v-Triazolo[4,5-*d*]pyrimidines. II. *O*-Substituted Derivatives of 8-Azaguanine and 8-Azahypoxanthine[1]

Y. FULMER SHEALY, JOE D. CLAYTON, C. ALLEN O'DELL, AND JOHN A. MONTGOMERY

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham 5, Alabama

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5-Amino-7-chloro-*v*-triazolo[4,5-*d*]pyrimidine (IV) has been prepared from 2,4,5-triamino-6-chloropyrimidine and isoamyl nitrite. 7-Chloro-*v*-triazolo[4,5-*d*]pyrimidine (V) has been obtained in dioxane solution by the same method. These compounds, which are useful intermediates for the preparation of a variety of 7-substituted *v*-triazolo[4,5-*d*]pyrimidines, have been employed in the synthesis of 7-alkoxy- and 7-aryloxy-*v*-triazolo[4,5-*d*]pyrimidines.

v-Triazolo[4,5-*d*]pyrimidines with amino, alkoxy, thio, or other groups at position 7 are of interest as analogs of 6-substituted purines. The usual method of synthesis of *v*-triazolo[4,5-*d*]pyrimidines requires the preparation of a suitably substituted 4,5-diaminopyrimidine as a starting material for each *v*-triazolo[4,5-*d*]pyrimidine desired. The synthesis of 3-substituted *v*-triazolo[4,5-*d*]pyrimidines with a 7-chloro substituent permitted the introduction of a variety of groups at position 7.[2] The preparation of 7-chloro-*v*-triazolo[4,5-*d*]pyrimidines without the alkyl or aryl substituents at position 3 was expected to be more troublesome, but successful syntheses of these derivatives would eliminate the need for a large number of 4,5-diaminopyrimidines in preparing variously substituted *v*-triazolo[4,5-*d*]-pyrimidines. Recently, 7-amino derivatives were prepared by Weiss, Robins, and Noell[3a] from 7-(alkylthio)-*v*-triazolo[4,5-*d*]pyrimidines, but attempts to prepare 7-chloro-*v*-triazolo[4,5-*d*]pyrimidine (V) by cyclization of 4,5-diamino-6-chloropyrimidine or by treatment of 8-azahypoxanthine (*v*-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one) with phosphorus oxychloride were reported[3b] to be unsuccessful. The work described herein was concerned with the synthesis of 5-amino-7-chloro-*v*-triazolo[4,5-*d*]-pyrimidine (IV) and 7-chloro-*v*-triazolo[4,5-*d*]pyrimidine (V) and with substitution reactions of these compounds, emphasis being placed on the preparation of *O*-substituted derivatives of 8-azaguanine (5-amino-*v*-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one) (VIII. R = H) and 8-azahypoxanthine. The incentive for the preparation of these 7-alkoxy (or aryloxy)-*v*-triazolo[4,5-*d*]pyrimidines was the supposition that they would be less toxic than 8-azaguanine and 8-azahypoxanthine and that, as ether derivatives of the enol forms of these two compounds, they would be susceptible to hydrolysis at strategic sites *in vivo* to 8-azaguanine or 8-azahypoxanthine.

2,4,5-Triamino-6-chloropyrimidine (II) was prepared by reducing the 5-*p*-chlorophenylazo derivative (I) with zinc and acetic acid. Specimens of II purified by sublimation slowly became discolored during storage at room temperature; however, the unpurified reduction product gave good yields in the subsequent cyclization reaction. Treatment of the pyrimidine (II) with isoamyl nitrite in dioxane by the method of Bitterli and Erlenmeyer[4] gave a high yield of a product that, according to ultraviolet absorption data, appeared to be the desired 5-amino-7-chloro-*v*-triazolo[4,5-*d*]pyrimidine (IV). Analytical data from several specimens indicated that IV was solvated with dioxane. Drying at elevated temperatures caused some deterioration, but eventually a sample with a definite proportion of dioxane was obtained. Dioxane in a specimen recrystallized from dioxane–hexane was identified by vapor phase chromatography.

In order to confirm the structure of IV, it was treated with aqueous ethanolic sodium hydroxide by the procedure used to prepare 9-alkyl-8-azaguanines (VIII. R = alkyl) from 3-alkyl-7-chloro-3*H*-*v*-triazolo[4,5-*d*]pyrimidines.[2] In contrast to the behavior of the 3-alkyl derivatives, IV gave 5-amino-7-ethoxy-*v*-triazolo[4,5-*d*]pyrimidine (X). Treatment of IV with aqueous sodium hydroxide then gave a good yield of 8-azaguanine (VIII. R = H).

Initial diazotizations of 2,4,5-triamino-6-chloropyrimidine, or its hydrochloride, were performed in aqueous media with sodium nitrite. Examination of the products by paper chromatography and ultraviolet spectroscopy indicated the presence of both IV and 8-azaguanine, but it was not certain whether the 8-azaguanine was formed during the diazotization or during the chromatographic and spectroscopic determinations. However, a specimen of IV was obtained free of 8-azaguanine and successfully used in replacement reactions. After IV had been obtained by the isoamyl nitrite–dioxane procedure, it was found that ultraviolet and chromatographic determinations could be performed without replacing the 7-chloro group, provided that the solutions were prepared without applying heat. It

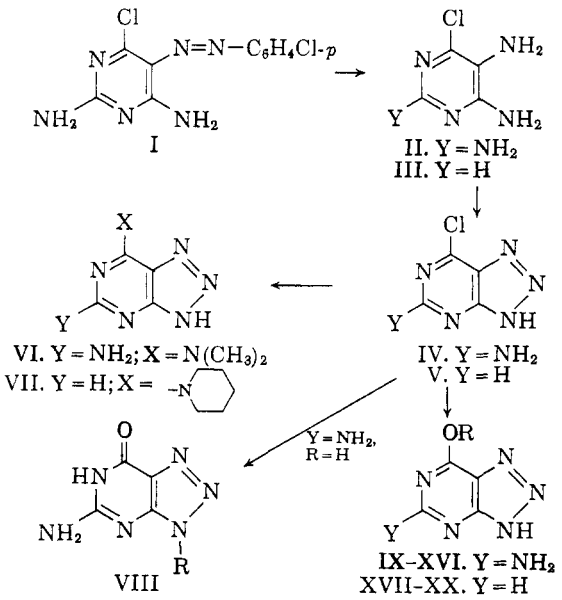
(1) This investigation was supported by the C. F. Kettering Foundation and by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740.

(2) Y. F. Shealy, R. F. Struck, J. D. Clayton, and J. A. Montgomery, *J. Org. Chem.*, **26**, 4433 (1961).

(3) (a) R. Weiss, R. K. Robins, and C. W. Noell, *ibid.*, **25**, 765 (1960); (b) R. Weiss, R. K. Robins, and C. W. Noell, Abstracts of Papers, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., September 13–18, 1959, p. 32-O.

(4) P. Bitterli and H. Erlenmeyer, *Helv. Chim. Acta*, **34**, 835 (1951).

was then shown that a reaction carried out in accordance with the procedure used to prepare 3-alkyl - 7 - chloro - 3*H* - *v* - triazolo[4,5 - *d*]pyrimidines[2] gave IV as a precipitate. A second crop was 8-azaguanine. Despite the lability of the 7-chloro group, 5-amino-7-chloro-*v*-triazolo[4,5-*d*]-pyrimidine can be prepared, therefore, by diazotization in aqueous solution, but 8-azaguanine may be formed in amounts that depend on the *modus operandi*.



Treatment of 5-amino-7-chloro-*v*-triazolo[4,5-*d*]-pyrimidine with alkoxides in mixtures of the corresponding alcohol and dioxane gave 7-alkoxy-5-amino-*v*-triazolo[4,5-*d*]pyrimidines (IX–XV; *cf.* Table I). The 7-*p*-chlorophenoxy derivative (XVI) was prepared in dioxane solution. 5-Amino-7-benzyloxy - *v* - triazolo[4,5 - *d*]pyrimidine (XV) was also prepared without isolating IV by treating a diazotization reaction mixture with sodium benzyloxide. In addition to these replacements by alkoxy groups and the hydrolytic replacement of chlorine, facile reaction of IV with amines was demonstrated with the preparation of 5-amino-7-(dimethylamino)-*v*-triazolo[4,5-*d*]pyrimidine (VI).

When the isoamyl nitrite–dioxane method of diazotization was applied to 4,5-diamino-6-chloropyrimidine (III), evidence for the formation of 7-chloro-*v*-triazolo[4,5-*d*]pyrimidine (V) was obtained from the ultraviolet spectrum of the reaction solution; but initial attempts to prepare a pure specimen were unsuccessful. In order to confirm the presence of V in solution and to estimate the yield, a reaction solution was treated with piperidine. 7-Piperidino-*v*-triazolo[4,5-*d*]pyrimidine (VII) was isolated in 82% yield. Subsequently, an isolated specimen of V gave analytical results that approached the calculated values, although the analytical data were not entirely satisfactory. Since the formation of the 7-piperidino derivative showed that 7-chloro-*v*-triazolo[4,5-*d*]pyrimidine (V) could be prepared and used in solution for replacement reactions, no further effort was expended in preparing pure V. Treatment of dioxane solutions containing V with sodium or potassium alkoxides or aryloxides gave 7-alkoxy (or aryloxy)-*v*-triazolo-[4,5-*d*]pyrimidines (XVII–XX; *cf.* Table I).

Experimental[5]

2,4,5-Triamino-6-chloropyrimidine (II).—A suspension of 20.4 g. (72 mmoles) of 2,4-diamino-6-chloro-5-(*p*-chlorophenylazo)pyrimidine[6] in 510 ml. of ethanol, 510 ml. of water, and 51 ml. of glacial acetic acid was heated to 70° under an atmosphere of nitrogen. Sixty grams of zinc dust was introduced into the vigorously stirred mixture in small portions over a period of 1 hr. The mixture was stirred at 70° for an additional hour, and the unchanged zinc was then removed from the orange-red solution by filtration under nitrogen. The filtrate was cooled in an ice bath, the pH was raised to 10 with 10% sodium hydroxide solution (370 ml.), and the precipitated zinc hydroxide was removed by filtration under nitrogen through a layer of diatomaceous silica (Celite). After the dark red filtrate had been neutralized to pH 7 with glacial acetic acid, the solution was concentrated *in vacuo* (oil pump) at temperatures below 35° to approximately 300 ml. The mixture was diluted with 50 ml. of water to redissolve inorganic salts that separated from the cooled concentrated solution, made alkaline to pH 9 with 10% sodium hydroxide solution, and stored at 5°. The red-brown crystalline product was collected on a filter, washed with water, slurried with ether, and dried *in vacuo* at 35°; yield, 8.24 g. (72%); m.p., 226–227° (oil bath). This material was suitable for use in the diazotization reaction since the melting point and ultraviolet absorption data were in good agreement with those of pure material. Crude 2,4,5-triamino-6-chloropyrimidine (500 mg.) dissolved in 1 *N* hydrochloric acid (6 ml.) was treated with acid-washed, activated carbon. Addition of concentrated sulfuric acid to the filtrate precipitated a yellow crystalline sulfate; chilling a hydrochloric acid solution prepared in the same manner gave a yellow crystalline hydrochloride.

Anal. Calcd. for $C_4H_6N_5Cl\cdot HCl$: Cl, 36.17. Found: Cl, 35.86.

A white crystalline specimen of the free base was obtained by twice subliming crude material under reduced pressure at 180–185°; m.p. 226–227° (oil bath); λ_{max} in mμ ($\epsilon \times 10^{-3}$): 229 (13.3), 306 (5.6) at pH 1; 236 (sh), 305 (6.5) at pH 7; 236 (sh), 304 (6.2) at pH 13.

Anal. Calcd. for $C_4H_6ClN_5$: C, 30.20; H, 3.76; N, 43.90; Cl, 23.30. Found: C, 30.41; H, 3.81; N, 44.07; Cl, 23.10.

The pure white crystalline free base gradually became discolored during storage under ordinary laboratory conditions; however, the crude pyrimidine apparently remains unchanged after storage for several months at 5°.

Preparation of 5-Amino-7-chloro-*v*-triazolo[4,5-*d*]pyrimidine (IV). A. Isoamyl Nitrite in Dioxane.—A solution consisting of 44.1 g. (276 mmoles) of 2,4,5-triamino-6-chloropyrimidine, 37.1 ml. (276 mmoles) of freshly distilled iso-

(5) Ultraviolet spectra were determined in 0.1 *N* hydrochloric acid (pH 1), phosphate buffer (pH 7), and 0.1 *N* sodium hydroxide (pH 13) and were recorded with Beckman Model DK-2 (with optical densities at the maxima measured with a Beckman Model DU) or Cary Model 14 spectrophotometers. Infrared spectra were determined with samples in pressed potassium bromide disks and were recorded with Perkin–Elmer Model 21 or Perkin–Elmer Model 221 spectrophotometers. Unless otherwise noted, melting points were determined on a Kofler Heizbank melting point apparatus and are corrected

(6) G. M. Timmis, D. G. I. Felton, H. O. J. Collier, and P. L. Huskinson, *J. Pharm. Pharmacol.*, **9**, 46 (1957).

TABLE I

7-ALKOXY(OR ARYLOXY)-*v*-TRIAZOLO[4,5-*d*]PYRIMIDINES

Compound No.	Y	R	Yield, %	Recryst. solvent	M.p., °C.	Empirical formula		Calcd.	Found	λ_{max} in mμ (ε × 10^{-3}) pH 1	pH 7[b]	pH 13
IX	NH_2	CH_3[c]	65	A	>280	$C_5H_6N_6O$	C	36.14	35.95	238 (5.6)	240 (sh.)	
							H	3.64	3.96	283 (9.6)	288 (7.0)	289 (6.8)
							N	50.59	50.57			
X	NH_2	C_2H_5	77	A	214	$C_6H_8N_6O$	C	40.02	40.08	239 (6.4)	240 (sh.)	
							H	4.48	4.62	282 (10.1)	287 (7.7)	291 (7.0)
							N	46.68	46.93			
XI	NH_2	$(CH_3)_2CH$	60	A + B 1:9	190	$C_7H_{10}N_6O$	C	43.29	43.26	240 (6.8)	240 (sh.)	
							H	5.19	5.28	283 (10.0)	289 (7.4)	290 (7.0)
							N	43.28	43.15			
XII	NH_2	C_4H_9	76	A + B 4:1	182	$C_8H_{12}N_6O$	C	46.14	46.22	239 (6.5)	240 (sh.)	
							H	5.81	5.67	282 (9.8)	287 (7.4)	290 (7.2)
							N	40.36	40.21			
XIII	NH_2	C_8H_{17}	25	A + B	169	$C_{12}H_{20}N_6O$	C	54.52	54.36	240 (6.6)	240 (sh.)	
							H	7.63	7.46	283 (9.9)	288 (7.6)	290 (7.3)
							N	31.80	31.73			
XIV	NH_2	$C_{12}H_{25}$	42	A + B 1:1	166	$C_{16}H_{28}N_6O$	C	59.97	59.68			
							H	8.81	8.74			
							N	26.23	26.16			290 (7.0)[d]
XV	NH_2	$C_6H_5CH_2$	53	A + B 1:1	192–193	$C_{11}H_{10}N_6O$	C	54.54	54.73	240 (6.8)	240 (sh.)	
							H	4.16	4.35	283 (9.6)	290 (7.4)	289 (7.3)
							N	34.70	34.61			
XVI	NH_2	*p*-ClC_6H_4		A + C	263	$C_{10}H_7N_6ClO$	C	45.72	46.02	237 (sh.)		
							H	2.69	2.99	288 (11.4)	296 (8.4)	296 (8.3)
							N	32.00	31.96			
XVII	H	C_4H_9	46[e]	D + E	108	$C_8H_{11}N_5O$	C	49.73	49.61	251 (10.8)	259 (9.4)	259 (9.4)
							H	5.74	5.48			
							N	36.25	36.12			
XVIII	H	C_8H_{17}		D + E A + B	106	$C_{12}H_{19}N_5O$	C	57.81	57.74	251 (10.7)	259 (9.3)	259 (9.3)
							H	7.68	7.63			
							N	28.10	27.76			
XIX	H	$C_6H_5CH_2$	54[e]	D	150	$C_{11}H_9N_5O$	C	58.14	58.12	251 (10.7)	259 (9.9)	260 (10.0)
							H	4.00	3.91			
							N	30.82	31.15			
XX	H	*p*-$CH_3C_6H_4$	79[e]	D A + B	214 dec.	$C_{11}H_9N_5O$	C	58.14	57.83	252 (11.1)	263 (11.0)	263 (11.2)
							H	4.00	4.08			
							N	30.82	30.76			

[a] A = water, B = ethanol, C = dimethylformamide, D = benzene, E = petroleum ether. [b] A weak, but distinct, shoulder or plateau consistently occurs on the side of the end absorption in the spectra of 5-amino-7-alkoxy-*v*-triazolo[4,5-*d*]pyrimidines at pH 7; slight, weaker plateaus may be recognizable near 240 and 260 mμ at pH 13. [c] Ref. 3a. [d] Sparingly soluble at pH 1 and 7; λ_{max} in mμ (ε × 10^{-3}) in ethanol: 241 (6.3), 283 (10.2). [e] Based on 4,5-diamino-6-chloropyrimidine.

amyl nitrite, and 2 l. of dry purified dioxane was heated with stirring for 2 hr. at 90°. The reaction mixture was cooled, treated with activated carbon, and filtered. The red filtrate, after concentration to about 500 ml. under reduced pressure at temperatures below 50°, was diluted with 1 l. of petroleum ether (b.p. 30–60°). The buff-colored crystalline precipitate was removed by filtration, washed with petroleum ether, and dried *in vacuo* at 50°; yield, 46.5 g. (78% calculated as a one-half dioxanate). The material darkened on heating and did not melt below 300° (oil bath). Paper chromatography[7] indicated the absence of 8-azaguanine and starting material. Elemental analyses of specimens from several different experiments indicated that the product was solvated to the extent of one-fourth to one-half molecule of dioxane per molecule of IV. A specimen dried *in vacuo* at 110° for 3 hr. had the composition of a one-fourth dioxanate, although some darkening occurred during the drying; λ_{max} in mμ: 240 (sh), 312 at pH 1; 272, 320 at pH 7; 272, 320 at pH 13.

Anal. Calcd. for $C_6H_3N_6Cl \cdot {}^1/_4C_4H_8O_2$: C, 31.18; H, 2.62; N, 43.64; Cl, 18.41. Found: C, 31.07; H, 2.91; N, 43.56; Cl, 18.68.

Purification, if necessary, could be effected by treating crude material with warm dioxane (*ca.* 1 g./50 ml.), removing insoluble material by filtration, treating the solution with activated carbon, and reprecipitating IV (as a dioxanate) with hexane or petroleum ether. The cream-colored needles were shown by routine paper chromatography to be essentially free of 8-azaguanine and starting material, and more detailed paper chromatographic analyses based on the preparation of synthetic mixtures of 8-azaguanine and a reprecipitated specimen of IV showed that the amount of 8-azaguanine, if any, in the reprecipitated material was less than 1%. Elemental analyses again were in accord with a one-fourth to one-half dioxanate, and solvation with dioxane was confirmed by identifying the dioxane by vapor phase chromatography. Specimens of IV not used immediately were routinely stored over a drying agent at 5°.

B. Aqueous Media.—Ultraviolet spectra and paper chromatograms of products obtained from initial diazotizations of 2,4,5-triamino-6-chloropyrimidine, or its hydrochloride, in aqueous media suggested that both IV and 8-azaguanine were formed. However, essentially pure IV was obtained by leaching the crude product (57% yield) of one of these diazotizations with warm ethyl acetate, removing insoluble impurities by filtration, and evaporating the solvent in a nitrogen current. The white residue [λ_{max} in mμ ($\epsilon \times 10^{-3}$): 240 (sh), 313 (6.6) at pH 1; 272 (4.0), 320 (5.2) at pH 7; 273 (4.1), 319 (5.0) at pH 13] gave good yields in replacement reactions with alkoxides. In addition, evidence was obtained that IV was converted partly—sometimes completely—to 8-azaguanine or to 5-amino-7-ethoxy-*v*-triazolo [4,5-*d*]pyrimidine (X) when crude specimens were warmed in aqueous or ethanolic media in order to obtain homogeneous solutions for the chromatographic and ultraviolet determinations. Subsequently, solutions of crude IV for these determinations were prepared at room temperature.[8] In order to clarify the course of the aqueous diazotization the following experiment was performed.

A solution of 300 mg. (4.35 mmoles) of sodium nitrite in 5 ml. of water was added during a 15-min. period to a cold (0°) solution of 638 mg. (4.0 mmoles) of twice-sublimed 2,4,5-triamino-6-chloropyrimidine in 60 ml. of water and 12 ml. of acetic acid. A solid began to form 10 min. after the nitrite had been added. The mixture was stirred at 0–5° for 1 hr. following the addition of sodium nitrite; and the light orange precipitate was collected by filtration, washed with water, and dried *in vacuo* over phosphorus pentoxide at room temperature; yield, 412 mg. (60%). This material was soluble in ethanol. Paper chromatograms and ultraviolet spectra gave no evidence of contamination with 8-azaguanine and showed that this material was identical with IV obtained from the isoamyl nitrite–dioxane method.

White crystals began to form in the filtrate soon after the first crop had been removed. The filtrate was stored at −5° overnight, and the precipitate was collected by filtration, washed with water, and dried *in vacuo* over phosphorus pentoxide at room temperature; wt., 150 mg. This material, which was insoluble in ethanol and soluble in cold dimethylformamide, was shown to be identical with 8-azaguanine by paper chromatography and ultraviolet and infrared[9] spectral determinations.

8-Azaguanine from 5-Amino-7-chloro-*v*-triazolo[4,5-*d*]pyrimidine.—A homogeneous solution prepared by adding 2.9 ml. of 1 *N* sodium hydroxide to a suspension of 100 mg. of 5-amino-7-chloro-*v*-triazolo[4,5-*d*]pyrimidine dioxanate in 12 ml. of water was heated at the reflux temperature for 25 min. The reaction mixture was filtered, reheated to boiling, and acidified with acetic acid to pH 4. The white crystalline precipitate was collected by filtration, washed with water, and dried *in vacuo* over phosphorus pentoxide at 100°; wt., 68 mg. (96% yield based on a one-half dioxanate of IV); λ_{max} in mμ ($\epsilon \times 10^{-3}$): 250 (7.9), 265 (sh) at pH 1; 247 (6.4), 276 (5.8) at pH 7; 244 (5.8), 280 (7.7) at pH 13. The ultraviolet and infrared spectra[9] and paper chromatograms of this material showed that it was 8-azaguanine.

5-Amino-7-(dimethylamino)-*v*-triazolo[4,5-*d*]pyrimidine (VI).—A solution of 300 mg. of 5-amino-7-chloro-*v*-triazolo-[4,5-*d*]pyrimidine in 10 ml. of 25% aqueous dimethylamine was heated slowly (1.25 hr.) to the refluxing temperature (68°), maintained under reflux for 2 hr., and evaporated to dryness under reduced pressure. A suspension of the white residue in 25 ml. of water was acidified with acetic acid to pH 4–5, stirred for 15 min., and filtered. The white solid, which amounted to 265 mg. after it had been washed with water and dried *in vacuo* at 100° over phosphorus pentoxide, was recrystallized twice from dimethylformamide–water, m.p., 321–322° dec. (inserted in Al block at 305°); λ_{max} in mμ ($\epsilon \times 10^{-3}$): 269 (17.0) at pH 1; 259 (13.2), 284 (13.5) at pH 7; 254 (7.2), 295 (11.5) at pH 13.

Anal. Calcd. for $C_8H_9N_7$: C, 40.21; H, 5.06; N, 54.72. Found: C, 40.26; H, 5.21; N, 54.49.

7-Alkoxy (or aryloxy)-*v*-triazolo[4,5-*d*]pyrimidines (IX–XX).—Properties of these compounds are summarized in Table I; procedures for their preparation are illustrated below.

5-Amino-7-isopropoxy-*v*-triazolo[4,5-*d*]pyrimidine (XI).—To a solution of sodium isopropoxide prepared from 100 mg. (4.3 mg.-atoms) of sodium and 20 ml. of isopropyl alcohol was added 171 mg. (1 mmole) of 5-amino-7-chloro-*v*-triazolo-[4,5-*d*]pyrimidine (IV). The reaction mixture, protected from atmospheric moisture with a tube of calcium chloride, was heated at the reflux temperature for 1 hr. and 10 min., cooled, and filtered to remove sodium chloride. The filtrate was acidified to pH 5, filtered to remove additional sodium chloride, and evaporated to dryness *in vacuo*. The white residual solid was dissolved in a mixture of hot

(7) Paper chromatography was performed by the descending technique on Whatman no. 1 paper in the following solvent systems: (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) phosphate buffer (pH 7) or acetate buffer (pH 6.1). Chromatograms were examined under two ultraviolet lamps that emit light principally at 365 mμ and at 254 mμ.

(8) Pure specimens of IV are soluble in cold ethanol, and ethanolic solutions can be used to apply the material to chromatographic paper or to make appropriate dilutions for ultraviolet spectral determinations. Crude samples of IV containing insoluble impurities could be brought into solution for these purposes by dissolving a specimen, without heating, in a small amount of dimethylformamide. The latter solvent was also used in applying 8-azaguanine as a reference compound in the paper chromatographic determinations. The isopropyl alcohol–ammonia solvent system gives the best separation of IV and 8-azaguanine.

(9) There is some variation in the solid state (KBr) spectra of different specimens of 8-azaguanine.

water (11 ml.) and hot ethanol (4 ml.). The white needles that separated from the cold solution were removed by filtration, washed with water (2 ml.), and dried *in vacuo* over phosphorus pentoxide at 100°; wt., 116 mg.; m.p., 190° with sublimation (unchanged after recrystallization).

5-Amino-7-methoxy-*v*-triazolo[4,5-*d*]pyrimidine[9a] (IX) and 5-amino-7-butoxy-*v*-triazolo[4,5-*d*]pyrimidine (XII) were prepared by procedures similar to that used for XI.

5-Amino-7-dodecanoxy-*v*-triazolo[4,5-*d*]pyrimidine (XIV).—To a solution prepared by heating a mixture of 312 mg. of potassium and 15 ml. of anhydrous 2-dodecanol was added 342 mg. of 5-amino-7-chloro-*v*-triazolo[4,5-*d*]pyrimidine dioxanate. The resulting orange suspension, protected from atmospheric moisture with a drying tube of calcium chloride, was heated at 60° for 4 hr. The reaction mixture was cooled to room temperature, and the resulting gelatinous mass was diluted with 30 ml. of benzene and centrifuged. The supernatant solution was decanted, the sediment was resuspended in 20 ml. of benzene, and the resulting mixture was centrifuged. The pasty sediment was then suspended in 20 ml. of water, the mixture was filtered, and the filtrate was acidified to pH 5–6 with acetic acid. The curdy precipitate was removed by filtration, washed with 20 ml. of 50% ethanol, and dried *in vacuo* over phosphorus pentoxide at 55°; wt., 509 mg. Two recrystallizations of the crude product from 50% ethanol gave white needles.

5-Amino-7-octyloxy-*v*-triazolo[4,5-*d*]pyrimidine (XIII) and 5-amino-7-benzyloxy-*v*-triazolo[4,5-*d*]pyrimidine (XV) were prepared by procedures similar to that used for XIV except for (1) the use of sodium benzyloxide to prepare XV and (2) the removal of the metal salts of XIII and XV from reaction mixtures by filtration rather than centrifugation. In addition, the 5-amino-7-benzyloxy derivative (XV) was prepared without isolating 5-amino-7-chloro-*v*-triazolo[4,5-*d*]pyrimidine (IV). A reaction mixture prepared by heating a solution of 500 mg. (3.14 mmoles) of 2,4,5-triamino-6-chloropyrimidine (II), 25 ml. of anhydrous dioxane, and 368 mg. of isoamyl nitrite at 90–95° for 2 hr. was added to a solution of 227 mg. of sodium in 7 ml. of anhydrous benzyl alcohol. The resulting reaction mixture was maintained at 60° for 4.5 hr., refrigerated, and filtered to remove a precipitate, which was washed with dioxane and dissolved in 50 ml. of water. Acidification of the filtered aqueous solution to pH 5.5 precipitated XV (423 mg.) in 56% yield from II.

5-Amino-7-ethoxy-*v*-triazolo[4,5-*d*]pyrimidine (X).—A reaction mixture prepared by adding 6.9 ml. of 1 *N* sodium hydroxide to 200 mg. of 5-amino-7-chloro-*v*-triazolo[4,5-*d*]-pyrimidine in 25 ml. of ethanol was heated at the reflux temperature for 2 hr., cooled, and acidified to pH 5 with 1 *N* hydrochloric acid. Concentration of the mixture gave white needles, isolated in two crops, that proved to be X rather than 8-azaguanine.

5-Amino-7-(*p*-chlorophenoxy)-*v*-triazolo[4,5-*d*]pyrimidine (XVI).—A mixture consisting of 156 mg. (4 mg.-atoms) of potassium, 565 mg. (4.4 mmoles) of *p*-chlorophenol, and 20 ml. of dry purified dioxane was heated at the reflux temperature for 1.5 hr. to dissolve the potassium. To this mixture, which contained an amorphous solid in suspension, was added 171 mg. (1 mmole) of IV. The resulting reaction mixture was heated at the reflux temperature for 1.5 hr., concentrated to a low volume under reduced pressure, and diluted with water. Acidification of the aqueous solution, after it had been treated with activated carbon, precipitated 117 mg. of crude product. A second crop (57 mg.), obtained by concentrating the filtrate, raised the yield of crude XVI (m.p., 253–255° dec.) to 66%.

7-Chloro-*v*-triazolo[4,5-*d*]pyrimidine (V) and 7-Piperidino-*v*-triazolo[4,5-*d*]pyrimidine (VII).—A mixture consisting of 289 mg. (2.0 mmoles) of 4,5-diamino-6-chloropyrimidine,[10] 257 mg. (2.2 mmoles) of freshly distilled isoamyl nitrite, and 15 ml. of purified anhydrous dioxane was heated at 90° for 1.5 hr. The reaction mixture was protected from atmospheric moisture with a tube of drying agent. To the cooled solution, which was now homogeneous and presumably contained V, was added 376 mg. (4.4 mmoles) of redistilled piperidine. The resulting mixture was heated at 90° for 45 min. and allowed to stand at room temperature overnight. The white precipitate of 7-piperidino-*v*-triazolo-[4,5-*d*]pyrimidine was collected by filtration, washed three times with 6-ml. portions of water, and dried *in vacuo* over phosphorus pentoxide at 56°; yield, 337 mg. (82%); m.p., 280–281° dec. (oil bath). This material was recrystallized from ethanol; there was no change in the melting point or the ultraviolet extinction coefficients; λ_{max} in mμ ($\epsilon \times 10^{-3}$): 285 (sh), 295 (13.6), 317 (sh) at pH 1; 296 (18.5), 303 (sh) at pH 7; 296 (18.8), 303 (sh) at pH 13.

Anal. Calcd. for $C_9H_{12}N_6$: C, 52.92; H, 5.92; N, 41.15. Found: C, 52.76; H, 5.78; N, 41.13.

Several attempts were made to isolate a pure specimen of 7-chloro-*v*-triazolo[4,5-*d*]pyrimidine. The specimen giving the best analytical data was obtained in the following way. A solution of the 7-chloro derivative identical with that used in the preparation of the 7-piperidino derivative (VII) was diluted with 20 ml. of hexane and cooled to −5°. A yellow powder was collected by filtration, washed with hexane, and dried *in vacuo* at 78°; wt., 98 mg. This material in a capillary tube would explode when placed suddenly in an oil bath at temperatures above 265°.

Anal. Calcd. for $C_4H_2N_5Cl$: C, 30.88; H, 1.29; N, 45.05. Found: C, 31.85; H, 1.82; N, 44.92.

Material isolated in this way could be reprecipitated from dioxane by adding a hydrocarbon solvent. After a first crop of powder had been removed, the filtrate would yield crystals, but the analytical results were not improved.

Diazotization of 4,5-diamino-6-chloropyrimidine with sodium nitrite in acidic aqueous solutions was not thoroughly investigated, but a few experiments indicated that the results may be erratic and complex. A product of one experiment in aqueous acetic acid was explosive, contained chlorine, and gave ultraviolet absorption data (λ_{max} in mμ: 262 at pH 1, 268 at pH 7 and pH 13) indicating that it was crude V.

7-Butoxy-*v*-triazolo[4,5-*d*]pyrimidine (XVII).—A solution of 7-chloro-*v*-triazolo[4,5 *d*]pyrimidine was prepared by heating a mixture of 6.5 g. (45 mmoles) of 4,5-diamino-6-chloropyrimidine, 6.0 ml. (45 mmoles) of freshly distilled isoamyl nitrite, and 187 ml. of purified dry dioxane at 90° for 1.5 hr. To this solution, cooled to 60°, was added a solution of sodium butoxide prepared from 4.14 g. of sodium and 300 ml. of anhydrous butanol. The reaction mixture was heated at 60° for 1 hr. The reactant solutions and the final reaction mixture were maintained under an atmosphere of nitrogen and were protected from moisture with tubes of drying agent throughout the foregoing operations. A yellow precipitate was removed by filtration after the reaction mixture had been chilled overnight, and the filtrate was concentrated to a volume of about 250 ml., diluted with 250 ml. of benzene, and extracted twice with 250-ml. portions of water. The aqueous extract was washed twice with 100-ml. portions of benzene, concentrated to 400 ml., cooled, and acidified to pH 5. A precipitate of white crystals, which were chromatographically homogeneous and which had the same ultraviolet extinction coefficients as the analytical sample, formed; wt., 4.0 g.; m.p., 108°.

7-Benzyloxy-*v*-triazolo[4,5-*d*]pyrimidine (XIX) and 7-octyloxy-*v*-triazolo[4,5-*d*]pyrimidine (XVIII) were prepared by procedures similar to that described for XVII except that potassium was employed to form the alkoxide solution used in the preparation of XVIII.

7-(*p*-Tolyloxy)-*v*-triazolo[4,5-*d*]pyrimidine (XX).—The aryloxide was prepared by adding 1.3 g. (12 mmoles) of redistilled *p*-cresol to a solution prepared from 276 mg. (12

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mg.-atoms) of sodium and 10 ml. of anhydrous methanol. This mixture was evaporated to dryness *in vacuo* at 40°. A solution of the residual white solid in 10 ml. of pure dioxane was added to a solution of 7-chloro-*v*-triazolo[4,5-*d*]pyrimidine prepared by the procedure described above (*cf.* XVII) from 434 mg. (3 mmoles) of 4,5-diamino-6-chloropyrimidine, 350 mg. of freshly distilled isoamyl nitrite, and 20 ml. of purified dry dioxane. Reaction conditions were identical with those used to prepare XVII. The cooled reaction mixture was diluted with 100 ml. of water, and the aqueous solution was extracted with three 100-ml. portions of ether. Acidification of the aqueous layer to pH 5 precipitated a white crystalline solid that was separated by filtration, washed with water, and dried *in vacuo* at 56°; wt., 536 mg.; m.p., 214° dec.

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Stereospecificity of the Addition of Bromine to *cis*- and *trans*-Stilbene[1]

ROBERT E. BUCKLES, JANE M. BADER, AND ROLAND J. THURMAIER

Department of Chemistry, University of Iowa, Iowa City, Iowa

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The reaction of bromine with *cis*- or *trans*-stilbene in relatively nonpolar solvents (dielectric constant 2–3) was found to involve 90–100% stereospecific, *trans* addition. As solvents of higher and higher dielectric constant were used the addition became progressively less stereospecific giving more and more *meso*-α,α'-dibromobibenzyl from *cis*-stilbene in place of the *dl* isomer. With solvents of dielectric constant around 35 or higher, the reaction was essentially nonstereospecific with both stilbenes giving 80–100% *meso*-dibromide. With a bromide (or tribromide) salt present much of the stereospecificity was restored in these relatively polar solvents; that is, *cis*-stilbene gave more *dl*-dibromide.

Almost since its first synthesis[2] the addition of bromine to *cis*-stilbene under the usual mild conditions favoring the polar mechanism rather than the free radical mechanism[3] has been found to be essentially stereospecific and *trans*. Although the original report[2] on *cis*-stilbene gave the product of bromine addition in ether solution in sunlight as *meso*-α,α'-dibromobibenzyl, the reaction was reported[4] a few years later to give an 83% yield of *dl*-α,α'-dibromobibenzyl in cold carbon disulfide in the dark. Since these original reports, varying amounts of *dl*- and *meso*-dibromides have been reported as products of the reaction, but always with the *dl*-isomer predominating for the polar mechanism.[5] Free radical addition, on the other hand has led[5b] to *meso*-dibromide as the major product just as has the isomerization[5c] of the *dl*-dibromide or the bromination of bibenzyl.[6] With *trans*-stilbene all additions of bromine have been reported[5b,c,6a,7] to give the *meso*-dibromide as the major product, but in some experiments[7ac,] isolable yields of the order of 10% have been reported for the *dl*-isomer. With pyridinium tribromide [pyridinium dibromobromate (I)] as a brominating agent in acetic acid more clean-cut, stereospecific additions have been reported[8]; that is, there was neither isolable *dl*-dibromide from *trans*-stilbene nor *meso*-dibromide from pure *cis*-stilbene. Such results appear to be analogous to the stereospecific additions of chlorine to *cis*- and *trans*-stilbene with tetrabutylammonium iodotetrachloride [tetrabutylammonium tetrachloroiodate (III)] as a source of chlorine.[9]

The present investigation is concerned with the stereospecificity of the addition of bromine to *cis*- and *trans*-stilbenes under conditions favorable to the polar mechanism. Additions were carried out in various solvents either with or without a bromide salt present. The water-insoluble, solid product mixtures were isolated with no attempt being made to separate solid impurities such as *trans*-stilbene or other addition products from the dibromides. The amounts of *meso*- and *dl*-dibromides in a mixture were estimated by two methods: infrared analysis of the dibromide mixture and debromination by sodium iodide followed by spectrometric analysis of the stilbene mixture. In each case the analysis was, at best, a semiquantitative estimate of the composition of the dibromide mixture.

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