

## Synthesis and Antiinflammatory Activity of Some 1-Alkyl-4-phenylpyrido[2,3-*d*]pyrimidin-2(1*H*)-ones

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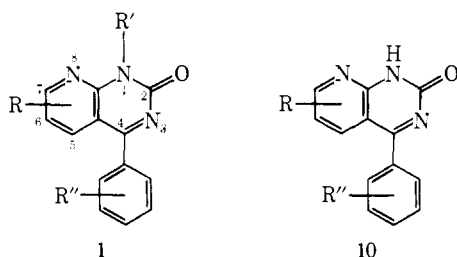
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Two approaches for the synthesis of 1-substituted 4-phenylpyrido[2,3-*d*]pyrimidin-2(1*H*)-ones are described. One pathway utilizes 2-amino-3-benzoylpyridine as a starting material while the second proceeds *via* 2-alkylaminonicotinitriles. The antiinflammatory activity of these compounds is discussed.

We recently<sup>1</sup> described the synthesis and the pharmacological evaluation of 1-alkyl-4-phenylquinazolin-2(1*H*)-ones, a new class of nonsteroidal antiinflammatory agents. In continuation of our investigations we decided to prepare the 8-aza analogs 1 of these compounds and to test these in the standard antiinflammatory screens.



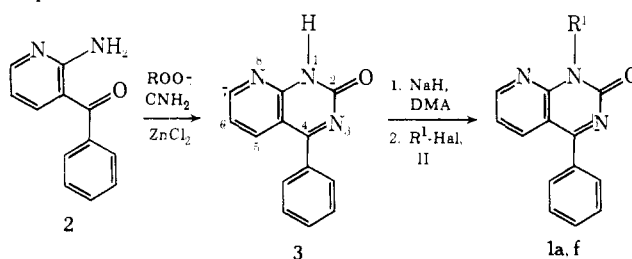
Two synthetic pathways were developed and they are shown in Scheme I. As we have discussed previously<sup>1</sup> the N-alkylation of compounds of type 10 with secondary and tertiary halides proceeds only sluggishly (yielding a mixture of O and N-1 alkylated products) or not at all. (In the system 3 alkylation could additionally occur on N-8 rather than on N-1.) The yields of reaction II (in Scheme I) are indeed low even with primary alkyl halides.

The question of whether the alkylation occurred on N-1 or elsewhere in the molecule could, however, be answered by unambiguous synthesis of 1a by sequence B. The reaction product was identical with the only product isolated on reaction of 3 with NaH followed by MeI. For the preparation of most final products, sequence B was chosen for which starting materials were readily available.<sup>2</sup>

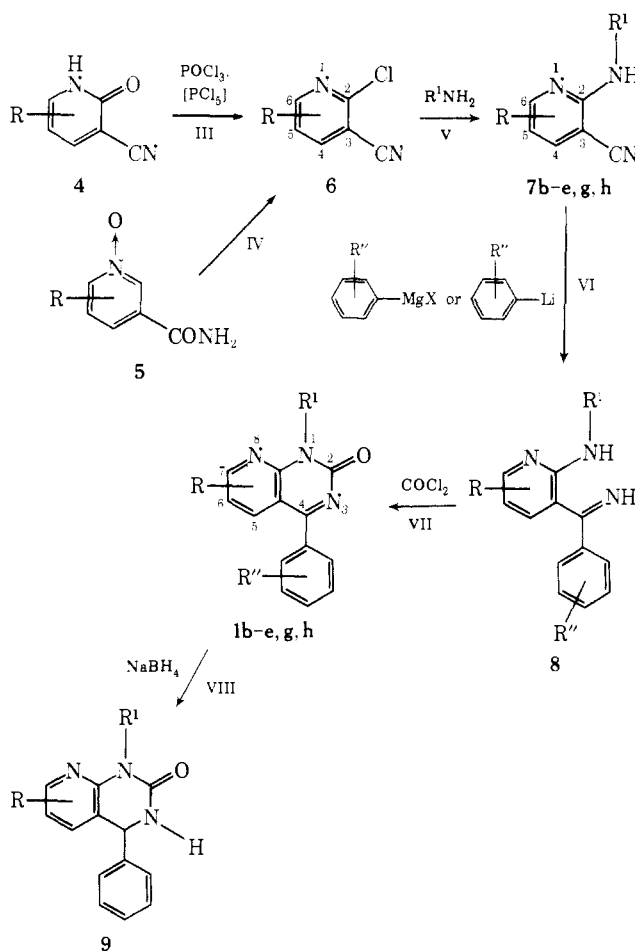
Although most of the reactions were uneventful, the following facts may be noteworthy. The conversion of 4g to 6g<sup>3</sup> had to be carried out with POCl<sub>3</sub> alone. The use of POCl<sub>3</sub>-PCl<sub>5</sub> mixtures gave rise to the formation of 2-chloro-6-trichloromethylnicotinitrile as a by-product. To obtain acceptable yields in the conversion of 7 to 8 (reaction VI) the organometallic reaction was usually started at room temperature or below and then followed by tlc. In some cases several hours of heating under reflux were required until all 7 had reacted. Insufficient amounts of phosgene in reaction VII or too brief reaction times led to the formation of substantial amounts of 2-alkylamino-3-pyridyl phenyl ketones after acidic work-up (Tables I and II).

**Pharmacology.** The antiinflammatory activity was determined in rats utilizing the carrageenin foot edema assay<sup>4</sup> as the primary test. Compounds of interest were also tested in the carrageenin test using bilaterally adrenalectomized rats to determine the influence of the pituitary-adrenal axis on antiinflammatory activities of these

Scheme I  
sequence A

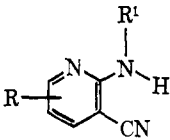


sequence B



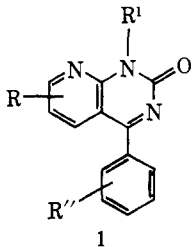
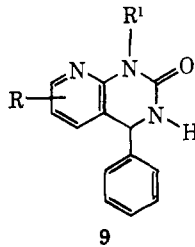
compounds and the effect against pressure thresholds of the inflamed paw<sup>5</sup> to determine the "nonnarcotic" analgesic property and against the established arthritis induced by *Mycobacterium butyricum*.<sup>6,†</sup>

Table I

						
	R	R <sup>1</sup>	Mp, °C	Solvent	Yield, %	
7a	H	CH <sub>3</sub>	83-86	Et <sub>2</sub> O	65 <sup>a</sup>	
7b	H	CH <sub>3</sub> CHCH <sub>3</sub>	50-55	Pent. <sup>b</sup>	66	
7c	H	<i>t</i> -Bu	Oil		25	
7d	H	CH <sub>3</sub> CH <sub>2</sub>	73-75	CH <sub>2</sub> Cl <sub>2</sub> -pent.	65	
7e	H	Cyclopropyl	91-94	Pent.	62	
7g	6-Methyl	CH <sub>3</sub> CHCH <sub>3</sub>	100-04	Et <sub>2</sub> O-pent.	80	
7h	5-Phenyl	CH <sub>3</sub> CHCH <sub>3</sub>	78-80	Pent.	68	

<sup>a</sup>Reaction temperature in step V, 100-110°. <sup>b</sup>Pent. = pentane.

Table II

									
Compd	R	R <sup>1</sup>	R <sup>2</sup>	Rxn sequence	Reagent in rxn IV	Yield, %	Mp, °C	Solvent	Analyses
1a	H	CH <sub>3</sub>	H	A		40	197-198	EtOH	C, H, N
				B	Mg	60			
1b	H	CH <sub>3</sub> CHCH <sub>3</sub>	H	B	Mg	60	193-196	CH <sub>2</sub> Cl <sub>2</sub> -Et <sub>2</sub> O	C, H, N, O
1c	H	<i>t</i> -Bu	H	B	Mg	53	138-141	Et <sub>2</sub> O	C, H, N
1d	H	CH <sub>2</sub> CH <sub>3</sub>	H	B	Mg	40	181-185	CH <sub>2</sub> Cl <sub>2</sub> -Et <sub>2</sub> O	C, H, N, O
1e	H	Cyclopropyl	H	B	Mg	55	155-159	EtOH-Et <sub>2</sub> O	C, H, N, O
1f	H	CH <sub>2</sub> C≡CH	H	A		22	175-178	CH <sub>2</sub> Cl <sub>2</sub> -Et <sub>2</sub> O	H, N; C <sup>b</sup>
1g	7-CH <sub>3</sub>	CH <sub>3</sub> CHCH <sub>3</sub>	H	B	Li <sup>c</sup>	25	155-157	Et <sub>2</sub> O	C, H; N <sup>c</sup>
1h	6-Phenyl	CH <sub>3</sub> CHCH <sub>3</sub>	H	B	Mg	68	146-148	EtOAc, Et <sub>2</sub> O, pent. <sup>d</sup>	C, H, N
1i	H	CH <sub>3</sub> CHCH <sub>3</sub>	4-CH <sub>3</sub>	B	Li	40	149-152	EtOAc, Et <sub>2</sub> O, pent	C, H, N
1k	H	CH <sub>3</sub> CHCH <sub>3</sub>	4-OCH <sub>3</sub>	B	Li	32	135-137	EtOAc, Et <sub>2</sub> O	C, H, N
1l	H	CH <sub>3</sub> CHCH <sub>3</sub>	4-Cl	B	Mg	26	180-183	EtOAc, pent.	C, H, N
1m	H	CH <sub>3</sub> CHCH <sub>3</sub>	3,4-Cl <sub>2</sub>	B	Li	15	168-172	EtOAc, Et <sub>2</sub> O	C, H, N
9b	H	CH <sub>3</sub> CHCH <sub>3</sub>	H	B		86	149-153	CH <sub>2</sub> Cl <sub>2</sub> , Et <sub>2</sub> O	C, H, N
9e	H	Cyclopropyl	H	B		82	179-181	MeOH, pent.	C, H, N, O
9h	H	CH <sub>3</sub> CHCH <sub>3</sub>	H	B		75	151-161	EtOAc, pent.	C, H, N

<sup>a</sup>Reagent added at -10° and reaction mixture stirred for 1 hr at 0 to -10°. <sup>b</sup>C: calcd, 73.9; found, 63.3 <sup>c</sup>N: calcd, 15.0; found, 14.5. <sup>d</sup>Pent. = pentane

All doses were administered orally as a suspension in 0.5% carboxymethylcellulose and the dosage schedules were: carrageenin tests, 1 hr before carrageenin; Randall-Selitto test, 2 hr after yeast; and adjuvant arthritis, days 12-16 after the injection of mycobacterium. The results of these tests are found in Table III.

**Structure-Activity Relations.** As was the case in our recent publication<sup>1</sup> on the antiinflammatory activity of 1-alkyl-4-phenyl-2(1H)-quinazolinones this group of compounds also shows improvement in the inhibition of carrageenin-induced paw edema when the 1 position was substituted by an isopropyl group (1b and 1g vs. 1a and 1d) rather than a straight-chain alkyl group. Substitution in the 4-phenyl group led to decreased activity as did the introduction of the bulky phenyl group in the 6 position. Interestingly, the introduction of a 7-methyl group (1g) led

to a compound with somewhat less activity in the primary carrageenin test but much improved overall activity. The antiinflammatory activity of these compounds appears to be retained when the 3,4 double bond is reduced. In the adjuvant arthritis test, compound 1g proved to be the best of the ones discussed here, being about twice as potent as phenylbutazone.

In general, the compounds described here exhibited less activity than their carbon analogs, reported about in our recent publication.<sup>1</sup> Cardiovascular and CNS screening of these compounds revealed no outstanding activities.

#### Experimental Section

Melting points were determined with a Hoover capillary melting point apparatus and are uncorrected. All intermediates and final products were checked by ir and nmr spectroscopy (Perkin-Elmer 237 and Varian A-60 or T-60, respectively) and their spectra were found to be in agreement with the assigned structures. No attempt has been made to optimize the yields of the described reactions.

<sup>†</sup> The mycobacterium-adjuvant mixture was injected into the distal portion of the tail.

**Table III.** Antiinflammatory Activity. Oral ED<sub>50</sub>, mg/kg (95% Confidence Limits) (Number of Animals)<sup>a</sup>

Compd	Carrageenin edema		Adjuvant arthritis	Randall-Selitto
	Normal	Adrex		
1a	49 (34-69) (30)	91 (70-117) (50)	NA at 25 (35)	33 (22-48) (20)
1b	16 (11-23) (35)	70 (47-103) (20)	WK at 25 (40)	WK at 100 (20)
1c	39 (24-62) (10)	NT	NT	NT
1d	WK at 100 (10)	NT	NT	WK at 100 (10)
1e	34 (22-52) (15)	NT	NT	32 (22-47) (20)
1f	94 (58-150) (10)	NT	NT	WK at 100 (10)
1g	28 (21-36) (45)	34 (23-50) (10)	3 (2-4) (25)	43 (29-63) (20)
1h	WK at 100 (10)	NT	NT	WK at 100 (10)
1i	WK at 100 (5)	NT	NA at 25 (10)	WK at 25 (10)
1k	WK at 100 (5)	NT	NA at 25 (5)	WK at 25 (10)
1l	WK at 100 (5)	NT	NA at 25 (5)	WK at 25 (10)
1m	WK at 100 (5)	NT	NA at 25 (5)	WK at 25 (10)
9b	29 (18-46) (10)	NT	NT	NT
9e	40 (25-64) (10)	NT	13 (9-18) (25)	WK (25) (20)
9h	WK at 100 (10)	NT	28 (20-38) (35)	49 (30-78) (30)
Phenylbutazone	24 (19-30) (80)	30 (20-44) (24)	5 (3-7) (64)	9 (6-13) (32)

<sup>a</sup>NT = not tested. WK = little or no activity at dose tested.

All intermediates [except for some of the chloronicotinitriles (6)] were analyzed and their elemental analysis (C, H, N) results were within  $\pm 0.4\%$  of the theoretical values except where noted in the tables.

**Reaction I.** 4-Phenylpyrido[2,3-*d*]pyrimidin-2(1*H*)-one (3). A mixture of 2-amino-3-pyridyl phenyl ketone<sup>7</sup> (4.6 g, 0.023 mol), ethyl carbamate (18.4 g, 0.21 mol), and ZnCl<sub>2</sub> (0.5 g) was heated to 210-220° for 45 min. After cooling the residue was triturated with CHCl<sub>3</sub> (200 ml) and the insoluble material was filtered off. The filtrate was extracted with H<sub>2</sub>O (three times) and dried (Na<sub>2</sub>SO<sub>4</sub>). The residue which remained on evaporation was crystallized from EtOH to obtain 2.9 g of 3 (60%), mp 245-246°. *Anal.* C, H, N.

**Reaction II.** 1-Methyl-4-phenylpyrido[2,3-*d*]pyrimidin-2(1*H*)-one (1a). Sodium hydride (0.468 g, 0.011 mol, 57% in mineral oil) was added to a suspension of 4-phenylpyrido[2,3-*d*]pyrimidin-2(1*H*)-one (2.0 g, 0.009 mol) in DMA (30 ml). After 5 min a thick precipitate had formed which was diluted with 10 ml of DMA and stirred at room temperature for 1 hr. CHI<sub>3</sub> (1.4 ml) was added over a period of 5 min to this mixture and the reaction was maintained at 25° for 15 hr. Water and ice were added and the crystalline precipitate which formed was filtered off and washed with H<sub>2</sub>O. The crude crystalline material was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, and the solution was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The residue was taken up in EtOH, treated with charcoal, and concentrated to obtain 0.8 g of 1a (40%), mp 197-198°. *Anal.* C, H, N.

**Reaction III.** 2-Chloro-6-methylnicotinonitrile (6g). A suspension of 6-methyl-3-cyano-2-pyridone (26.8 g, 0.22 mol) in POCl<sub>3</sub><sup>8</sup> (200 ml) was heated under reflux for 90 min. A solution resulted which was evaporated to dryness *in vacuo*. The resulting paste was poured over 2 *N* NaOH and more 2 *N* NaOH was added to make the mixture basic. After two extractions with CH<sub>2</sub>Cl<sub>2</sub> the organic phase was washed with 2 *N* NaOH and twice with H<sub>2</sub>O and dried (Na<sub>2</sub>SO<sub>4</sub>). On evaporation a solid (28.4 g) was obtained which was redissolved in CH<sub>2</sub>Cl<sub>2</sub>, treated with activated charcoal, filtered through Al<sub>2</sub>O<sub>3</sub>, and evaporated. The residue was crystallized from Et<sub>2</sub>O to obtain 24.9 g of 6g (82%), mp 113-115°<sup>9</sup> (lit.<sup>10b</sup> mp 117°). The use of the PCl<sub>5</sub><sup>10</sup>-POCl<sub>3</sub> mixture for this reaction resulted in partial formation of 2-chloro-6-trichloromethylnicotinonitrile (6, R = CCl<sub>3</sub>) which could be transformed into 7 (R = CCl<sub>3</sub>; R<sup>1</sup> = isopropyl), mp 77-79°, under standard conditions.

**Reaction IV.** See ref 11.

**Reaction Va.** 2-Isopropylamino-5-phenylnicotinonitrile (7h). A mixture of 2-chloro-5-phenylnicotinonitrile (12, 25 g, 0.15 mol) and isopropylamine (125 ml) was heated for 4 hr at 130° (bath temperature) in a Parr steel cylinder. After cooling, the material was transferred with CH<sub>2</sub>Cl<sub>2</sub> into a flask and evaporated to dryness. H<sub>2</sub>O was added and the mixture was extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The organic extract was dried (Na<sub>2</sub>SO<sub>4</sub>), treated with charcoal, and filtered through Celite. On evaporation 21 g of oil was obtained, which crystallized on addition of pentane to give 18.8 g of 7h (68%), mp 78-80°. *Anal.* C, H, N.

**Reaction Vb.** 2-*tert*-Butylaminonicotinonitrile (7c). 2-Chlo-

ronicotinonitrile (10 g, 0.072 mol) was dissolved in *tert*-butylamine (30 ml) and the mixture treated in a Parr steel cylinder for 5 hr at 130-140° (bath temperature). After cooling the mixture was transferred into a flask and evaporated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and extracted with 2 *N* NaOH and twice with H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. The crude yellow product was crystallized from CH<sub>2</sub>Cl<sub>2</sub>-pentane (1:4), yielding mostly *starting material* (mp 98-100°). The mother liquor was filtered through silica gel (solvent, benzene). The first fractions contained 3.2 g (25%) of the oily 2-*tert*-butylaminonicotinonitrile.

**Reaction VI.** 2-*tert*-Butylamino-3-pyridyl Phenyl Ketone Imine (8c). The crude oily 2-*tert*-butylaminonicotinonitrile (2.3 g, 0.013 mol) dissolved in 15 ml of THF was added to an excess of PhMgBr (prepared from 5.2 g, 0.033 mol of PhBr and 0.8 g of Mg in THF) and the mixture refluxed for 16 hr. During this period the reaction progress was followed by tlc. After cooling, the mixture was poured on ice-H<sub>2</sub>O and extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo* at 40°. The crude imine (3 g) was obtained.

**Reaction VII.** 1-*tert*-Butylamino-2,3-dihydro-4-phenylpyrido[2,3-*d*]pyrimidin-2(1*H*)-one (1c). The imine (3 g, 0.012 mol) obtained in reaction VI was dissolved in C<sub>6</sub>H<sub>6</sub> (50 ml, anhydrous), Et<sub>3</sub>N (4 ml) and phosgene (15 ml, 0.178 mol, 12.5% solution in C<sub>6</sub>H<sub>6</sub>) were added subsequently, and the resulting mixture was stirred at room temperature for 10 min. Water (100 ml) and 2 *N* NaOH (30 ml) were added and the mixture was extracted twice with C<sub>6</sub>H<sub>6</sub>. The extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. The crude oil (3.1 g) crystallized from Et<sub>2</sub>O-pentane to afford 1.75 g (53%) of 1c, mp 138-141°.

**Reaction VIII.** 3,4-Dihydro-1-isopropyl-4-phenylpyrido[2,3-*d*]pyrimidin-2(1*H*)-one (9b). Sodium borohydride (6 g, 0.15 mol) was added to a solution of 1-isopropyl-4-phenylpyrido[2,3-*d*]pyrimidin-2(1*H*)-one (8 g, 0.03 mol) in EtOH (95%, 200 ml) and the mixture was stirred at room temperature for 60 hr. The reaction was then evaporated (to about 100 ml) and H<sub>2</sub>O (500 ml) added. The precipitate which formed was filtered off and thoroughly washed with water. After drying (50°, 0.1 mm) the material was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O to afford 6.9 g (58%) of 9b, mp 149-153°.

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## Substituted Azapurines. 1. Synthesis of 8,8'-Dioxo-6,6'-azapurine

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8,8'-Dioxo-6,6'-azapurine (DOAP), a member of a new class of compounds designated as the oxoazapurines, was synthesized from adenine using sulfuric acid, potassium bromide, potassium permanganate, and hydrogen peroxide. The compound normally exists in the form of a monohydrate and the anhydrous form can be obtained by drying at 100° for 1 hr. Conversion of the anhydrous compound to the monohydrate occurs within 15 min following exposure to the atmosphere at room temperature. The nmr spectrum indicates the presence of C-H, amide N-H, and imidazole N-H protons. The compound can undergo reductive cleavage to two molecules of 8-hydroxyadenine in the presence of strong acid and granulated tin. Preliminary biological evaluation shows that 8,8'-dioxo-6,6'-azapurine is a cholinergic smooth muscle stimulant and an anticurare agent, as well as being an electron acceptor and an extremely potent inhibitor of xanthine oxidase *in vitro*.

A previous report from this laboratory has described a rapid and specific colorimetric analysis for microgram amounts of adenine compounds using sulfuric acid, potassium bromide, potassium permanganate, and hydrogen peroxide.<sup>1</sup> However, when large amounts of adenine, greater than 1 mg/ml of reaction mixture, were employed under the conditions of the colorimetric analysis, not only did the reaction mixture turn yellow, but a bright orange precipitate occurred. Because of the important and varied role occupied by adenine compounds and their analogs in physiological systems, the present studies were designed to investigate the chemical nature and possible biological activity of this orange precipitate.

### Experimental Section

Uv spectra were determined in the solvents specified with a Beckman DB-G recording spectrophotometer and the nmr spectra were determined in DMSO-*d*<sub>6</sub> with a Varian A-60A spectrometer. Elemental analyses were performed by Schwarzkopf Microanalytical Lab., Woodside, N. Y. Where analyses are indicated only by symbols of the elements, results obtained for these elements were within ±0.4% of the theoretical values.

**8,8'-Dioxo-6,6'-azapurine (I).** To 2.5 l. of 1 N H<sub>2</sub>SO<sub>4</sub> was added with stirring 15.0 g (111 mmol) of adenine.† The solution was filtered through Whatman No. 3 filter paper and KBr (1.8 g in 120 ml of H<sub>2</sub>O, 15.12 mmol) added to the filtrate and stirred for 1 hr. To this solution 800 ml of 1 N KMnO<sub>4</sub>‡ (800 mmol) was added and stirred for 1 hr, resulting in a brownish purple suspension. A total of 50 ml of 30% H<sub>2</sub>O<sub>2</sub> was then slowly added in 10-ml portions with stirring which decolorized the mixture and resulted in a bright orange precipitate. The reaction mixture was stirred for 1 hr and allowed to stand in the dark for 16 hr at 4°. The orange precipitate, designated as the orange adenine chromophore (abbreviated as OAC) was collected by centrifugation at 600g for 15 min employing four 150-ml capacity glass centrifuge bottles. The OAC solid present in each of the four centrifuge bottles was then successively washed 12 times with 150-ml portions of 4 N H<sub>2</sub>SO<sub>4</sub> and collected by centrifugation at 600g for 15 min until no absorbency at 327 nm could be detected in the decanted acid wash. The OAC solid in each centrifuge bottle was then successively washed six times with 150-ml portions of H<sub>2</sub>O and col-

lected by centrifugation at 600g for 1 hr, followed by successive washing with four 150-ml portions of acetone with collection by centrifugation at 600g for 1 hr. The final washed OAC solid was combined from all four centrifuge bottles as an acetone suspension, allowed to evaporate to dryness on a large watch glass at room temperature, and then placed in a drying oven at atmospheric pressure for 16 hr at 75°; yield, 0.78 g (5.2%) of an orange microcrystalline product; mp >300°; λ max (absolute EtOH) 230 (17.1 × 10<sup>3</sup>), 302 (5.6 × 10<sup>3</sup>), 442 (11.5 × 10<sup>3</sup>), and 490 mμ (7.4 × 10<sup>3</sup>); λ max (0.1 N KOH) 220 (25.2 × 10<sup>3</sup>), 243 (20.7 × 10<sup>3</sup>), and 513 mμ (16.3 × 10<sup>3</sup>). Ascending paper chromatography run on Whatman No. 1 sheets using 60:30:10 1-propanol-ammonia-H<sub>2</sub>O, 67:20:13 absolute ethanol-pyridine-H<sub>2</sub>O, and 5:2 absolute ethanol-0.5 M ammonium acetate showed one spot at R<sub>f</sub> of 0.32, 0.12, and 0.08, respectively. *Anal.* (C<sub>10</sub>H<sub>6</sub>N<sub>10</sub>O<sub>2</sub>·H<sub>2</sub>O) C, H, N, O.

In order to confirm the presence of 1 mol of water of hydration per mole of the OAC solid, the sample was dried under a stream of nitrogen for 1 hr at 100° and the elemental analyses were performed immediately after drying, keeping the sample in a sealed container to avoid picking up H<sub>2</sub>O. *Anal.* Calcd for C<sub>10</sub>H<sub>6</sub>N<sub>10</sub>O<sub>2</sub>: C, 40.28; H, 2.03; N, 46.97; O, 10.73. Found: C, 39.87; H, 2.28; N, 46.53; O, 10.70. The trapped H<sub>2</sub>O was found to be 5.41% corresponding to a theoretical value of 5.70%. Subsequent drying of the sample for 1 hr at 150 and 200° did not result in any further loss of H<sub>2</sub>O. Conversion of the anhydrous compound to the monohydrate was found to occur within 15 min following exposure to the atmosphere at room temperature.

Inasmuch as the number of carbon and nitrogen atoms in the anhydrous empirical formula of C<sub>10</sub>H<sub>6</sub>N<sub>10</sub>O<sub>2</sub> was double that of the starting material adenine, it appeared that OAC was a substituted purine dimer with two oxo groups present in the molecule. The nmr spectrum of OAC at a concentration of 20 mg/ml was taken in DMSO-*d*<sub>6</sub> (TMS) on a Varian A-60A (δ). Three peaks were found at δ 8.84, 12.05, and 12.64 ppm relative to the TMS reference. Integration of the three proton peaks revealed an integer ratio of 1:1:1, respectively, confirming the presence of six hydrogens in the OAC molecule. Peak assignments, made on the basis of D<sub>2</sub>O exchange and ranges of known δ ppm values,<sup>2-6</sup> indicated the presence of two C-H protons (8.84 ppm), two amide N-H protons (12.05 ppm), and two imidazole N-H protons (12.64 ppm). Since the two protons originally present on the nitrogen attached to C-6 of adenine were found to be absent in the nmr spectrum of OAC, it appeared that the dimerization of adenine occurred through the formation of an azo linkage resulting in an oxoazapurine as shown in Figure 1, having the chemical structure of 8,8'-dioxo-6,6'-azapurine (I) abbreviated as DOAP.

Oxidation of adenine by KMnO<sub>4</sub> with KBr, followed by H<sub>2</sub>O<sub>2</sub>, appears most likely at the C-8 position in view of the fact that

= A longer period of centrifugation is required in H<sub>2</sub>O because of the fine microcrystalline nature of OAC.

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‡Supplied by Aldrich Chemical Co. It was found that solution of adenine in acid could be facilitated by initially homogenizing small portions of the solid in 1 N H<sub>2</sub>SO<sub>4</sub> using a Teflon pestle homogenizer.

§A 1 N KMnO<sub>4</sub> solution was prepared by adding 32 g of solid KMnO<sub>4</sub> to 1 l. of H<sub>2</sub>O and heating at 90° for 1 hr, after which time the solution was cooled to room temperature and filtered before use.