Imidazoles. I. Coupling Reactions of 5-Diazoimidazole-4-carboxamide[1,2]

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5-Diazoimidazole-4-carboxamide (IIa) undergoes the coupling reaction with aromatic compounds under conditions typical of those employed in coupling reactions of benzenoid diazonium salts. Reaction of 5-diazoimidazole-4-carboxamide with aliphatic amines gives 5(or 4)-(substituted triazeno)imidazole-4(or 5)-carboxamides, which are of chemotherapeutic interest as potential anticancer agents. Light-catalyzed dissociation of the 5(or 4)-(disubstituted triazeno)imidazole-4(or 5)-carboxamides results in the formation of 2-azahypoxanthine (III).

5 - Diazoimidazole - 4 - carboxamide (IIa) and 5-diazo-*v*-triazole-4-carboxamide (IIb) may be isolated from reactions of the corresponding aminoheterocycles (Ia and Ib) with nitrites in acidic solution.[2,3] Although 5-diazoimidazole-4-carboxamide is a stable compound that can be stored under anhydrous conditions for long periods of time, it cyclizes readily in aqueous solutions, over a wide range of pH values, to 2-azahypoxanthine (imidazo-[4,5-*d*]-*v*-triazin-4(3*H*)-one)(III), a compound that had been reported earlier[4] as the product of diazotization of 5-(or 4)-aminoimidazole-4(or 5)-carboxamide (Ia). The diazoimidazole may be regarded[2,3] as a diazonium salt in which the imidazole ring, rather than an inorganic ion, serves as the anionic component. As suggested previously,[3] the formation of such diazo compounds may be a general reaction of aminoheterocycles with an —NH— member in the ring from which a proton can be lost during diazotization. Protonation of the heterocyclic ring would form the normal diazonium salt. The ease of cyclization of IIa militates against the isolation of such a salt (IV), but hypsochromic shifts of the long wavelength ultraviolet absorption maximum of IIa in strongly acidic solutions were ascribed[5] to the formation of IV prior to cyclization to 2-azahypoxanthine (III). The behavior of the diazoimidazole (IIa) in the coupling reaction with aromatic compounds and with aliphatic amines has been investigated in order to relate it chemically to aryldiazonium salts and to prepare derivatives expected to be of interest in cancer chemotherapy.

5-Diazoimidazole-4-carboxamide gave the *p*-dimethylaminophenylazo derivative (Va) by coupling with *N*,*N*-dimethylaniline at room temperature in aqueous medium at pH 4. Similarly, the diazoimidazole readily coupled with 2-naphthol at pH 8. Intramolecular coupling to 2-azahypoxanthine, a competing reaction, is especially rapid in neutral and alkaline media.[3] Despite this fact, pure 5(or 4)-(2-hydroxy-1-naphthylazo)-imidazole-4(or 5)-carboxamide (Vb) was obtained in 46% yield, and 5(or 4)-(*p*-dimethylaminophenylazo)imidazole - 4 (or 5) - carboxamide (Va) precipitated in 61% yield. The reaction conditions are typical of those employed in coupling reactions of benzenoid diazonium salts with aromatic amines and phenols.[6] The ease of coupling of IIa is in contrast to the behavior of diazopyrroles recently described by Tedder and Webster.[7]

In agreement with the behavior of aryldiazonium salts, 5-diazoimidazole-4-carboxamide formed triazenes by reaction with aliphatic amines. 5(or 4)-(Disubstituted-triazeno)imidazole-4(or 5)-carboxamides (VI–XIII)[8] were prepared by reaction of IIa with secondary amines representative of the dialkylamines, aralkylamines, cyclic amines, and alkylarylamines. These reactions were conducted in methanol or in an excess of the amine, as solvent, in the absence of light.

The dimethyltriazeno (VI), dibutyltriazeno (VIII), and methylphenyltriazeno (XIII) derivatives were chosen for studies of the stability of the disubstituted triazenoimidazoles in solution. In phosphate buffer at *p*H 7 these three triazenes exhibited essentially no change, for at least twenty-four hours, provided that the solutions were protected from light. Solutions of the dimethyltriazene (VI) in 0.1 *N* hydrochloric acid and of the methylphenyltriazene (XIII) in ethanol were also stable, in the absence of light, for at least forty-eight hours and twenty-four hours, respectively. For all five of these solutions absorbance values at the long-

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740, and by the C. F. Kettering Foundation.

(2) Part of the work described in this paper was presented at the 137th meeting of the American Chemical Society: Y. F. Shealy, R. F. Struck, L. B. Holum, and J. A. Montgomery, Abs. of Papers, 137th Meeting of the American Chemical Society, Cleveland, Ohio, April 5–14, 1960, p. 4N.

(3) Y. F. Shealy, R. F. Struck, L. B. Holum, and J. A. Montgomery, *J. Org. Chem.*, **26**, 2396 (1961).

(4) (a) D. W. Woolley and E. Shaw, *J. Biol. Chem.*, **189**, 401 (1951). (b) M. R. Stetten and C. L. Fox, Jr., *ibid.*, **161**, 333 (1945).

(5) Table I of ref. 3. Recently, the isolation of both the diazo derivative and the diazonium chloride obtained by diazotization of 3-aminopyrazole has been reported by H. Reimlinger, A. van Overstraeten, and H. G. Viehe (*Chem. Ber.*, **94**, 1036 (1961)).

(6) "The Aromatic Diazo Compounds and Their Technical Applications," K. H. Saunders, Edward Arnold and Co., London, 2nd Ed., 1949.

(7) J. M. Tedder and B. Webster, *J. Chem. Soc.*, 3270 (1960).

(8) Structural formulas III–XIII are drawn with mobile hydrogen atoms arbitrarily placed. Other forms are possible; for example, several tautomeric and hydrogen-bonded structures involving the imidazole, azo, and naphthol (or *o*-naphthoquinoid) moieties may be drawn for the *trans* form of Vb.

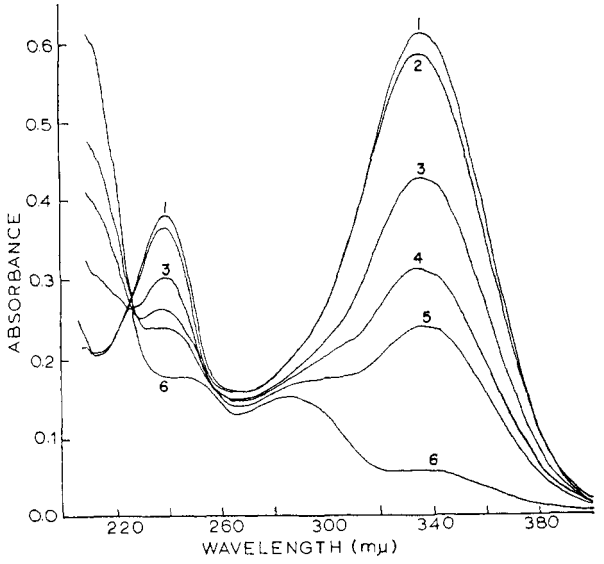
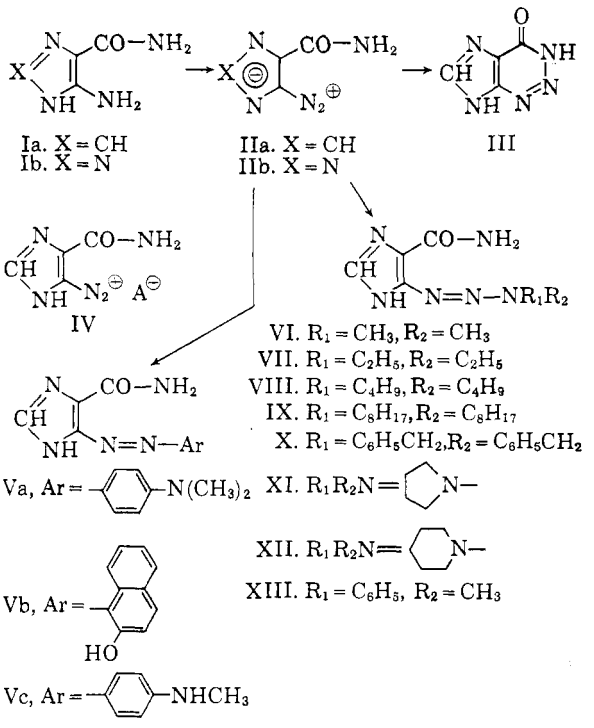


Fig. 1.—Conversion of 5(or 4)-(dibutyltriazeno)imidazole-4(or 5)-carboxamide (VIII) to 2-azahypoxanthine (III) in phosphate buffer at pH 7 ($3.78 \times 10^{-5} M$): 1, ΔT = 7 min. (curve 1 unchanged at ΔT = 7 hr.); 2, ΔT = 24 hr.; 3, ΔT_L = 4 hr.; 4, ΔT_L = 7 hr.; 5, ΔT_L = 24 hr.; 6, ΔT_L = 48 hr. ΔT = time interval between the addition of solvent and the tracing of a given curve; ΔT_L = time interval between the initial exposure of the solution to light and the tracing of a given curve.

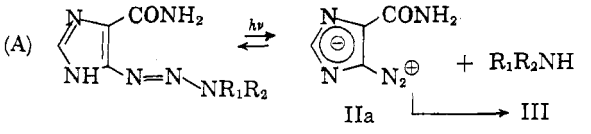
wave length maxima (322–360 mμ) after twenty-four hours, or more, were 95–100% of those recorded within a few minutes of the preparation of the solutions (*cf.* curves 1 and 2, Fig. 1). Exposure of these solutions to light resulted in a decrease in the intensity of, and the eventual disappearance of, the long wave length maxima. This behavior is illustrated in Fig. 1 with the dibutyltriazeno derivative (VIII). Curve 6 is identical with the spectrum of 2-azahypoxanthine[3] at *p*H 7 except for the weak residual maximum at 337 mμ due to the persistence of a small amount of the unchanged triazene. Similar sets of curves for the other four solutions studied indicate that 2-azahypoxanthine is the end-product of the light-catalyzed decomposition of the disubstituted triazenes in solution. The methylphenyltriazeno derivative (XIII), in contrast to the dimethyltriazene, was unstable in 0.1 *N* hydrochloric acid even in the dark.

Evidence from the ultraviolet studies for the light-catalyzed formation of 2-azahypoxanthine was confirmed by isolation. A specimen of 2-azahypoxanthine from an aqueous ethanol solution of 5(or 4)-(dibutyltriazeno)imidazole-4(or 5)-carboxamide that had been exposed to light was shown to be identical with authentic 2-azahypoxanthine monohydrate by paper chromatography and by comparison of the infrared spectra. The formation of 2-azahypoxanthine from the pure triazenes must result from a light-catalyzed, or—under certain conditions—an acid-catalyzed, dissociation of the



triazenes to 5-diazoimidazole-4-carboxamide and an amine. Irreversible cyclization[9] of the diazo compound to 2-azahypoxanthine (III) would then shift the equilibrium to the right (equation A).

Decomposition of 5(or 4)-(3-methyl-3-phenyltriazeno)imidazole-4(or 5)-carboxamide (XIII) according to equation A would yield an ultraviolet-absorbing amine. Calculation of molar



extinction coefficients (ϵ) at the absorption maxima of 2-azahypoxanthine, *N*-methylaniline, and solutions of XIII showed that the sums of the ϵ values of 2-azahypoxanthine and *N*-methylaniline agree well with the observed extinction coefficients of solutions of XIII after exposure to light. The final spectra of the solutions of XIII in phosphate buffer, ethanol, and 0.1 *N* hydrochloric acid[10] were, therefore, the resultant spectra of *N*-methylaniline and 2-azahypoxanthine.

The product of the reaction of 5-diazoimidazole-4-carboxamide with *N*-methylaniline is represented by, and has been discussed as, the triazene structure XIII; but 5(or 4)-(*p*-methylaminophenylazo)-imidazole-4(or 5)-carboxamide (Vc), which would be formed by coupling at the *para* position,

(9) The studies of the cyclization of IIa reported previously[3] were conducted on aqueous solutions. By similar methods, the rapid formation of 2-azahypoxanthine from IIa has been shown to occur in methanol and in ethanol solutions.

(10) Since *N*-methylaniline shows only a weak maximum near 250 mμ in 0.1 *N* hydrochloric acid, the final curve in this solution is essentially the same as that given by 2-azahypoxanthine.

is also a possible product of this reaction. The assignment of the triazene, rather than the azo, structure to the product obtained is based on the following properties: the presence in the infrared spectrum of bands, characteristic of a monosubstituted phenyl group, at 690 cm.$^{-1}$ and 755 cm.$^{-1}$; the less intense color relative to that of the *p*-dimethylaminophenylazo derivative (Va); and the spontaneous dissociation, mentioned above, of the product in 0.1 *N* hydrochloric acid. Dissociation in the acidic solution in the absence of light is evidence for the triazene structure, for the azo compound would not be expected to decompose under these conditions. Furthermore, the absence of the azo compound as a contaminant was indicated by the presence of only one spot on paper chromatograms of the reaction product.

Experimental[11]

5-Diazoimidazole-4-carboxamide (IIa).—The following modifications in the procedure[3] for the preparation of the diazoimidazole were designed to avoid contamination of IIa with 2-azahypoxanthine and with trace amounts of red dyes: a 20% excess of sodium nitrite was used; precautions were taken to avoid a localized excess of 5(or 4)-aminoimidazole-4(or 5)-carboxamide hydrochloride by preventing premature contact of the amine, as it was being added, with nitrous fumes and droplets of the nitrite solution; and the precipitated product was dried as rapidly as possible after the filtration and washing. The precipitate of faintly yellow needles amounted to a yield of 75%.

Anal. Calcd. for $C_4H_3N_5O$: C, 35.04; H, 2.21. Found: C, 35.04; H, 2.41.

5(or 4)-(*p*-Dimethylaminophenylazo)imidazole-4(or 5)-carboxamide (Va).—A mixture of 1.84 ml. of *N*,*N*-dimethylaniline, 20 ml. of water, and 20 ml. of ethanol was acidified to *p*H 4 with 1 *N* hydrochloric acid. To the well stirred mixture 400 mg. of 5-diazoimidazole-4-carboxamide was added slowly over a period of 2 hr., and stirring was continued for an additional 0.5 hr. The red crystalline precipitate was removed by filtration, washed with four 10-ml. portions of water and with two 10-ml. portions of ethanol, and dried: yield, 460 mg. (61%); m.p., 280°, dec. (cap.). Two recrystallizations of the product from dimethylformamide gave 286 mg. (38%) of red crystals (dried at 110° for 4 hr.) with the same melting (decomposition) temperature. λ_{max} in mμ ($\epsilon \times 10^{-3}$) from 220–400 mμ: 298 (8.8) and 335 (10.5) in 0.1 *N* hydrochloric acid; 273 (8.9) and 315 (sh.) in *p*H 7 phosphate buffer; 258 (11.2) and 330 (4.4) in 0.1 *N* sodium hydroxide; 271 (9.8) and 316 (4.4) in ethanol.

Anal. Calcd. for $C_{12}H_{14}N_6O$: C, 55.80; H, 5.46; N, 32.59. Found: C, 55.56; H, 5.49; N, 32.30.

5(or 4)-(2-Hydroxy-1-naphthylazo)imidazole-4(or 5)-carboxamide (Vb).—A solution of 3.13 g. of 2-naphthol in 60 ml. of 50% ethanol was made alkaline to pH 7.9 with 1 *N* aqueous ammonia, and 600 mg. of 5-diazoimidazole-4-carboxamide was added slowly over a period of 1.5 hr. The reaction was conducted in an atmosphere of nitrogen, and the reaction mixture was protected from light. A red precipitate formed during the addition of the diazo derivative. After the mixture had been stirred an additional 2 hr., the bright red crystals were separated by filtration and washed with water. Washing the product with anhydrous ethanol caused a change in the physical state from red crystals to a red-brown powder: yield, 575 mg. (46%). The product does not melt below 300° (cap.); it darkens to a black solid below 200°. λ_{max} in mμ ($\epsilon \times 10^{-3}$) from 250–700 mμ: 287 (10.8), 420 (sh.), 474 (14.7) at pH 1; 300 (sh.), 420 (6.8), 509 (16.7), 540 (sh.) at *p*H 3.9; 280 (sh.), 351 (7.1), 468 (11.8), 508 (12.6) in 0.1 *N* sodium hydroxide.

Anal. Calcd. for $C_{14}H_{11}N_5O_2$: C, 59.78; H, 3.94; N, 24.90. Found: C, 59.90; H, 4.22; N, 24.76.

The change in crystal form on washing with ethanol and variations in the infrared spectrum, depending on techniques used in preparing the specimen, suggest that a tautomeric change may occur in the solid state.[12]

5(or 4)-(Substituted-triazeno)imidazole-4(or 5)-carboxamides. Method A.—Compounds VII, IX, X, XI, and XII were prepared by the following procedure. 5-Diazoimidazole 4-carboxamide (IIa) was added in small portions during 1–1.5 hr. to a well stirred solution of the anhydrous amine in anhydrous methanol. The reaction mixture was kept under nitrogen and was protected from atmospheric moisture. Five milliliters of the amine and 5 ml. of methanol were used for each 400-mg. quantity of the diazo compound employed. The reaction mixture was stirred for additional periods of 1.5–2.5 hr. after all of the diazo compound had been added, and the precipitated product was then collected by filtration, washed with a solvent, and dried. Infrared spectra of the crude products were examined for the presence of 2-azahypoxanthine or of unreacted diazo compound. All operations, including subsequent purifications, were conducted in the absence of light. Because of the thermal instability of the triazenoimidazoles and the precautions necessary in obtaining ultraviolet absorption data, an infrared spectrum or elemental analyses, or both, must be obtained for each specimen of a triazenoimidazole prepared.

5(or 4)-(1-Pyrrolidinylazo)imidazole-4(or 5)-carboxamide (XI), obtained as a light orange-beige[13] microcrystalline powder by the procedure described above, was washed with ether and dried: yield, 75%; explosive decomposition, 254–258°. No further purification was required.

Anal. Calcd. for $C_8H_{12}N_6O$: C, 46.14; H, 5.81; N, 40.36. Found: C, 46.11; H, 5.86; N, 40.29.

5(or 4)-(Piperidinoazo)imidazole-4(or 5)-carboxamide (XII) was obtained analytically pure as a light yellow microcrystalline powder: yield, 17%; m.p., 248–252°, dec. A second crop with the same infrared spectrum and decomposition temperature raised the yield to 26%. The second crop was isolated by evaporating the solvents from the filtrate from the first crop, dissolving the residue in methanol, and diluting the methanol solution with benzene and hexane.

Anal. Calcd. for $C_9H_{14}N_6O$: C, 48.63; H, 6.35; N, 37.82. Found: C, 48.42; H, 6.34; N, 37.81.

The piperidinoazo derivative was also prepared by Method C. The precipitate obtained from the reaction mixture appeared to be the piperidinium salt of XII. Stirring the precipitate, in suspension, in water at pH 6 afforded XII (47% yield).

5(or 4)-(Diethyltriazeno)imidazole-4(or 5)-carboxamide (VII), obtained as a light tan powder, wasw ashed with water and dried *in vacuo* over phosphorus pentoxide at room temperature: crude yield, 25%; decomposition temperature 232–236°. A second crop that raised the crude yield to 44% was obtained by evaporating the solvents from the filtrate under reduced pressure and then slurrying the residue with water at pH 6. Since the two crops had similar infrared

(11) All melting points and decomposition temperatures were determined with a Kofler Heizbank melting point apparatus except those designated "cap."; those so designated were determined in a capillary tube heated in an oil bath. When a compound decomposed explosively, the temperature at which explosion occurred a few seconds after the specimen came into contact with the Kofler Heizbank was read as the decomposition temperature. There was some variation depending on the degree of subdivision of the specimen.

(12) V. C. Farmer, *Spectrochim. Acta*, **8**, 374 (1957); for a recent discussion of a tautomeric change in the solid state, see N. Campbell and A. G. Cairns-Smith, *J. Chem. Soc.*, 1191 (1961).

(13) The colors of the triazenoimidazoles, like those of triazene derivatives of benzenediazonium salts,[5] are pale or light. The authors are indebted to Mrs. Ellen Cole, a student of art, for the descriptions of color used in this paper.

TABLE I

ULTRAVIOLET SPECTRA[a,b] OF 5(OR 4)-(DISUBSTITUTED TRIAZENO)IMIDAZOLE-4(OR 5)-CARBOXAMIDES

Compound			λ_{max} in mμ (ε × 10⁻³)			
No.	R_1	R_2	0.1 *N* HCl	pH 7	0.1 *N* NaOH	Alcohol
VI	CH_3	CH_3	223(7.5)[c]	237(11.2)[c]		
			275(sh)			
			322(18.7)	329(16.0)		
VII	C_2H_5	C_2H_5	225(7.0)[c]	238(11.6)	250(13.1)	
			275(sh)			
			328(19.5)	334(17.6)	348(15.4)	
VIII	C_4H_9	C_4H_9	226...	240(10.1)[c]	251(11.8)	
			275(sh)			
			330(18.1)	337(16.1)	351(13.8)	
IX	C_8H_{17}	C_8H_{17}	226(7.0)[c]	248(14.5)[d]	247(14.6)[d]	238(12.3)[e]
			275(sh)			
			330(19.5)	340(17.5)	337(17.5)	332(17.8)
X	$C_6H_5CH_2$	$C_6H_5CH_2$	225(sh)[c]	236(12.5)	248(13.3)	
			259(6.1)			
			328(19.1)	335(16.7)	352(15.8)	
XI	$R_1R_2N=$		224(7.4)	238(11.6)	251(13.4)	237(12.2)[f]
			275(sh)			
			328(21.1)	334(18.5)	348(16.3)	330(18.3)
XII	$R_1R_2N=$		225(7.5)	239(11.3)	251(13.3)	237(12.1)[f]
			275(sh)			
			330(22.0)	336(19.0)	351(16.6)	332(18.3)
XIII	C_6H_5	CH_3	234(8.9)[c]	230(sh)[c]		233(12.3)[c,e]
			355(24.5)	360(23.9)		356(23.8)

[a] Determined with solutions protected from light [b] sh = shoulder (wave length estimated). [c] ΔT = 1–8 min. [d] ε values are approximate because the compound tends to precipitate. [e] Ethanol. [f] Methanol.

spectra and decomposition temperatures, they were combined for further purification. The total product was suspended in water, the pH was adjusted to 5–6, and the solid phase was separated by filtration and washed well with water. The product was then stirred in aqueous medium at *p*H 9–10, and the light tan microcrystalline powder was collected by filtration, washed thoroughly with water (pH 5–6), and dried at room temperature: yield, 35%; explosive decomposition, 238–240°.

Anal. Calcd. for $C_8H_{14}N_6O$: C, 45.70; H, 6.71; N, 39.98. Found: C, 45.53; H, 6.40; N, 39.62.

5(or 4)-(1-Dioctyltriazeno)imidazole-4(or 5)-carboxamide (IX), obtained as a white crystalline precipitate, was washed with methanol and dried *in vacuo* over phosphorus pentoxide at room temperature (crude yield, 33%; m.p., 198–200°, dec.). The product was recrystallized from ethanol and then treated in aqueous media by a procedure similar to that used to purify the diethyltriazeno derivative (VII): yield, 18%; m.p., 200–202°, dec.

Anal. Calcd. for $C_{20}H_{38}N_6O$: C, 63.45; H, 10.12; N, 22.20. Found: C, 63.09; H, 10.29; N, 22.45.

5(or 4)-(Dibenzyltriazeno)imidazole-4(or 5)-carboxamide (X).—The precipitate was washed with hexane, dried, and then slurried with several portions of water until the pH of the filtrate stabilized at 6. Fine ivory needles were obtained by purifying the crude product by a procedure similar to that used with VII: yield, 52%; m.p., 256–258°, dec.

Anal. Calcd. for $C_{18}H_{18}N_6O$: C, 64.65; H, 5.43; N, 25.14. Found: C, 64.36; H, 5.64; N, 24.88.

Method B.—Compounds VI and XIII were prepared by the general procedure of method A except for the use of different proportions of reactants and solvent.

5(or 4)-(Dimethyltriazeno)imidazole-4(or 5)-carboxamide (VI) was obtained from 8.0 g. of the diazoimidazole (IIa) and an anhydrous reagent solution prepared by passing dimethylamine into 500 ml. of methanol for 20 min. at 5°. The ivory microcrystalline product was washed with methanol and dried *in vacuo:* yield, 5.05 g. (47.5%); explosive decomposition, 250–255°.

Anal. Calcd. for $C_6H_{10}N_6O$: C, 39.55; H, 5.53; N, 46.13. Found: C, 39.44; H, 5.50; N, 46.25.

5(or 4)-(3-Methyl-3-phenyltriazeno)imidazole-4(or 5)-carboxamide (XIII).—The precipitate obtained from 5.0 g of IIa (added during 2.5 hr.), 20 ml. (5 equivalents) of *N*-methylaniline, and 125 ml. of anhydrous methanol was washed with hexane. Analytically pure material (6.44 g.) was obtained by stirring the product in water at pH 9–9.5 for 20 min., washing it thoroughly with water, and drying the light orange needles *in vacuo* over phosphorus pentoxide: m.p., 248–255°, dec. This material (72% yield) appeared to be free of the azo compound (Vc) as a contaminant, for paper chromatograms developed in four solvent systems[14] contained only one spot. Since the movement of the material in all four solvent systems was different from that of 2-azahypoxanthine, dissociation did not occur under the conditions used for chromatography.

Anal. Calcd. for $C_{11}H_{12}N_6O$: C, 54.09; H, 4.95; N, 34.41. Found: C, 53.82; H, 4.94; N, 34.19.

Method C.—Compounds VIII and XII (described above) were prepared by using the amine, in excess, as the solvent.

5(or 4)-(Dibutyltriazeno)imidazole-4(or 5)-carboxamide (VIII).—To 20 ml. of stirred, anhydrous dibutylamine was added 1.0 g. of 5-diazoimidazole-4-carboxamide during a period of 2.5 hr., and the reaction mixture was stirred for an additional 3 hr. The precipitated solid was separated by filtration, washed thoroughly with benzene, and dried *in vacuo* at room temperature. The product was slurried twice with water for periods of 10 min. It was then resuspended in water; the pH of the mixture was adjusted to 6.0–6.3; and the light coral microcrystalline solid was collected by filtration, washed well with water, and dried *in vacuo*. During these operations the reaction mixture and the product were protected from light. The yield of analytically pure material was 70%; m.p. 195°, dec.

Anal. Calcd. for $C_{12}H_{22}N_6O$: C, 54.11; H, 8.33; N, 31.56. Found: C, 54.15; H, 8.20; N, 31.61.

2-Azahypoxanthine (III) from 5(or 4)-(Dibutyltriazeno)-imidazole-4(or 5)-carboxamide (VIII).—Because the dibutyltriazeno derivative is only slightly soluble in water, the

(14) Paper chromatograms were developed in (1) butanol saturated with water, (2) butanol–acetic acid–water (5:2:3 by volume), (3) 2-propanol–water–concentrated aqueous ammonia (70:25:5 by volume), and (4) acetate buffer (pH 6.1) and were examined under an ultraviolet lamp.

reaction was carried out in aqueous ethanol. Three hundred milligrams of 5(or 4)-(dibutyltriazeno)imidazole-4(or 5)-carboxamide was dissolved in 30 ml. of ethanol at room temperature. The solution was diluted with 60 ml. of water, and a small additional quantity of ethanol was added to redissolve a small amount of the dibutyltriazene precipitated by the addition of the water. The solution was stirred in the presence of light for 2 days, the solvents were removed under reduced pressure, and 122 mg. of crystals (explosive decomposition at 201–204°) were obtained by recrystallizing the residue from 2.5 ml. of water. This material was identical with 2-azahypoxanthine according to paper chromatography.[14] The infrared spectrum was similar to that of 2-azahypoxanthine monohydrate, but C—H absorption bands at 2875, 2930, and 2960 cm.$^{-1}$ indicated that the crystals contained dibutylamine, which was probably present as the dibutylammonium salt of 2-azahypoxanthine. Accordingly, a portion (110 mg.) of the product was dissolved in 2.5 ml. of water and reprecipitated by lowering the pH to 1–2 with hydrochloric acid: weight, 60 mg. (adjusted yield, 38%); explosive decomposition, 204–208°. The infrared spectrum was identical with that of a specimen of 2-azahypoxanthine monohydrate.[3] Paper chromatograms[14] developed in four solvent systems showed only 2-azahypoxanthine.

Ultraviolet spectra were recorded with a Cary Model 14 recording spectrophotometer. Solutions of the 5(or 4)-(disubstituted-triazeno)imidazole-4 (or 5)-carboxamides were protected from light during their preparation, and stock solutions were stored in the dark. During studies on the stability of a triazene derivative, a fresh portion of the stock solution was transferred to the spectrophotometer cell for the tracing of each curve at a given ΔT or ΔT_L. After a triazene had been shown to be stable for 24–48 hr. in the dark, the solution being studied was exposed to indirect sunlight. ΔT_L is the time interval between the initial exposure of a solution to light and the tracing of a given curve, and it includes periods of darkness for studies that extended beyond 8 hr. The wavelength of the radiation catalyzing the dissociation was not determined. Data from the first curves traced during the stability studies (ΔT = 1–7 min.) are included in Table I. Since the stability studies show that the triazenes (except XIII in 0.1 *N* hydrochloric acid) are stable in the dark, ΔT values for the remainder of the determinations summarized in Table I were somewhat greater; but they were usually less than 45 min.

Infrared spectra were determined, using the potassium bromide disc method, with either a Perkin-Elmer Model 21 double-beam spectrophotometer, equipped with a sodium chloride prism, or with a Model 221-G, equipped with a sodium chloride prism and a 240 line-per-mm. grating. Some of the bands, exclusive of aliphatic C—H bands, that appear to be common to most or all of the triazenoimidazoles occur in the following regions (in cm.$^{-1}$): 3390–3350s (sharp), 3305–3260w, 3170–3130m (broad), 2760–2730w (or sh.), 2600w (broad), 1660–1650s (amide I), 1610–1590s, 1555–1545w, 1085–1075ms, 880–850wm, 800–780wm, 700–685wm. Several strong bands appear in the spectra of all of the triazenes in the region 1500–1250 cm.$^{-1}$, especially near 1400 cm.$^{-1}$, but association of these bands with the triazenoimidazolecarboxamide structure is complicated by C—H absorption in the alkyl groups. Bands characteristic of monosubstituted phenyl groups at 770–760 cm.$^{-1}$ and at 690 cm.$^{-1}$ in the spectra of the dibenzyl (X) and the methylphenyl (XIII) triazenes are readily distinguishable from weak or medium bands near these regions in the other triazenes.

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Thiadiazoles. I. Synthesis and Properties of [1,2,5]Thiadiazolo[3,4-*d*]pyrimidines[1]

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[1,2,5]Thiadiazolo[3,4-*d*]pyrimidines have been synthesized from 4,5-diaminopyrimidines and *N*-sulfinylaniline. An intermediate in this reaction has been isolated. Replacement reactions have been observed to occur readily at position 7, and reductive cleavage of the thiadiazole ring has been demonstrated. Similarities in the properties of [1,2,5]thiadiazolo-[3,4-*d*]pyrimidines and pteridines have been noted.

[1,2,5]Thiadiazolo[3,4-*d*]pyrimidines (8-thiapurines) may be considered analogs of two biologically important heterocyclic ring systems: They are formally analogous to the purines[2] by virtue of the 3,4-*d* fusion of the five-membered ring to the pyrimidine ring, and they are iso-π-electronic with the pteridines.[4] Schrage and Hitchings[5] proposed

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740, and by the C. F. Kettering Foundation.

(2) Biological analogy is suggested by the report[3] of antiguanine activity by 8-thiaguanine.

(3) G. M. Timmis, *J. Pharm. Pharmacol.*, **9**, 85 (1957).

(4) The electronic similarity of structures differing only in the substitution of a sulfur atom for an ethylenic grouping is well known: for example, H. C. Longuet-Higgins, *Trans. Faraday Soc.*, **45**, 173 (1949); J. de Heer, *J. Am. Chem. Soc.*, **76**, 4802 (1954); J. Koutecký, *Collection Czech. Chem. Comm.*, **24**, 1608 (1959). *Cf.* O. Hinsburg, *J. prakt. Chem.*, **93**, 302 (1916). This type of substitution has frequently been used in applying the concept of bio-isosterism. Consult, for example, H. L. Friedman, "Influence of Isosteric Replacements upon Biological Activity," First Symposium on Chemical-Biological Correlation, National Research Council-National Academy of Sciences Publication **206**, Washington, D. C., 1951; V. B. Schatz in A. Burger's "Medicinal Chemistry," 2nd ed., Interscience Publishers, Inc., New York, 1960, Chap. 8.

(5) A. Schrage and G. H. Hitchings, *J. Org. Chem.*, **16**, 207 (1951).