red residue (6.0 g.) was dissolved in *ca.* 8 ml. of dimethylformamide at room temperature, and the resultant solution was allowed to drop slowly into 300 ml. of ethanol. The red solution thus produced deposited crimson leaflets. Repetition of the solution-precipitation process afforded 4.0 g. (36%): m.p., 142° dec.

Anal. Calcd. for $C_{31}H_{23}Cl_2NO_8$: C, 64.59; H, 4.02; Cl, 12.32; N, 2.43. Found: C, 64.25; H, 4.29; Cl, 12.61, 12.72; N, 2.48.

Attempts to use several of the more conventional recrystallization techniques were unsuccessful, either achieving no purification or producing tar.

Reactions of Mannich products with acetic acid. In one experiment 0.10-g. samples of III, IV, V, and VIII were added to 2.5 ml. of glacial acetic acid and allowed to stand at room temperature. From III and IV there was obtained 0.05 g. (each), and from V and VIII there was obtained 0.06 g. (each) of I, which was identified by infrared spectrum and melting point. The order in which the original color was replaced by the yellow of I was IV > V > VIII > III. In a separate experiment VII was shown to change color more rapidly than III.

Reactions of Mannich products with acetic anhydride. In a typical experiment a small sample of the substituted aminomethyllawsone was added to 1 ml. of acetic anhydride containing 2 drops of concd. sulfuric acid. Upon being allowed to stand overnight a yellow precipitate appeared. This was identified by infrared spectrum and m.p. (235–237° dec.) as the diacetate of I. The authentic sample for comparison was prepared according to the directions of Fieser[6]: m.p. 235–237° dec., reported m.p., 132–133°.[12]

Anal. Calcd. for $C_{25}H_{16}O_8$: C, 67.57; H, 3.63. Found: C, 67.63; H, 3.72.

Reactions with acetaldehyde. A slight excess of the amine (0.007–0.008 mole) and 0.5 ml. of acetaldehyde was dissolved in 10 ml. of absolute ethanol and treated dropwise with a filtered solution of 1.0 g. (0.006 mole) of lawsone in 100 ml. of absolute ethanol by means of a Hershberg (slow addition) dropping funnel. Addition required 1 hr. The initial precipitate was suction filtered and washed well with 1:1 ethanol-ether and then vacuum dried. Data are collected in Table I. Appreciable additional quantities of less pure products were obtained in every case by evaporation or further dilution of mother-liquors with ether and/or petroleum ether.

ANN ARBOR, MICH.

(12) This value is apparently erroneous and should be 232–233°. In order to confirm this, our synthetic product was analyzed.

[CONTRIBUTION FROM THE KETTERING-MEYER LABORATORY, SOUTHERN RESEARCH INSTITUTE]

Synthesis of Potential Anticancer Agents. XXIX. 5-Diazoimidazole-4-carboxamide and 5-Diazo-*v*-triazole-4-carboxamide[1,2]

Y. FULMER SHEALY, ROBERT F. STRUCK, LEE B. HOLUM, AND JOHN A. MONTGOMERY

Received October 19, 1960

The initial product of the diazotization of 5(or 4)-aminoimidazole-4-(or 5)-carboxamide has been isolated and shown to be 5-diazoimidazole-4-carboxamide. The diazo derivative, stable in the absence of moisture, cyclizes in aqueous solutions to the fused-ring isomer, 2-azahypoxanthine. 5-Diazo-*v*-triazole-4-carboxamide and 2,8-diazahypoxanthine have likewise been obtained from 5-amino-*v*-triazole-4-carboxamide. 5-Diazoimidazole-4-carboxamide has anticancer activity *in vitro* and *in vivo*. The structure of the diazoheterocycles is discussed.

The 2-azapurines (imidazo[4,5-*d*]-*v*-triazines) belong to the group of heterocyclic analogs of purines that have shown activity as inhibitors of neoplastic cells[3,4] and of microorganisms.[5] The few known 2-azapurines have been obtained by diazotization of the appropriate aminoimidazoles.[5–8] The reaction of 5(or 4)-aminoimidazole-4(or 5)-carboxamide (I) hydrochloride with sodium nitrite in aqueous solution has been reported to furnish 2-azahypoxanthine (imidazo[4,5-*d*]-*v*-triazin-4-(3*H*)-one) (III) directly in 85% yield.[5]

In the present work, a compound different from 2-azahypoxanthine has been obtained as the initial product of diazotization of 5(or 4)-aminoimidazole-4(or 5)-carboxamide (I) (AIC). The new compound forms, in yields of 70-94%, as a crystalline precipitate when a solution of AIC hydrochloride in 1*N* hydrochloric acid is added to an aqueous solution of sodium nitrite. The nature of the precipitate was first revealed by a positive Bratton-Marshall test,[9] indicative of an aromatic diazo group; by a sharp, intense infrared band—at 2190 cm.$^{-1}$—in the region characteristic of triple-bond and cumulative double-bond structures; and by analytical data in accord with the empirical formula $C_4H_3N_5O$. These and subsequent observations show that the initial product of the diazotization of AIC (I) is 5-diazoimidazole-4-carboxamide, which is represented here by the dipolar structure of

(1) The work described in this paper was presented before the Division of Medicinal Chemistry, 137th Meeting of the American Chemical Society, Cleveland, Ohio, April 5–14, 1960.

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

(3) A. Fjelde, *Z. Krebsforsch.*, **61**, 364 (1956).

(4) J. J. Biesele, *Cancer*, **5**, 787 (1952).

(5) D. W. Woolley and E. Shaw, *J. Biol. Chem.*, **189**, 401 (1951).

(6) M. R. Stetten and C. L. Fox, Jr., *J. Biol. Chem.*, **161**, 333 (1945).

(7) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **194**, 641 (1952).

(8) M. A. Stevens, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, **82**, 3189 (1960).

(9) A. C. Bratton and E. K. Marshall, Jr., *J. Biol. Chem.*, **128**, 537 (1939).

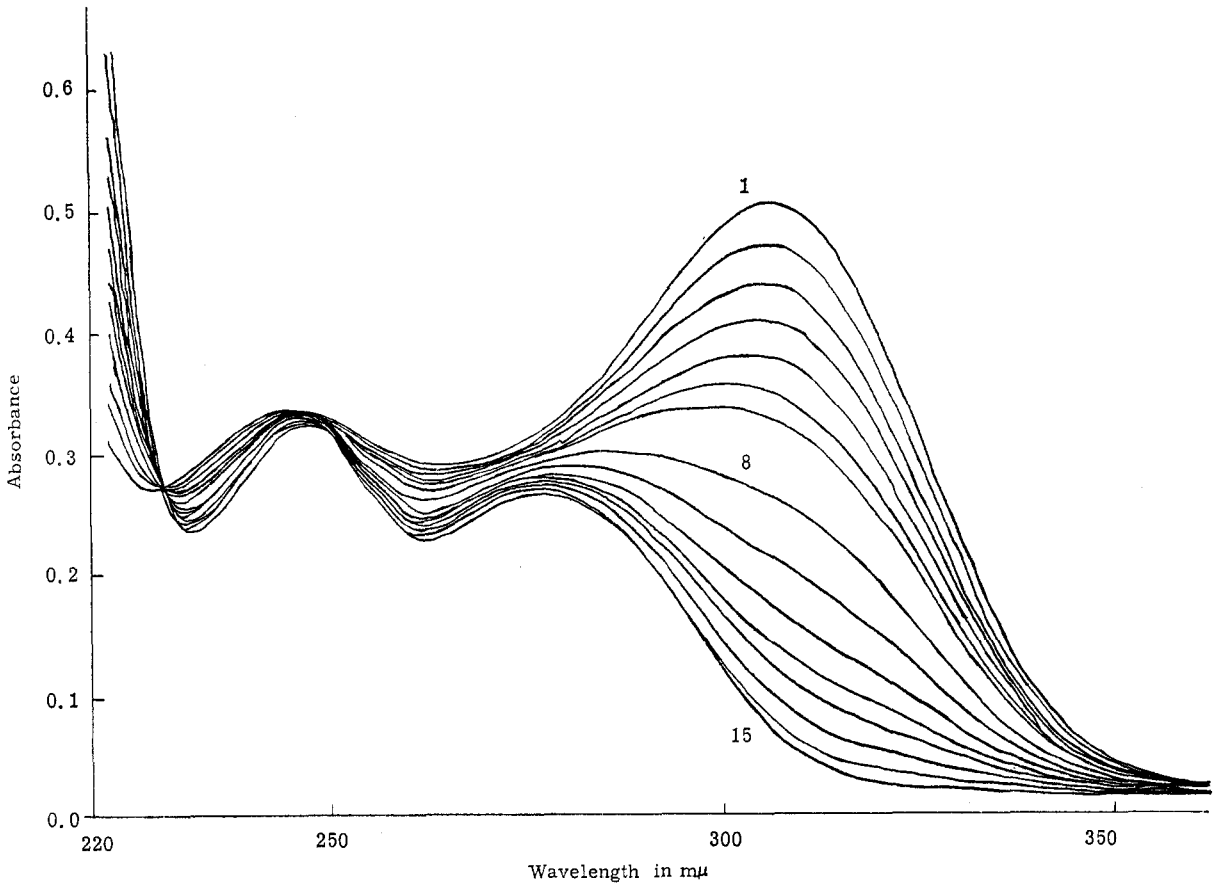
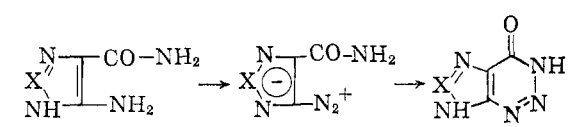


Fig. 1. Ultraviolet spectra showing the cyclization of II to III in 0.1 *N* hydrochloric acid. Curves 1–7 were traced at five-minute intervals after the addition of the solvent to II; curves 8–12, at fifteen-minute intervals after No. 7; and curves 13–15, at thirty-minute intervals after No. 12

an internal diazonium salt (II). The diazo derivative decomposes explosively near 210°; its infrared



I. X = CH II. X = CH III. X = CH
IV. X = N V. X = N VI. X = N

spectrum clearly distinguishes it from 2-azahypoxanthine. A specimen of II stored for two and one-half years in a stoppered, clear-glass vial under ordinary laboratory conditions had darkened somewhat, but its infrared spectrum was practically identical with that of freshly prepared, analytically pure material.

5-Diazoimidazole-4-carboxamide was readily converted to 2-azahypoxanthine in yields up to 96% by 1*N* aqueous ammonia. In contrast to the diazo intermediate, 2-azahypoxanthine does not give a positive Bratton-Marshall test, displays no distinct absorption in the 2300–2000 cm.$^{-1}$ region of its infrared spectrum, and crystallizes from aqueous solution as a monohydrate. 2-Azahypoxanthine was first isolated as a monohydrate by Stetten and Fox[6] when they diazotized an amine, later[10] shown to be 5(or 4)-aminoimidazole-4(or 5)-carboxamide, which they had isolated from biological sources. The crystallization of 2-azahypoxanthine from aqueous solutions as a monohydrate is in agreement with the original observation of Stetten and Fox rather than that reported later.[5] The strong carbonyl band at 1690 cm.$^{-1}$ indicates that it exists in the keto, rather than the enol, form.

Subsequently, ultraviolet absorption studies revealed that 5-diazoimidazole-4-carboxamide (II) cyclizes to 2-azahypoxanthine in acidic solutions as well as in basic solutions. The course of the cyclization at one level of acidity (0.1*N* hydrochloric acid) is depicted in Fig. 1. Similar families of curves traced at various time intervals were obtained from solutions of II in 6*N* hydrochloric acid, *p*H 3 buffer solution, distilled water (*p*H 5.9), *p*H 7 buffer solution, and 0.1*N* sodium hydroxide. In each of the six solutions the spectrum eventually became identical with that given by 2-azahypoxanthine at the same *p*H. Some of the data obtained in these studies[11] are summarized in Table I and in Fig. 2.

Diazotization of 5-amino-*v*-triazole-4-carboxamide (IV) gave results paralleling those of the

(10) W. Shive, W. W. Ackermann, M. Gordon, M. E. Getzendaner, and R. E. Eakin, *J. Am. Chem. Soc.*, 69, 725 (1947).

TABLE I

ABSORPTION MAXIMA OF 2-AZAHYPOXANTHINE AND 5-DIAZOIMIDAZOLE-4-CARBOXAMIDE

Solvent	2-Azahypoxanthine (III) λ_{max} (mμ)	$\epsilon \times 10^{-3}$	Solutions of II ΔT (min.)[a]	λ_{max} (mμ)
0.1*N* NaOH	296, 256	6.19, 4.82	2.5	296, 256[b]
*p*H 7	286, 250	4.23, 5.04	3	304,[c] 249
			33	285, 250
Water (*p*H 5.9)	275–277, 249	4.22, 5.1	7	312, 246
			1190[d]	278, 248
*p*H 3			4	312, 246
			1440[e]	278, 248
0.1*N* HCl	277, 248	4.03, 4.98	5[f]	308,[g] 243
			170	277, 248
6*N* HCl	273–274, 245	3.66, 5.01	3.5	293,[g] 232–242
			129	273–274, 245

[a] ΔT as defined in Figure 2. [b] Absorption by II could not be observed because cyclization to III was complete within 2.5 min. [c] Evidently the resultant, due to the rapid rate of cyclization, of the long-wavelength maxima of II and III; therefore, curve E (Fig. 2) was plotted from absorbancies at 312 mμ. [d] Cyclization essentially complete within 3 hr. [e] Cyclization essentially complete within 4–6 hr. [f] λ_{max} same at ΔT = 3.5 min. [g] The hypsochromic shifts in the strongly acidic media may result from protonation of the imidazole ring to a "normal" diazonium salt. The fact that the spectra eventually become identical with those of III in the same media is evidence that replacement of the diazo group by chlorine did not occur.

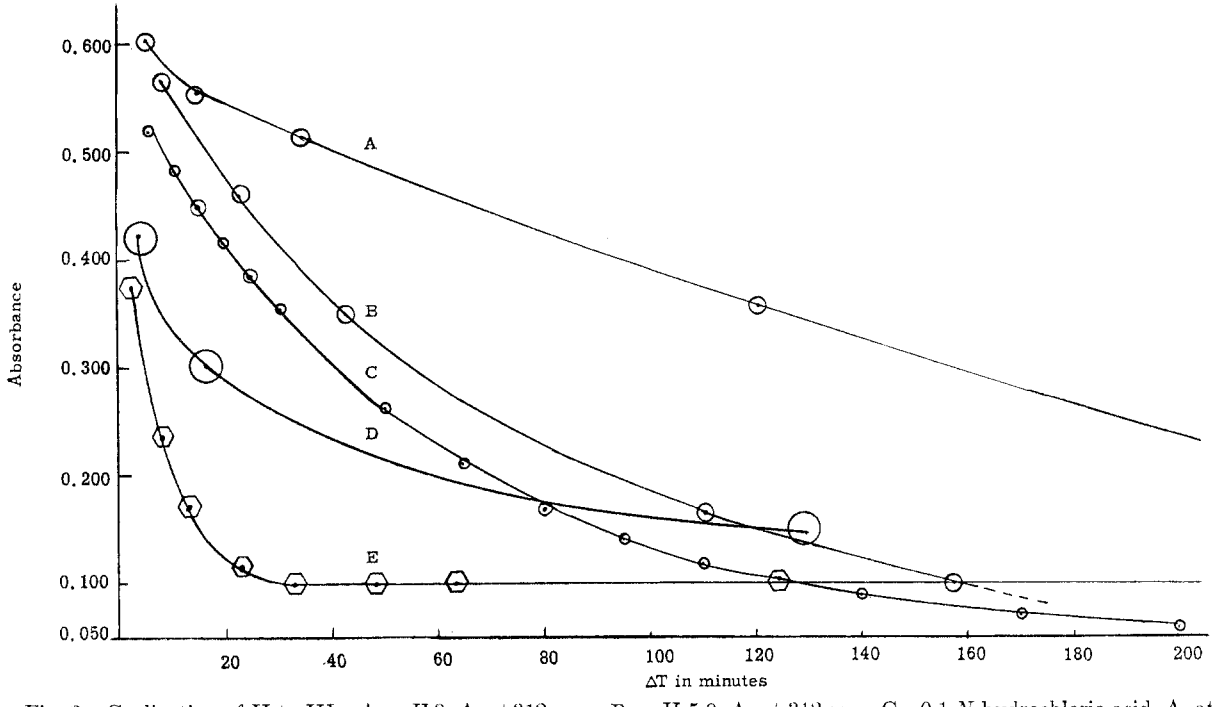


Fig. 2. Cyclization of II to III. A—*p*H 3, A_s at 312 mμ; B—*p*H 5.9, A_s at 312 mμ; C—0.1 *N* hydrochloric acid, A_s at 308 mμ; D—6 *N* hydrochloric acid, A_s at 293 mμ; E—*p*H 7, A_s at 312 mμ (footnote c, Table I). ΔT is the difference between the time at which solvent was added to II and the time at which the recording of a spectrum was begun

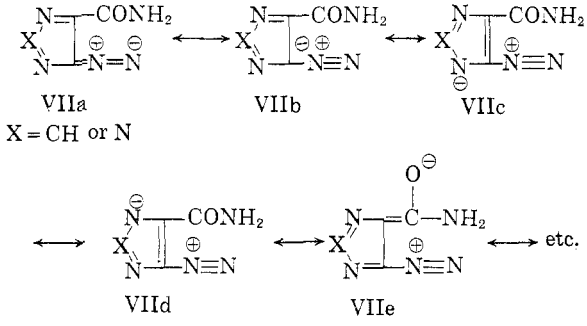
imidazole series. 5-Diazo-*v*-triazole-4-carboxamide (V) was isolated in 52% yield as a crystalline solid which decomposed explosively near 175°, gave a positive Bratton-Marshall test, and exhibited very strong absorption at 2210 cm.$^{-1}$ Ring closure to 2,8-diazahypoxanthine (*v*- triazolo[4,5-*d*]-*v*-triazin-7(6*H*)-one) (VI) was effected in alkaline solution. The diazotriazole is easily distinguished from its fused-ring isomer (isolated as the dihydrate) by the infrared spectra, the diazo frequencies being absent from the spectrum of 2,8-diazahypoxanthine. The keto structure VI is assigned to 2,8-diazahypoxanthine on the basis of a very strong band at 1740 cm.$^{-1}$

An examination of the infrared spectra of the two diazoheterocycles suggests further details of their structures. The broad doublets in the 3300–3100 cm.$^{-1}$ region are typical of the NH-stretching

(11) All of these cyclization studies were made with solutions protected from light. A solution of II at *p*H 5.9 prepared without excluding light and then exposed continuously in the spectrophotometer cell to light at 312 mμ displayed a faster rate of cyclization than a solution of the same *p*H kept in the dark.

vibrations of primary amides.[12] The most prominent bands in the spectra are those of the diazo group[13] near 2200 cm.$^{-1}$ The frequencies of the diazo bands of II (2190 cm.$^{-1}$) and V (2210 cm.$^{-1}$) lie approximately between those of typical aryldiazonium salts[14,15] and those of diazophenols,[15,16] *p*-diazoanilines,[15] and the more complex diazocarbonyl compounds.[17,18,19] Aroney, LeFèvre, and Werner[14] and Whetsel, Hawkins, and Johnson[15] have found that the diazonium group absorbs in the region 2310–2235 cm.$^{-1}$ with only slight shifts due to variation of the anion. More recently, frequency ranges extending to those of II and V have been reported[20]; some typical aryldiazonium cations in the form of triiodides produced bands in the region 2260–2200 cm.$^{-1}$ A strong band in the 1430–1330 cm.$^{-1}$ region of the spectra of certain diazocarbonyl compounds has been observed by Yates, Shapiro, Yoda, and Fugger[17] and by Fahr.[18] The spectrum of the diazoimidazole (II) shows a strong band at 1380 cm.$^{-1}$, and that of the diazotriazole (V) has a band at 1390 cm.$^{-1}$ comparable in intensity to the band at 2210 cm.$^{-1}$

The close similarity of these diazoheterocycles to aromatic diazonium compounds is suggested by the diazo band near 2200 cm.$^{-1}$ and by the formation of coupling products[21,22] typical of those of aryldiazonium salts. Some of the possible contributing forms to a resonance hybrid are represented by VIIa–e. Structures VIIa and VIIb correspond to the two major forms contributing to the structure of diazomethane.[23] Forms VIIc and VIId may be viewed formally and arbitrarily as being formed by ionization of the acidic ring hydrogen atom during the diazotization process. If the contributions of forms having a triply bonded diazo group (-N$^+$≡N) can be correlated with the infrared absorption



frequency, as suggested by Whetsel *et al.*,[15] then the importance of forms such as VIIb–d would appear to be greater in these two heterocyclic systems than similar forms are in the carbocyclic series where diazocyclopentadiene[24] absorbs at 2082 cm.$^{-1}$ The localized electron pair of forms VIIb, VIIc, VIId, and other canonical forms is potentially capable of being incorporated into the π-electron system of the ring, the negative charge then becoming associated with the π-electron sextet (II and V). Such diazoheterocycles may be regarded as diazonium salts in which the ring system serves as the anionic component, the degree of aromaticity varying with the magnitude of charge localization on the heteroatoms. This representation may be considered analogous to the formulation of mesoionic compounds as ring structures bearing a negatively charged substituent and having a positive charge associated with the π-electron sextet.[25] These considerations suggested that other heterocycles having an easily ionizable hydrogen and a suitably placed amino group will form stable diazo (or diazonium) derivatives. It is probable that earlier workers[26] were dealing with derivatives of this type in the pyrazole, pyrrole, 1,2,4-triazole, and tetrazole series. Stable diazo derivatives of one of these ring systems have recently been isolated; subsequent to our preliminary report,[21] a note recording the preparation and characterization of diazopyrazoles has appeared.[27]

Biological activity. 5-Diazoimidazole-4-carboxamide and 5-diazo-*v*-triazole-4-carboxamide are of interest as potential anticancer agents. Both are analogs of 5(or 4)-aminoimidazole-4(or 5)-carboxamide, whose ribonucleotide is a precursor of nu-

(12) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., N. Y., 1958.

(13) A detailed tabulation of wavelengths of the diazo group in other types of diazo compounds is presented in reference 18, p. 18.

(14) M. Aroney, R. J. W. Le Fèvre, and R. L. Werner, *J. Chem. Soc.*, 276 (1955).

(15) K. B. Whetsel, G. F. Hawkins, and F. E. Johnson, *J. Am. Chem. Soc.*, **78**, 3360 (1956).

(16) R. J. W. Le Fèvre, J. B. Sousa, and R. L. Werner, *J. Chem. Soc.*, 4686 (1954).

(17) P. Yates, B. L. Shapiro, N. Yoda, and J. Fugger, *J. Am. Chem. Soc.*, **79**, 5756 (1957); spectra determined in solution.

(18) E. Fahr, *Ann.*, **617**, 11 (1958).

(19) J. H. Looker and D. N. Thatcher, *J. Org. Chem.*, **22**, 1233 (1957).

(20) J. G. Carey and I. T. Millar, *Chem. and Ind.*, 97 (1960); J. G. Carey, G. Jones, and I. T. Millar, *Chem. and Ind.*, 1018 (1959).

(21) Y. F. Shealy, R. F. Struck, L. B. Holum, and J. A. Montgomery, Abstracts of Papers, 137th Meeting of the American Chemical Society, Cleveland, Ohio, April 5–14, 1960, p. 4N.

(22) Y. F. Shealy, C. A. Krauth, C. A. O'Dell, and J. A. Montgomery, unpublished.

(23) G. W. Wheland, *Resonance in Organic Chemistry*, John Wiley & Sons, Inc., N. Y., 1955, p. 181.

(24) W. von E. Doering and C. H. DePuy, *J. Am. Chem. Soc.*, **75**, 5955 (1953); solution and vapor-phase spectra.

(25) W. Baker and W. D. Ollis, *Quart. Revs.*, **11**, 15 (1957).

(26) *E.g.*, L. Knorr, *Ber.*, **37**, 3520 (1904); J. Thiele and W. Manchot, *Ann.*, **303**, 33 (1898); J. Reilly and D. Madden, *J. Chem. Soc.*, 815 (1929); J. Thiele and J. T. Marais, *Ann.*, **273**, 144 (1893); F. Angelico, *Atti. Accad. Lincei*, [V], **14II**, 167 (1905) [Beilstein's *Handbuch Der Organischen Chemie*, XXII, pp. 468, 479].

(27) D. G. Farnum and P. Yates, *Chem. and Ind.* 659 (1960). More recently the isolation of diazopurines has been reported: J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **82**, 3773 (1960).

cleic acids[28]; and, like certain other anticancer agents such as azaserine[29] and 6-diazo-5-oxo-L-norleucine,[30] they possess a reactive function. The information on the stability of 5-diazoimidazole-4-carboxamide gained from the ultraviolet absorption studies was essential to the demonstration of biological activity. With suitable precautions in administration, the diazoimidazole (II) inhibits the growth of Human Epidermoid Carcinoma (H. Ep. -2) cells in tissue culture, the Ehrlich Ascites Carcinoma in mice, and the Walker 256 Carcinoma in rats.[31] The distinction between 5-diazoimidazole-4-carboxamide and 2-azahypoxanthine shown spectroscopically and chemically is further confirmed by the biological data. 2-Azahypoxanthine was not inhibitory to H. Ep.-2 cells in tissue culture at 5×10^{-4} g./ml. and was nontoxic at 125 mg./kg./day in mice bearing Sarcoma 180 or Adenocarcinoma 755. In these same tests in mice, 5-diazoimidazole-4-carboxamide was toxic at 2.5–10 mg./kg./day.[31]

EXPERIMENTAL

5-Diazoimidazole-4-carboxamide. A stirred solution of 4.7 g. (68 mmoles) of sodium nitrite in 120 ml. of water was maintained at 0–5° while a solution of 10 g. (61.6 mmoles) of 5(or 4)-aminoimidazole-4(or 5)-carboxamide hydrochloride[32] in 80 ml. of cold 1 *N* hydrochloric acid was introduced dropwise. A crystalline precipitate began to form after a small portion of the aminoimidazole solution had been added; after about 90% of the aminoimidazole solution had been added, the reaction mixture began to assume a pink color. The addition was discontinued, and the precipitate was removed by filtration, washed three times with 20-ml. portions of water, and dried *in vacuo* over phosphorus pentoxide. The small crystalline needles of 5-diazoimidazole-4-carboxamide weighed 5.9 g. (70% yield), decomposed explosively[33] at 205–210°, gave a positive Bratton-Marshall test,[9] and produced a diazo absorption band at 2190 cm.$^{-1}$ A sample of the diazo derivative that had been dried at 55° *in vacuo* over phosphorus pentoxide was submitted for analysis.

Anal. Calcd. for $C_4H_3N_5O$: C, 35.04; H, 2.21; N, 51.09. Found: C, 34.99; H, 2.35; N, 51.10.

The total yield was brought to 73.5% by refiltering the filtrate, introducing additional sodium nitrite, and continuing the addition of the solution of 5(or 4)-aminoimidazole-4 (or 5)-carboxamide.

5-Diazoimidazole-4-carboxamide can be obtained as a crystalline solid ranging in color from ivory to faintly yellow. It is evident from the ultraviolet data that pure specimens can be isolated from aqueous media only if the reaction is conducted in such a way that the product precipitates. Unless the reaction conditions are closely controlled, intense red or purple reaction mixtures are formed; the colored products probably result from coupling of II with unreacted 5(or 4)-aminoimidazole-4(or 5)-carboxamide.

2-Azahypoxanthine monohydrate. A mixture of 2.30 g. of 5-diazoimidazole-4-carboxamide, 70 ml. of 1*N* ammonia, and a small quantity of decolorizing carbon was allowed to stand overnight. The mixture was filtered, the colorless filtrate was evaporated to dryness under diminished pressure, and the residual white solid was dried *in vacuo* over phosphorus pentoxide at 55° for 2 hr.: weight, 2.43 g. (93% yield); explosive decomposition, 210°; negative Bratton-Marshall test. A specimen was recrystallized from water and dried under the same conditions. In agreement with the statements of Stetten and Fox,[6] 2-azahydroxanthine monohydrate darkened near 150° when the temperature was raised gradually and, then, did not melt below 260°. It explodes when placed on the Kofler Heizbank at 210°.

Anal. Calcd. for $C_4H_3N_5O \cdot H_2O$: C, 30.95; H, 3.25; N, 45.12. Found: C, 31.10; H, 3.02; N, 44.99.

5-Diazo-v-triazole-4-carboxamide. A solution prepared from 1 g. of 5-amino-*v*-triazole-4-carboxamide, 7 ml. of water, and 43 ml. of 2:1 acetic acid–water was cooled to 5°. To the cold, stirred triazole solution 1.3 ml. of isoamyl nitrite was added dropwise, and stirring was continued at 5° for 1 hr. and at room temperature for 2 hr. The reaction solution was allowed to stand overnight, concentrated to 10 ml. under reduced pressure at room temperature, and chilled. The cold solution deposited 470 mg. of a crystalline product. This material gave a positive Bratton-Marshall test,[9] decomposed explosively near 175°, and showed the intense infrared absorption of the diazo group at 2210 cm.$^{-1}$ The filtrate furnished a second crop (100 mg.) of the diazotriazole: total yield, 570 mg. (52%). Two recrystallizations from water gave 5-diazo-*v*-triazole-4-carboxamide as white crystals which decomposed explosively near 175°.

Anal. Calcd. for $C_3H_2N_6O$: C, 26.09; H, 1.46; N, 60.85. Found: C, 26.06; H, 1.56; N, 60.87.

2,8-Diazahypoxanthine (v-triazolo[4,5-d]-v-triazin-7(6H)-one). a. *From 5-amino-v-triazole-4-carboxamide.* A solution of 0.69 g. (10 mmoles) of sodium nitrite in 6 ml. of water was added to a cold (0–5°) stirred solution composed of 1.0 g. (7.9 mmoles) of 5-amino-*v*-triazole-4-carboxamide, 2.4 ml. of glacial acetic acid, and 220 ml. of water. The nitrite solution was added dropwise over a period of 1 hr. The colorless reaction solution was allowed to warm to room temperature, stirred at room temperature for 4 hr., and then allowed to stand at room temperature overnight. The *p*H of the solution was raised with 1.0 *N* sodium hydroxide to *p*H 9.2. After the basic solution had been allowed to stand overnight, it was passed through a column (3.5 cm. × 13 cm.) of the cation exchange resin IRC-50 (acid form). The effluent was evaporated to dryness *in vacuo* at room temperature. Recrystallization of the residue from ethanol-water furnished 0.7 g. (51% yield) of crystalline 2,8-diazahypoxanthine dihydrate. This product did not give a positive Bratton-Marshall test, had no distinct absorption bands in the 2300–2000 cm.$^{-1}$ region of its infrared spectrum, and decomposed explosively at 270°. When the compound was heated gradually, it began to darken near 200° and did not melt below 290°. Recrystallization from water gave colorless needles of 2,8-diazahypoxanthine dihydrate: explosive decomposition, 270°.

Spectral data. λ_{max} in mμ ($\epsilon \times 10^{-3}$): 264 (6.44) in 0.1 *N* hydrochloric acid; 278 (5.15) at *p*H 7; 259 (4.37) and 294 (7.92) in 0.1 *N* sodium hydroxide.

Anal. Calcd. for $C_3H_2N_6O \cdot 2H_2O$: C, 20.67; H, 3.47; N, 48.29. Found: C, 20.90; H, 3.25; N, 48.46.

b. *From 5-diazo-v-triazole-4-carboxamide.* 5-Diazo-*v*-triazole-4-carboxamide isolated from the reaction of 5-amino-*v*-triazole-4-carboxamide with isoamyl nitrite in aqueous acetic acid cyclized during the following operations. A specimen of 5-diazo-*v*-triazole-4-carboxamide was stirred in aqueous

(28) H. E. Skipper and L. L. Bennett, Jr., *Annual Review of Biochemistry*, Annual Reviews, Inc., Palo Alto, Calif., 1958, Vol. 27, p. 137.

(29) S. A. Fusari, T. H. Haskell, R. P. Frohardt, and Q. R. Bartz, *J. Am. Chem. Soc.*, **76**, 2881 (1954).

(30) H. W. Dion, S. A. Fusari, Z. L. Jakubowski, J. G. Zora, and Q. R. Bartz, *Abstrs. of Papers*, 129th Meeting of the American Chemical Society, Dallas, Tex., April 8–13, 1956, p. 13M.

(31) Biological evaluations were carried out by Drs. F. M. Schabel, Jr., W. R. Laster, and associates of the Chemotherapy Division, Southern Research Institute.

(32) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **181**, 89 (1949); J. A. Montgomery, K. Hewson, R. F. Struck, and Y. F. Shealy, *J. Org. Chem.*, **24**, 256 (1959).

(33) Explosion temperatures and melting points were determined on a Kofler Heizbank melting-point apparatus.

acetic acid at *p*H 3–4 for approximately 1 day, and the solvent was evaporated in a stream of nitrogen. The solid residue was redissolved in aqueous solution and stirred at *p*H 6.4 for 3 hr. Evaporation of the water left a solid residue that gave a weakly positive Bratton-Marshall test. The solid was, therefore, redissolved in water, treated with activated carbon, and recrystallized from water. The colorless needles that separated gave ultraviolet and infrared spectra identical with those of 2,8-diazahypozanthine dihydrate prepared from 5-amino-*v*-triazole-4-carboxamide without isolation of the diazo derivative.

Spectroscopic determinations. Stock solutions of 5-diazoimidazole-4-carboxamide for the ultraviolet studies were prepared by adding the solvent in the dark to a specimen weighed to the nearest microgram. Each stock solution was stored in the dark during the determination of stability at a given *p*H. Initial concentrations of the diazoimidazole (II) were near 10 mg./l.

All ultraviolet spectra were recorded with a Beckman Model DK-2 spectrophotometer or with a Cary Model 14 spectrophotometer. The infrared spectra were determined in pressed potassium bromide disks with a Perkin-Elmer Model 21 spectrophotometer.

Acknowledgment. The authors are indebted to Mr. C. A. O'Dell for technical assistance; to Dr. W. J. Barrett, Dr. W. C. Coburn, Jr., and associates of the Analytical Section for spectral determinations; and to Mr. W. F. Fitzgibbon and associates of the Organic Preparations Section for large quantities of starting materials. Microanalyses were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

BIRMINGHAM, ALA.

[CONTRIBUTION FROM THE RADIUM INSTITUTE, UNIVERSITY OF PARIS]

Compounds with Potential Activity Against Lethal Radiations. VIII. Synthesis of Phenolic Ketones by Means of Boron Trifluoride

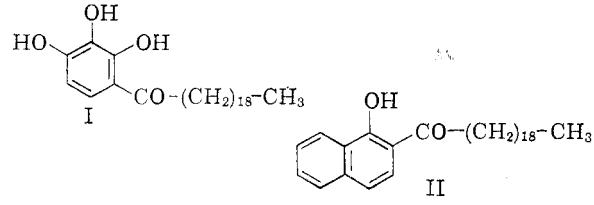
N. P. BUU-HOÏ AND N. D. XUONG

Received September 1, 1960

Boron trifluoride in the presence of hydrogen fluoride proved an excellent catalyst for the synthesis of phenolic ketones, prepared for evaluation of their protective action against lethal radiations. The naphthols and pyrogallol gave monoketones, while hydroquinone was disubstituted. 4-Acylcatechols were best prepared by acylation of guaiacol and subsequent demethylation.

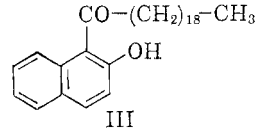
In earlier papers,[1] we described how a number of phenolic ketones, especially those bearing a long-chain acyl group, possess significant protective properties against whole-body x-ray irradiation in mice. Continuing this research, we have now synthesized phenolic ketones derived from di- and triphenols and from α- and β-naphthol.

The most convenient method for these syntheses was the condensation of carboxylic acids with the phenols in presence of boron trifluoride mixed with some hydrogen fluoride (*i.e.*, the gas produced by the reaction of oleum on potassium fluorborate), the hydrogen fluoride enhancing the condensing qualities of boron trifluoride. In these conditions, a temperature of 70° was sufficient to complete the condensation. The procedure is particularly useful for preparing ketones with long chains, as the Nencki, Friedel-Crafts, or Fries reactions customarily used may lead to splitting or rearrangement of such chains. Thus, with pyrogallol, arachidic acid gave 4-arachidoylpyrogallol (I), and with α- and β-naphthol, 2-arachidoyl-1-naphthol (II) and 1-arachidoyl-2-naphthol (III), all in excellent yields and without by-products. Similarly, 5-pentadecylresorcinol was easily converted with the appropriate acids, into 5-pentadecyl-4-resacetophenone (IV), 5-pentadecyl-4-respropiophenone

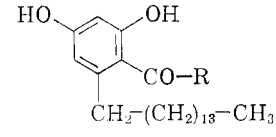


I

II



III



IV. R = CH_3
V. R = C_2H_5
VI. R = CH_2—C_6H_5

(V), and 5-pentadecyl-4-phenacetylresorcinol (VI), where in similar conditions the Nencki reaction gave but poor results.[2]

The acylation of catechol was far less easy to achieve (this lack of reactivity had already been noted in Nencki reactions[3]), and 4-acylcatechols were more readily accessible by boron trifluoride-catalyzed acylation of guaiacol and demethylation of the resulting 2-methoxy-4-acylphenols by means

(1) A. Lacassagne, J. F. Duplan, and N. P. Buu-Hoï, *J. Natl. Cancer Inst.*, **15**, 915 (1955).

(2) *Cf.* R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 999 (1946).

(3) N. P. Buu-Hoï, *J. Org. Chem.*, 19, 1770 (1954).