P. K. Bridson*, R. A. Davis and L. S. Renner

Department of Chemistry, Memphis State University,
Memphis, TN 38152

Received October 18, 1984

The reaction of 5-aminoimidazole-4-carbohydrazides with orthoesters is shown to yield 1-amino-9-alkylhypoxanthines. Similar reaction of anthranilic acid hydrazide is shown to yield 3-amino-4-quinazolone, and not 1,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one as previously reported.

J. Heterocyclic Chem., **22**, 753 (1985).

The reaction of anthranilic acid hydrazides with orthoesters has been shown to give 1,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones. Thus, reaction of the methylhydrazide, Ia, with triethyl orthoformate gave IIa in 89% yield [1]. The triazepine IIb was claimed as the product from the analagous reaction of the unsubstituted hydrazide, Ib, under similar conditions [2]. As part of an ongoing study in the synthesis of novel purine analogs, we have studied the related reaction of 5-aminoimidazole-4-carbohydrazides, IV, with orthoesters.

5-Aminoimidazole-4-carbohydrazides, IVa-d, were prepared by treating the corresponding ethyl esters, III [3], with hydrazine at reflux in 95% ethanol. Yields and analytical data are given in Table 1. The nmr spectra of the hydrazides show three exchangeable resonances, at 4.2 (2H), 5.7-5.8 (2H), and 8.4-8.7 (1H). The lowest field resonance can be assigned to the single amide proton of the hydrazide group. The resonance at 5.7 is also observed in the corresponding esters and amides, and is therefore assigned to the 5-amino group. The remaining resonance at 4.2 is thus assigned to the $-NH_2$ group of the hydrazide function.

The reaction of 5-amino-1-benzylimidazole-4-carbohydrazide, IVa, with a 20% excess of triethyl orthoformate in the presence of trifluoroacetic acid gives a single product as shown by tlc analysis in two solvent systems. This product is isolated as a crystalline solid in good yield. The nmr spectrum of this compound has a single exchangeable resonance, a broad singlet at 5.8, assigned to two protons attached to nitrogen. Panse and Kamat [2] assign the analagous resonance in their product to the two separate -NH groups in IIb. It seemed more reasonable to us, however, to assign the resonance to a single $-NH_2$ group. By the following methods, we have shown that our product is the 1-aminopurine Va, and not an imidazotriazepine.

Reaction of Va with sodium nitrite and acetic acid results in the formation of 9-benzylhypoxanthine, VI, identical with an authentic sample prepared from 5-amino-1-benzylimidazole-4-carboxamide by the method of Yamazaki [4]. The ultraviolet absorption spectra of Va and VI show identical maxima under neutral conditions. Under basic conditions, the spectrum of VI, but not Va, is shifted to longer wavelength. This shift is typical of unsubstituted hypoxanthine derivatives, but is not observed when N-1 is substituted, giving further evidence for the structure assigned to Va. Finally, direct amination of VI by an established method [5] gave Va, identical to material prepared from the hydrazide.

This result led us to reexamine the result reported by Panse and Kamat [2]. The data reported by these authors does not distinguish between the benzotriazepine, IIb, and 3-amino-4-quinazolone, VII, the product analogous to the 1-aminopurines formed in our reactions. We have repeated their reaction of anthranilic acid hydrazide with ethyl formate and isolated a product identical to that re-

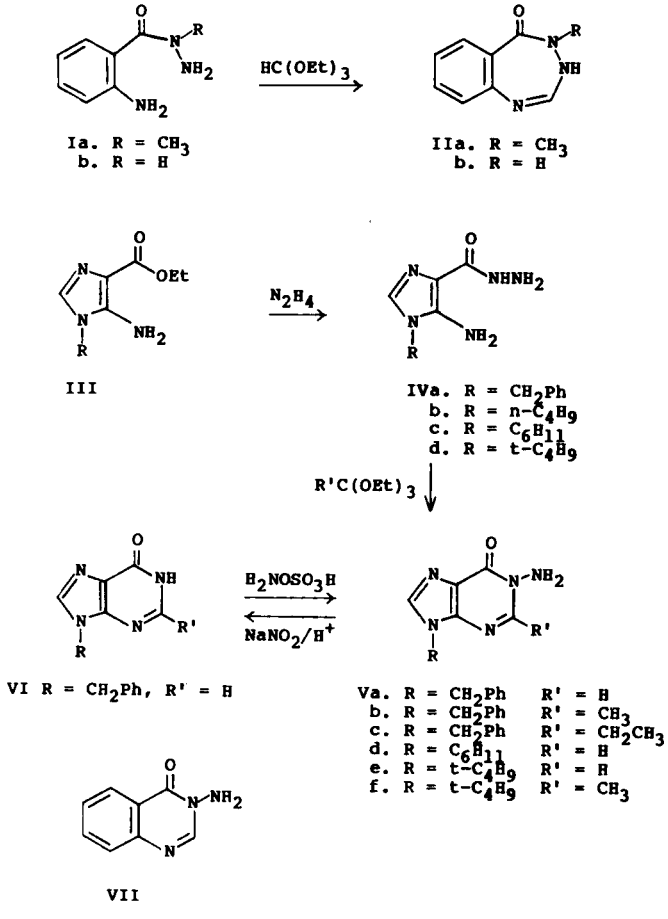

Table 1

5-Amino-1-alkylimidazole-4-carbohydrazides IV

Compound (R)	M.P. (°C)	Yield (%)	Found / (Calcd.) C	H	N	NMR (DMSO)
IVa (benzyl)	200-201	84	57.32 (57.14)	5.64 (5.63)	30.11 (30.30)	4.2 (s, 2H), 5.2 (s, 2H), 5.8 (s, 2H), 7.2 (s, 2H), 7.3 (s, 5H), 8.5 (br s, 1H)
IVb (*n*-butyl)	132-133	71	48.84 (48.73)	7.84 (7.61)	35.56 (35.53)	0.7-1.8 (br s, 7H), 3.9 (t, 2H), 4.2 (s, 2H), 5.7 (s, 2H), 7.1 (s, 1H), 8.4 (s, 1H)
IVc (cyclohexyl)	194-196	79	53.72 (53.81)	7.82 (7.62)	31.21 (31.39)	1.0-2.2 (br s, 10H), 3.9 (br s, 1H), 4.2 (s, 2H), 5.8 (s, 2H), 7.2 (s, 1H), 8.5 (s, 1H)
IVd (*t*-butyl)	201-203	76	48.87 (48.73)	7.80 (7.61)	35.56 (35.53)	1.5 (s, 9H), 4.2 (s, 2H), 5.7 (s, 2H), 7.2 (s, 1H), 8.7 (br s, 1H)

Table 2

1-Amino-9-alkylhypoxanthines V

Compound (R)	MP (°C)	Yield (%)	Found / (Calcd.) C	H	N	NMR (DMSO)
Va (benzyl)	217-218	75	59.61 (59.75)	4.73 (4.56)	28.91 (29.05)	5.3 (s, 2H), 5.8 (s, 2H), 7.3 (s, 5H), 8.2 (s, 1H), 8.4 (s, 1H)
Vb (benzyl)	207-208	48	61.23 (61.18)	5.18 (5.10)	27.35 (27.45)	2.6 (s, 3H), 5.3 (s, 2H), 5.7 (s, 2H), 7.3 (s, 5H), 8.1 (s, 1H)
Vc (benzyl)	175	32	62.50 (62.45)	5.70 (5.58)	25.99 (26.02)	1.1 (t, 3H), 2.9 (q, 2H), 5.3 (s, 2H), 5.7 (s, 2H), 7.3 (s, 5H), 8.1 (s, 1H)
Vd (cyclohexyl)	154-155	57	56.79 (56.65)	6.49 (6.44)	30.01 (30.04)	1.2-2.2 (br, 10H), 4.3 (m, 1H), 5.8 (s, 2H), 8.1 (s, 1H), 8.3 (s, 1H)
Ve (*t*-butyl)	173-175	69	52.20 (52.17)	6.35 (6.28)	33.73 (33.82)	1.7 (s, 9H), 5.8 (s, 2H), 8.0 (s, 1H), 8.3 (s, 1H)
Vf (*t*-butyl)	219-220	54	54.41 (54.30)	6.90 (6.79)	31.58 (31.67)	1.7 (s, 9H), 2.6 (s, 3H), 5.7 (s, 2H), 8.0 (s, 1H)

ported. This compound reacts with sodium nitrite in acetic acid to give 4-quinazolone, identical to an authentic sample prepared from anthranilamide. Amination of 4-quinazolone with hydroxylamine-*O*-sulfonic acid gives a product identical to that formed from the hydrazide. Thus the compound synthesized by Panse and Kamat is not the benzotriazepine reported, but rather 3-amino-4-quinazolone. Ring-closure of unsubstituted anthranilic acid hydrazides with other reagents has also been shown to yield aminoquinazolones rather than benzotriazepines [6].

We have found this method to be of general use for the synthesis of 1-amino-9-alkylhypoxanthines. Products and analytical data are given in Table 2.

EXPERIMENTAL

Melting points were determined on a Laboratory Devices Mel-Temp capillary apparatus and are uncorrected. Ultraviolet absorption spectra were obtained on a Varian Techtron 635 spectrophotometer. Nuclear magnetic resonance spectra were recorded in DMSO-d_6 on a Varian T-60 spectrometer, using TMS as an internal standard. Thin-layer chromatography was performed on pre-coated silica gel plates using ethanol:ethyl acetate (1:19), or methanol:chloroform (1:9) as eluant.

5-Amino-1-alkylimidazole-4-carbohydrazides IV.

Ethyl 5-amino-1-alkylimidazole-4-carboxylate (10 mmole) was heated at reflux in a mixture of 95% ethanol (10 ml) and 85% hydrazine hydrate (3 ml). After 1 week, more hydrazine hydrate (2 ml) was added. When tlc analysis indicated that reaction was complete (12-15 days), the mixture was cooled, and the crystalline product collected by filtration. Concentration of the filtrate gave a second crop of product. Analytical samples were obtained by recrystallization from aqueous ethanol. Yields and analytical data are given in Table 1.

1-Amino-9-alkylhypoxanthines V.

5-Amino-1-alkylimidazole-4-carbohydrazide (IV, 3 mmoles), triethyl orthoester (3.5 mmoles) and trifluoroacetic acid (3.25 mmoles) were heated at 85° for 2 hours with the exclusion of moisture. After cooling, the gum was dissolved in chloroform and washed with 2*M* sodium hydroxide. The organic extract was dried over magnesium sulfate and concentrated *in vacuo*, and the product was crystallized from aqueous ethanol. Yields and analytical data are given in Table 2.

9-Benzylhypoxanthine (VI). Method A.

5-Amino-1-benzylimidazole-4-carboxamide (VIII, 100 mg, 0.5 mmole), ethanolic sodium ethoxide (2*M*, 1.5 ml) and ethyl formate (0.5 ml) were heated under reflux for 6 hours. After cooling, the mixture was neutralized with aqueous acetic acid. The white precipitate was filtered, washed with water and dried to give 100 mg of VI (95%), mp 297-298°; nmr (DMSO-d_6): 5.4 (s, 2H), 7.3 (s, 5H), 7.9 (s, 1H), 8.1 (s, 1H); uv: max 248 nm (*p*H 7), 255 nm (*p*H 11).

Method B.

1-Amino-9-benzylhypoxanthine (Va, 250 mg, 1 mmole) was suspended in glacial acetic acid (3 ml) and sodium nitrite (70 mg, 1 mmole) in water (1 ml) was added. After standing at room temperature overnight, the crystalline solid was filtered, washed with water, and dried *in vacuo* to

give 160 mg (68%) 9-benzylhypoxanthine, identical to material prepared by method A.

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.72; H, 4.43; N, 24.78. Found: C, 63.65; H, 4.48; N, 24.61.

4-Quinazolone.

Anthranilamide (2 g, 5 mmoles), ethyl formate (6.5 m*l*) and ethanolic sodium ethoxide (2*M*, 50 m*l*) were heated under reflux for 3 hours. After cooling, the solution was neutralized with acetic acid and evaporated to dryness. The product was crystallized from water, giving 1.3 g (60%), mp 218-219°.

3-Amino-4-quinazolone.

4-Quinazolone (0.73 g, 5 mmoles) was suspended in aqueous sodium hydroxide (1*M*, 15 m*l*) and hydroxylamine-*O*-sulfonic acid (0.85 g, 7.5 mmoles) in water (10 m*l*) was added. The solution was kept at room temperature for 5 hours, then made strongly alkaline by addition of 6*M* sodium hydroxide. The product was extracted into chloroform. The organic extracts were dried over magnesium sulfate and concentrated, and the product was crystallized from aqueous ethanol yielding 0.18 g (22%), mp 211°; nmr: 5.8 (s, 2H), 7.6 (m, 3H), 8.2 (d, 1H), 8.4 (s, 1H).

REFERENCES AND NOTES

[1] R. W. Leiby and N. D. Heindel, *J. Org. Chem.*, **41**, 2736 (1976).

[2] G. T. Panse and S. K. Kamat, *Indian J. Chem.*, **13**, 834 (1975).

[3] N. J. Cusack, B. J. Hildick, D. H. Robinson, P. W. Rugg and G. Shaw, *J. Chem. Soc., Perkin Trans. I*, 1720 (1973).

[4] A. Yamazaki, I. Kumashiro and T. Takenishi, *J. Org. Chem.*, **32**, 3258 (1967).

[5] A. D. Broom and R. K. Robins, *J. Org. Chem.*, **34**, 1025 (1969).

[6] N. P. Peet and S. Sunder, *J. Org. Chem.*, **40**, 1909 (1975).