-neutralization point was equal to the logarithm of the reciprocal of the hydrogen ion concentration.

The substituent effects reported in Table I are smaller than that obtained by similar substitution in ethyl acetoacetate[4] and the evidence available suggests a largely enolate structure for the anion derived from this ester.[5]

In an attempt to prepare N-alkyl derivatives, compound I was treated with diethyl sulfate in aqueous alkali. A product (IV) was isolated which was soluble in water and benzene and was not acidic. The analysis and properties of this compound indicated that alkylation had taken place on either oxygen or nitrogen. This compound also was prepared by fusion of I with ethyl *p*-toluenesulfonate and then treatment with alkali and similarly a methyl derivative by fusion with methyl *p*-toluenesulfonate and treatment with alkali.

The O-ethyl derivative, synthesized unequivocally by the method suggested by Murobushi, *et al.*,[6]



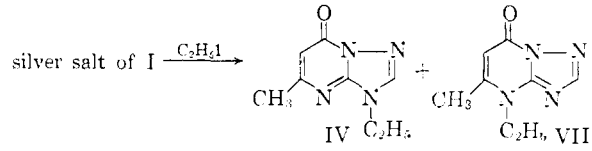
was not identical with IV and, moreover, was readily hydrolyzed by aqueous hydrochloric acid to I. This result indicated that IV was probably an N-ethyl derivative and is further evidence for the contribution of the N(−) resonance forms to the anion of I.

(4) R. G. Pearson and R. L. Dillon, THIS JOURNAL, **75**, 2439 (1953).

(5) J. E. Leffler, "The Reactive Intermediates of Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1956, p. 196–197.

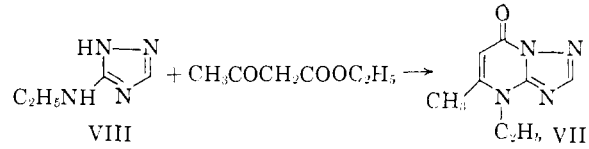
(6) K. Murobushi, Y. Kuwabara, S. Baba and K. Aoki, *Bull. Soc. Sci. Phot. Japan*, **4–6**, 23 (1955); no synthetic data were reported.

The silver salt of I was prepared in quantitative yield by reaction with silver nitrate at *p*H 7. When the dry silver salt was treated with ethyl iodide in benzene, a mixture of benzene-soluble products was obtained. The reaction was catalyzed by a trace of pyridine and two products separated by fractional crystallization.[7]



The structures IV and VII were tentatively assigned to these products on the basis of their analyses and non-identity with the known C-ethyl and O-ethyl derivatives; IV was identical with the product obtained by alkylation of I with diethyl sulfate.

Attempts to establish the identity of VII by synthesis involved the preparation and proof of structure of 3-ethylamino-1,2,4-triazole (VIII).



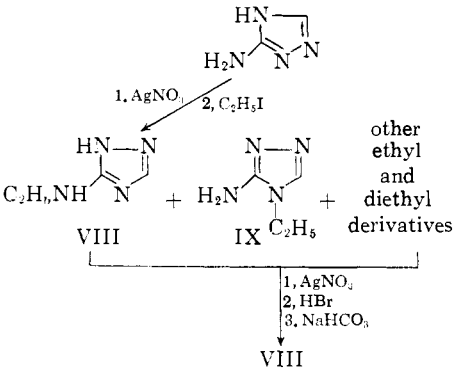
Efforts to prepare VIII by reductive alkylation of 3-amino-1,2,4-triazole with acetaldehyde and by reduction of an acetyl derivative of the triazole with lithium aluminum hydride were unsuccessful. The synthesis was finally accomplished by treatment of the silver salt of 3-amino-1,2,4-triazole with ethyl iodide and separation of the desired product from the resulting product mixture by titration with silver nitrate to the end-point which was indicated by both *p*Ag and *p*H measurements. Similar titrations of imidazoles had shown that *p*Ag and *p*H changes occurred when an amount of silver nitrate had been added which was equivalent to the amount of acidic imide present.[8] Compound VIII was the only product having an imide hydrogen. Unreacted 3-amino-1,2,4-triazole was also isolated from the reaction mixture by this procedure. The yield of silver iodide was quantitative, indicating that diethyl derivatives and possibly ethylene may be formed in the reaction.

The structure of VIII was established by analysis, reaction with silver nitrate and failure to produce a dye in reactions with nitrous acid and β-naphthol; VIII was converted readily to VII on treatment with ethyl acetoacetate to establish the structure of this triazolopyrimidine derivative.

Although efforts to separate IX and other derivatives from the reaction mixture were unsuccessful, a partially purified sample was obtained

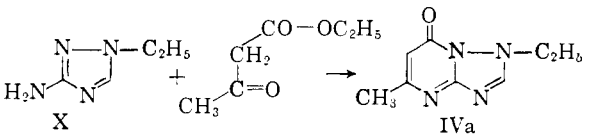
(7) Following the completion of this work, a Japanese publication was obtained, K. Murobushi, Y. Kuwabara, S. Baba and K. Aoki, *J. Chem. Soc., Japan, Ind. Chem. Sect.*, **58**, 440 (1955), which reported the separation of the products by chromatography. Subsequently this technique was used in the present investigation. The Japanese workers reported the isolation of O-ethyl derivative in addition to the compounds reported herein and also suggested the structures of the N-ethyl derivatives. No experimental details were given.

(8) H. D. Hunt, unpublished work.



(high carbon analysis indicating presence of diethyl contaminant). This material gave an orange dye on treatment with nitrous acid and β-napthol and was converted in poor yield to IV by treatment with ethyl acetoacetate.

The structure of IV has not been established unequivocally since IVa might also result from the reaction of I with silver nitrate and ethyl iodide and also from the reaction of ethyl acetoacetate with X, a possible constituent of the alkylated aminotriazole mixture



The evidence favoring the assignment of structure as in IV is based on the similarities in absorption spectra and physical properties of this compound and VII. This is anticipated from structures of VII and IV and not as readily from IVa. Moreover, the reaction of the anion of I with silver nitrate would be expected to give similar amounts of IV and VII and a distinctly different yield of IVa. IV was also obtained by quaternization of I with ethyl sulfate followed by treatment with alkali. Duffin et al.[9] have shown that quaternization of 1,2,4-triazole gave alkylation at the 4 position in agreement with the assignment of structure IV to this product.

The infrared spectra of I, IV, VI and VII lend additional support to the structural assignments already made. In Fig. 1, carbonyl bands are present in spectra of IV and VII at 5.90 and 5.92 μ, resp. The presence of a strong band at 5.90 μ in the spectrum of I is strong evidence for the existence of the tautomeric carbonyl forms of this compound. Conversion of the hydroxyl to the ether function as in VI is indicated by the absence of the carbonyl band in the spectrum of VI. The ultraviolet spectra of I, IV, VI and VII were quite similar. The absorption maxima are given in Table II.

The triazolopyrimidine nucleus was shown to be resistant to hydrogenation over a palladium catalyst by attempted reductions of I and VI. This feature was an important factor in the synthesis of 2-*p*-hydroxyphenyl-5-hydroxy-7-methyl-*s*-triazolo[2,3-a]pyrimidine which was desired for photographic evaluation.

(9) G. F. Duffin, J. D. Kendall, H. R. J. Waddington, *Chem. and Ind. (London)*, 1458 (1954).

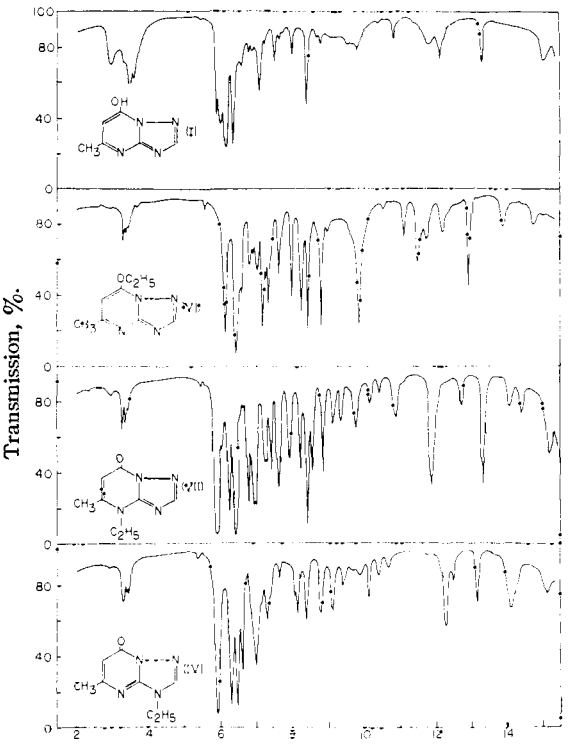


Fig. 1.—Infrared spectra.

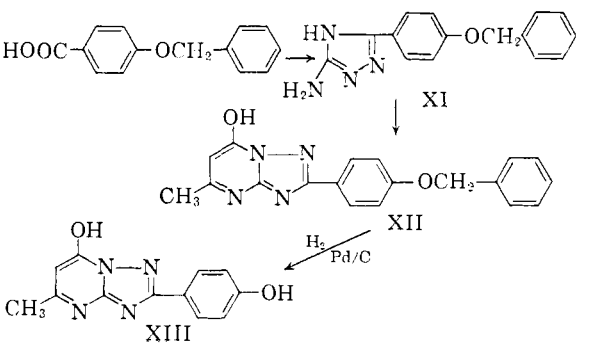
The acetyl and benzoyl derivatives of I were prepared, but the products were unstable in aqueous alkali. Compound I was converted smoothly to an acetone-soluble product by reaction with isopropenyl acetate in the presence of *p*-toluenesulfonic acid. The product decomposed in aqueous bicarbonate, precipitating I. Reaction of I with benzoyl chloride in pyridine gave a mixture of solid products, at least one of which was hydrolyzed in aqueous alkali at room temperature. Similar results

TABLE II

ULTRAVIOLET ABSORPTION MAXIMA OF SUBSTITUTED *s*-TRIAZOLO[2,3-a]PYRIMIDINES

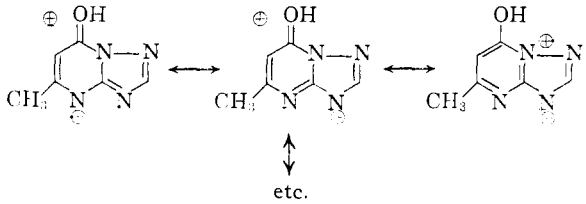
Compound	Absorption max.,[a] mμ
I	273
IV	279
VII	277
VI	272

[a] Spectra were obtained at 5×10^{-5} *M* concentration in distilled water.



were obtained in reactions of the silver salt of I with acetyl and benzoyl chlorides.

The hydrolysis under mild conditions of the O-alkyl and O-acyl derivatives and the resistance of I and VI to hydrogenation suggest that ionic forms may also contribute to the structure of I.



Experimental

5-Hydroxy-7-methyl-*s*-triazolo[2,3-a]pyrimidine (I) was prepared from ethyl acetoacetate and 3-amino-1,2,4-triazole by the method of Bülow and Haas.[1] Anhydrous material was obtained by recrystallization from absolute ethanol.

Anal. Calcd. for $C_6H_6N_4O$: C, 47.99; H, 4.03. Found: C, 48.20; H, 4.09.

6-Ethyl-5-hydroxy-7-methyl-*s*-triazolo[2,3-a]pyrimidine (II) was prepared by the method of Bülow[1] from ethyl α-ethylacetoacetate and 3-amino-1,2,4-triazole.

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66. Found: C, 54.02, 53.86; H, 5.59, 5.84.

2-Ethyl-5-hydroxy-7-methyl-*s*-triazolo[2,3-a]pyrimidine (III) was prepared by the method used in the synthesis of the preceding compounds from ethyl acetoacetate and 3-amino-5-ethyl-1,2,4-triazole. The yield of product, recrystallized from alcohol–ethyl acetate, m.p. 252–253.5°, was 59%.[10]

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66. Found: C, 53.75, 53.86; H, 5.64, 5.76.

5-Chloro-7-methyl-*s*-triazolo[2,3-a]pyrimidine (V).—A mixture of 15 g. (0.1 mole) of I and 50 g. (0.33 mole) of phosphorus oxychloride was heated under reflux for 30 min., during which time the solid dissolved and hydrogen chloride was evolved. The excess phosphorus oxychloride was removed by distillation at reduced pressure on a steam-bath and the residue triturated with ice-water. The product was extracted from the aqueous mixture with methylene chloride and the resulting solution evaporated to dryness. The residue was extracted with ether for two days in a Soxhlet extractor. The ether solution was evaporated to dryness and the residue recrystallized from benzene giving 11.8 g. (70%), m.p. 151–152°.

Anal. Calcd. for $C_6H_5N_4Cl$: C, 42.74; H, 2.99. Found: C, 42.91; H, 3.09.

5-Ethoxy-7-methyl-*s*-triazolo[2,3-a]pyrimidine (VI).—To 200 ml. of absolute ethanol in a 500-ml. flask fitted with magnetic stirrer, reflux condenser and drying tube was added 1.2 g. (0.52 g. atom) of sodium. When the reaction was complete, a hot solution of 10 g. (0.06 mole) of V in 155 ml. of ethanol was added and the resulting solution heated under reflux for 0.5 hr. The reaction mixture turned yellow and a white precipitate formed. The solution was neutral to litmus in 15 min. The solids were separated by filtration and the filtrate evaporated to dryness. The residue was recrystallized from benzene. The yield of white crystals, needles, m.p. 146.5–147°, was 8.18 g. (88%).

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66. Found: C, 53.94, 53.87; H, 5.89, 5.64.

Compound VI was recovered unchanged after hydrogenation at 50 p.s.i. for 3 hr. at 75° in alcohol solution over 20% by weight of a 10% palladium-on-carbon catalyst; VI was converted smoothly to I by hydrolysis in 6 *N* hydrochloric acid on a steam-bath.

1-Ethyl-7-methyl-*s*-triazolo[2,3-a]pyrimidin-5(1H)one (IV).—To a stirred solution of 15 g. (0.1 mole) of I in 100 ml. of 5% sodium hydroxide was added in small portions 30.8 g. (0.2 mole) of diethyl sulfate over a period of 2 hr. while heating on a steam-bath. An additional 70 ml. of sodium hydroxide solution was added after 1 hr. The resulting solution was cooled, diluted with 70 ml. of 12 *N* sodium hydroxide and extracted with four 50-ml. portions of chloroform. The extracts were combined, dried over magnesium sulfate and concentrated by distillation of chloroform. The residue was recrystallized from benzene giving 4.5 g. (25%), white needles, m.p. 197–198°.

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66. Found: C, 54.22, 53.99; H, 5.72, 5.72.

This product was also obtained by the fusion of ethyl *p*-toluenesulfonate with I at 100° for 16 hr. The product was separated by treatment with aqueous alkali and extraction as in the preceding synthesis.

1,7-Dimethyl-*s*-triazolo[2,3-a]pyrimidin-5(1H)one was prepared by the fusion of I with methyl *p*-toluenesulfonate as in the previous example. The product was recrystallized from benzene and finally from water to give a poor yield of product, m.p. 263–264.5° dec. The structure of this product was suggested by analogy with that of the corresponding ethyl derivative.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.21; H, 4.91. Found: C, 51.48; H, 4.96.

Reaction of the Silver Salt of I with Ethyl Iodide.—The silver salt was prepared in quantitative yield by the addition of 34 g. (0.2 mole) of silver nitrate in 100 ml. of water to a solution of 30 g. (0.2 mole) of I in 200 ml. of water. The *p*H was adjusted to 7 with ammonium hydroxide and the resulting precipitate separated by filtration, washed with water and dried in an oven at 100° overnight.

In a 500-ml. flask fitted with reflux condenser were placed 25 g. (0.09 mole) of the silver salt and 200 ml. of dry benzene. The apparatus was dried by azeotropic distillation of benzene and water. To the resulting mixture were added 12.9 g. (0.083 mole) of ethyl iodide and 1 ml. of pyridine. The mixture was heated under reflux overnight. The solids were separated by filtration and triturated with hot chloroform. The chloroform and benzene filtrates were combined and evaporated to dryness. The yield of crude material was 11 g. (In the absence of pyridine the yield was less than 1 g.) The crude product was dissolved in benzene and the benzene solution passed through a 30-cm. column (2 cm. diameter) of activated alumina. The products were eluted from the column with acetone–benzene (1:1)[7] at the rate of 50 ml. per hr. The first product was 8-ethyl-7-methyl-*s*-triazolo[2,3-a]pyrimidine-5(8H)one (VII), m.p. 214–215°, 5.4 g. The second product, m.p. and mixed m.p. with IV 198–199°, 2.1 g., was identical with the product IV obtained from the reaction of ethyl sulfate with I. The total yield was 7.5 g. (51%).

3-Ethylamino-1,2,4-triazole (VIII) and Proof of Structure of VII.—The silver salt of 3-amino-1,2,4-triazole was prepared as in the previous example. The silver salt (35.8 g., 0.188 mole) was heated under reflux for 48 hr. in a solution of 29.2 g. (0.188 mole) of ethyl iodide in 200 ml. of dry benzene. The resulting silver iodide was separated by filtration and triturated with ethanol. The yield of dry silver iodide was 44.2 g. (100%). The filtrates were combined and evaporated to dryness giving 18 g. (0.16 mole, 86%) of crude product. The residue was dissolved in 250 ml. of water and 25 ml. of the resulting solution diluted with 100 ml. of water and titrated with 1 *M* silver nitrate at *p*H 7. A sharp increase in *p*Ag occurred at 6.4 meq. of silver nitrate. A total of 6.8 meq. of sodium hydroxide were required to maintain the *p*H at 7. No further change in *p*H or *p*Ag occurred as additional silver nitrate (up to 13 meq.) was added. This result indicated that 41% of the product contained active hydrogen. The remaining product solution (225 ml.) was titrated with silver nitrate to just beyond the equivalence point and the resulting precipitate separated by filtration and slurried in 200 ml. of water. The *p*H was adjusted to 2.5 by the addition of 48% hydrobromic acid and the silver bromide separated by filtration. The filtrate was treated with 8 g. of sodium bicarbonate and evaporated to dryness. The residue was extracted with ethanol and the ethanol solution evaporated to dryness giving 5.82 g. of a mixture of 3-amino-1,2,4-triazole and VIII; VIII was separated by trituration with chloroform at room temperature. The insoluble 3-amino-1,2,4-triazole was purified by sublimation at 140° (0.1 mm.) and recrystallization from nitromethane, m.p. and mixed m.p. with an authentic sample, 155–156°. The product was readily converted to I by reaction with ethyl acetoacetate. Compound VIII was isolated from the chloroform solution by

(10) All melting points are uncorrected.

evaporation to dryness giving 1 g. (4.8%) of crude product, m.p. 118–121°. A small portion was converted smoothly to VII by reaction with ethyl acetoacetate in acetic acid. The product was recrystallized from benzene, m.p. and mixed m.p. with VII 214–215°. Compound VIII was purified by recrystallization from nitromethane and sublimation at 100° (0.1 mm.) giving a white crystalline product, m.p. 121–122.2°.

Anal. Calcd. for $C_4H_8N_4$: C, 42.84; H, 7.19. Found: C, 42.94, 42.94; H, 7.24, 7.09.

The organic material in the filtrate from the silver nitrate titration was isolated by a similar procedure giving 7.57 g. of oily liquid soluble in chloroform. Attempts to purify this material by sublimation gave a small amount of low melting solid and extensive decomposition. Several purifications by sublimation at 70° (0.1 mm.) gave a small amount of material, m.p. 80–90°, crude IX.

Anal. Calcd. for $C_4H_8N_4$: C, 42.84; H, 7.19. Found: C, 45.14, 45.19; H, 7.73, 7.80.

The crude IX was heated for 6 hr. with ethyl acetoacetate at 140°. A small amount of solid was recovered from the reaction mixture by sublimation at 200° (0.1 mm.). The solid was recrystallized from benzene, m.p. and mixed m.p. with IV 196.5–197.5°.

The products were tested for free amino groups by treatment with 5% sodium nitrite at 5° in 5% hydrochloric acid followed by addition of 5% β-naphthol in acetic acid. The starting material, 3-amino-1,2,4-triazole, gave a deep yellow dye solution and a precipitate of orange dye. The crude IX gave a deep orange dye solution; VIII gave a negative test.

3-Amino-5-*p*-benzyloxyphenyl-1,2,4-triazole (XI) was prepared by a modification of the method of Hoggarth.[11] In a 2-l. three-necked flask fitted with stirrer, azeotrope separator with reflux condenser and drying tube were placed 171 g. (0.75 mole) of *p*-benzyloxybenzoic acid,[12] 1 l. of benzene and 5 ml. of pyridine. The reaction mixture was dried by azeotropic distillation of benzene and water and then was cooled to 50° and stirred during the rapid addition of 119 g. (1.0 mole) of thionyl chloride. After completion of the addition, the mixture was slowly heated to reflux and finally under reflux for 2 hr. The resulting solution was evaporated to dryness at reduced pressure on a steam-bath and the residue dissolved in 450 ml. of pyridine at 50° and added rapidly with stirring to a solution of 102 g. (0.75 mole) of aminoguanidine bicarbonate in 800 ml. of pyridine at 0–6°. The resulting mixture was stirred and allowed to warm to room temperature overnight, and then evaporated to dryness on a steam-bath at reduced pressure. The residue was triturated with 800 ml. of 1.25 *N* sodium hydroxide and the solids separated by filtration. Recrystallization from alcohol separated some insoluble material. The alcohol-soluble portion was dissolved in a solution of 20 g. of sodium methoxide in 4 l. of methanol and precipitated by dilution with an equal volume of ice-water. The precipitate was separated by filtration and dried giving a solid, m.p. 178°, decomposing to a solid, m.p. 210–213°. Attempts to purify the aminoguanidine intermediate by recrystallization were unsuccessful and the solid was converted to the triazole by heating at 220° for 5 min. after melting. The product was cooled and recrystallized from ethanol and then from nitromethane giving 42 g. (21%), m.p. 220–220.5°.

Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.55; H, 5.30. Found: C, 67.70, 67.51; H, 5.56, 5.35.

The product gave an orange-red azo dye when treated with sodium nitrite and then with β-naphthol in acetic and hydrochloric acids.

2-*p*-Benzyloxyphenyl-5-hydroxy-7-methyl-*s*-triazolo[2,3-a]pyrimidine (XII) was prepared from XI and ethyl acetoacetate by the method used in the synthesis of I. The product was recrystallized from acetic acid giving 11.5 g. (70%), m.p. 310–311° dec.

Anal. Calcd. for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85. Found: C, 68.57, 68.67; H, 4.90, 5.01.

2-*p*-Hydroxyphenyl-5-hydroxy-7-methyl-*s*-triazolo[2,3-a]-pyrimidine (XIII).—A suspension of 10 g. (0.03 mole) of XII and 0.2 g. of 10% palladium-on-charcoal catalyst in 200 ml. of absolute alcohol was placed in a Parr hydrogenation bottle and reduced with hydrogen with shaking at 50 p.s.i. at 68° overnight. The uptake of hydrogen was 2.6 p.s.i. (theory 2.4 p.s.i.). The product was separated by filtration, dissolved in hot 5% sodium hydroxide and the catalyst removed by filtration. The product was precipitated by addition of concentrated hydrochloric acid and the solid separated by filtration, washed with water and dried. The yield of white solid, m.p. 395° dec., was 6.45 g. (88%). A portion was recrystallized from dimethylformamide for analysis.

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 59.50; H, 4.16. Found: C, 59.63, 59.44; H, 4.29, 4.30.

Infrared spectra of the triazolopyrimidines were obtained with the Perkin–Elmer model C-21 spectrophotometer. The samples were prepared in approximately 0.2% concentration in potassium bromide wafers. The curves so obtained are given in Fig. 1.

Ultraviolet spectra were obtained with the Cary recording spectrophotometer model 14. Samples were prepared in 5×10^{-5} *M* concentration in water. The maxima are given in Table II.

Apparent ionization constants were determined by titration of the samples in carbon dioxide free-water under nitrogen at 25 ± 0.5°. The *p*H values were obtained using the Beckman model G *p*H meter standardized against aqueous buffers. The pK_A and end-point values were obtained graphically. The results are given in Table I.

PARLIN, N. J.

(11) E. Hoggarth, *J. Chem. Soc.*, 612 (1950), prepared the phenyl, *p*-chlorophenyl and *p*-methoxyphenyl derivatives.

(12) J. B. Cohen and H. W. Dudley, *ibid.*, **97**, 1746 (1910).

[CONTRIBUTION FROM THE PHYSICS RESEARCH LABORATORY OF THE MASSACHUSETTS GENERAL HOSPITAL AND FROM THE RETINA FOUNDATION, DEPARTMENT OF OPHTHALMOLOGY OF THE MASSACHUSETTS EYE AND EAR INFIRMARY]

Benzoxazoles. I.[1,2]

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The synthesis of a number of bis-2-benzoxazoles, representing a new class is reported. The connecting unit linking the two benzoxazole nuclei has been varied from simple alkane chains to aryl chains. Some of the compounds having a conjugated double bond system may be potential solutes in liquid scintillators.

Since 2,5-diphenyloxazole (PPO) was discovered by Hayes and co-workers[4] to act as an efficient solute in liquid phosphors, the class of organic scintillators containing heterocyclic rings has received much attention. Previous to that only organic solutions of isocyclic compounds, especially

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(3) Recipient of the Sylvester Fellowship.

(4) F. N. Hayes, R. D. Hiebert and R. L. Schuch, *Science*, **116**, 140 (1952).