## Notes

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# Reaction of 5,6-Diamino-1,3-dimethyluracil with Isatoic Anhydrides

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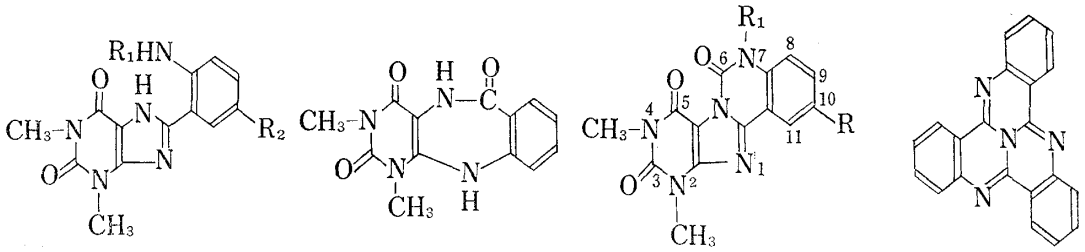
The reaction of 5,6-diamino-1,3-dimethyluracil (I) with isatoic anhydride (2*H*-3,1-benzoxazine-2,4(1*H*)-dione) (II) has recently been shown to give a mixture of 8-(2-aminophenyl)-theophylline (III) and 1,3-dimethyl-11*H*-pyrimido[4,5-*b*][1,4]benzodiazepine-2,4,6(1*H*,3*H*,5*H*)-trione (IV) ("homoalloxazine").[2] In the course of our investigations of purine chemistry we had occasion to repeat this reaction and detected another two by-products, 2,4-dimethylpurino[7,8-*c*]quinazoline-3,5,6-(2*H*,4*H*,7*H*)-trione (V) and tricycloquinazoline[3] (VI). The novel entry into these interesting products prompted us to look more closely into the reaction described above.



III : $R_1=R_2=H$
XIV : $R_1=H$, $R_2=Cl$
XVI : $R_1=CH_3$, $R_2=H$

IV

V : $R=R_1=H$
XV : $R=Cl$, $R_1=H$
XVII : $R=H$, $R_1=CH_3$

VI

Chart 1

Heating I under mild reflux with an equimolar amount of II for 30 min in sulfolane followed by cooling and dilution with three times as much water gave a mixture of III and VI, which could be separated by fractional crystallization from aqueous dimethylformamide. The filtrate was diluted doubly with water and allowed to stand overnight to precipitate IV. The filtrate was further diluted with a large amount of water and after a few days a precipitate of V was collected. The formation of V is best rationalized by assuming preferential nucleophilic attack of the more basic 5-amino group to the isocyanate (VII) which is in rapidly reversible equilibrium with isatoic anhydride anion,[4] followed by intramolecular cyclization of the resulting *o*-ureidobenzoic acid (VIII) with elimination of water to give the pyrimidinylquinazoline derivative (IX). This could then be cyclized to give V, whose structure was ascertained by its synthesis by the alternative route consisting of treatment of III with urea.

The one-step formation of tricycloquinazoline (VI) seems to be interesting, because this compound has been shown to be carcinogenic for mouse skin by Baldwin, *et al.*,[5,6] and its

1) Location: 5, *Oe-honmachi, Kumamoto.*
2) E.C. Taylor and F. Yoneda, *Angew. Chem.*, **79**, 901 (1967).
3) K. Butler and M.W. Partridge, *J. Chem. Soc.*, **1959**, 2396.
4) J.F. Bunnett and M.B. Naff, *J. Am. Chem. Soc.*, **88**, 4001 (1966).
5) R.W. Baldwin, G.J. Cunningham, and M.W. Partridge, *Brit. J. Cancer*, **13**, 94 (1959).
6) R.W. Baldwin, G.J. Cunningham, M.W. Partridge, and H.J. Vipond, *Brit. J. Cancer*, **16**, 275 (1962).

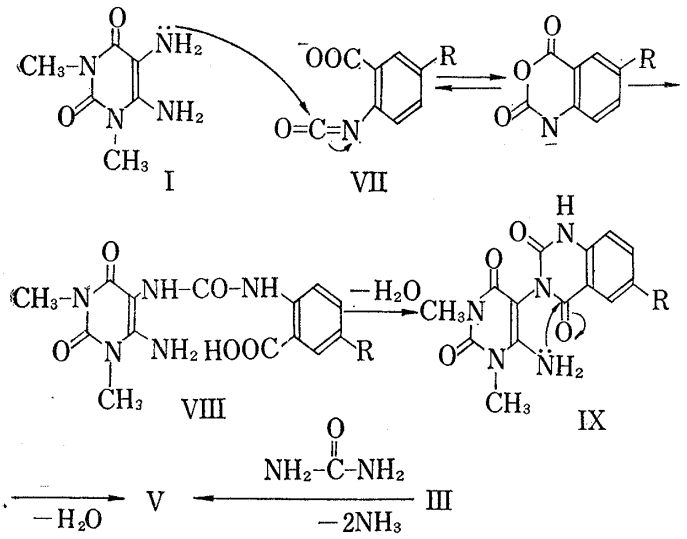


Chart 2

direct interaction with DNA has been discussed by Nagata, *et al.*[7] The probable reaction pathway for the formation of VI is as follows. The nucleophilic attack of I at C-4 of II with subsequent loss of carbon dioxide from a presumed intermediate of the carbamic acid type (X) forms 1,3-dimethyl-6-amino-5-(2-aminobenzoyl)aminouracil (XI). The amino group of benzene nucleus of XI attacks again at C-4 of II and the repeat of this procedure may give XII. The reductive cleavage (probably by I) of the carbon-nitrogen bond of 5-position of 1,3-dimethyluracil moiety gives XIII, a precursor of tricycloquinazoline (VI), which is cyclized with elimination of three moles of water to form VI. It is known that treatment of XIII prepared in several steps with phosphorus tentoxide gives VI.[3] Reaction of 5,6-diamino-1,3-dimethyluracil bisulfite instead of the free base (I) with II under the same conditions gave the similar results except that the yield of VI remarkably increased.

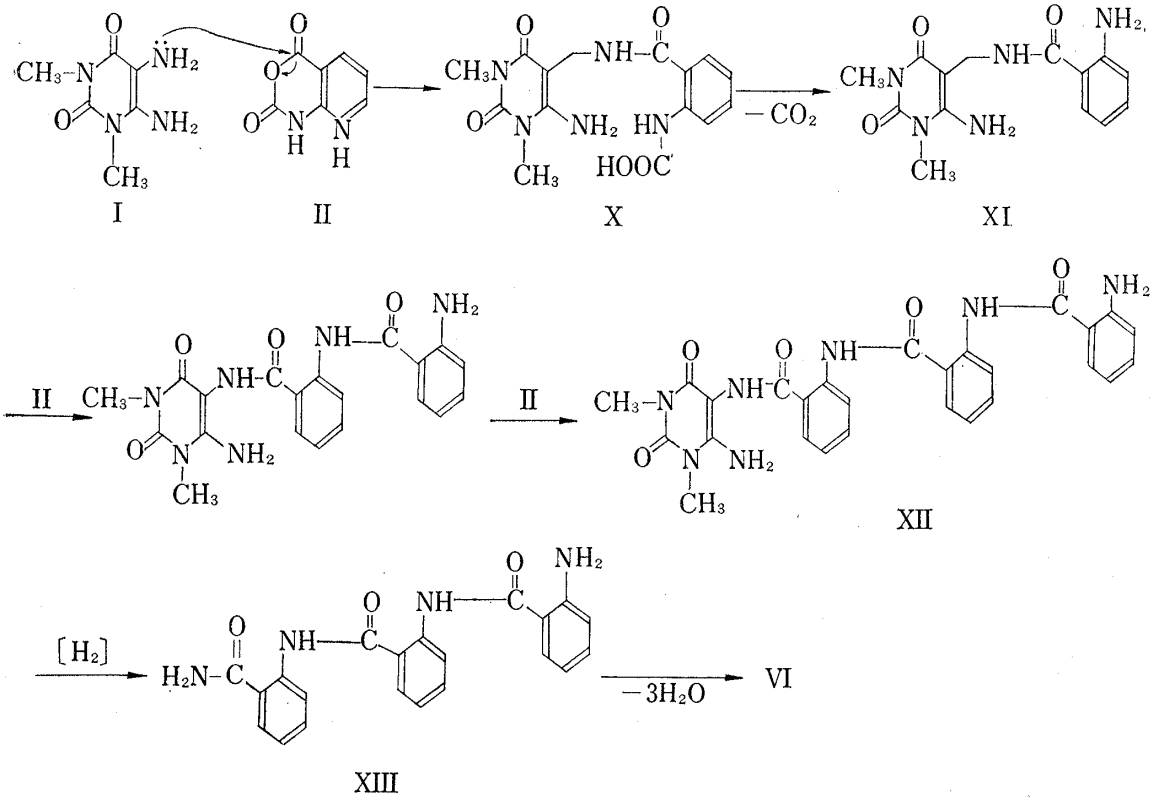


Chart 3

7) C. Nagata, M. Kodama, A. Imamura, and Y. Tagashira, *Gann*, **57**, 75 (1966).

Treatment of I with 6-chloroisatoic anhydride under the same conditions yielded a mixture of 8-(2-amino-5-chlorophenyl)theophylline(XIV) and 10-chloro-2,4-dimethylpurino-[7,8-*c*]quinazoline-3,5,6(2*H*,4*H*,7*H*)-trione(XV), but the corresponding "homoalloxazine" and tricycloquinazoline could not be detected. The structures of XIV and XV were ascertained by elemental analyses, molecular weight determinations by mass spectrometry and from their infrared spectra which were similar with those of III and V.

In consideration of the formation of VI from I and II, we have tried the reaction of II with ammonium acetate as a nitrogen source in sulfolane in order to get VI. As expected compound VI was formed although in poor yield. However the reaction of 6-chloroisatoic anhydride with ammonium acetate did not give the corresponding tricycloquinazoline derivative under these conditions. This fact consists with the failure of the formation of 3,8,13-trichlorotricycloquinzaoline from the reaction of I with 6-chloroisatoic anhydride.

Reaction of I with N-methylisatoic anhydride under the same conditions formed exclusively 8-(2-methylaminophenyl)theophylline (XVI), which was converted into 7-methyl-2,4-dimethylpurino[7,8-*c*]quinazoline-3,5,6(2*H*,4*H*,7*H*)-trione (XVII) by fusion with urea. Compound XVII was also synthesized by the methylation of V with methyl iodide in dimethylformamide containing potassium carbonate.

## Experimental

**Reaction of 5,6-Diamino-1,3-dimethyluracil (I) with Isatoic Anhydride (II)**——A mixture of 1.7 g (0.01 mole) of I and 1.6 g (0.01 mole) of II in 10 ml of sulfolane was heated under reflux for 30 min. After cooling, the reaction mixture was diluted with 30 ml of $H_2O$, the precipitated crystals were collected by filtration to give a mixture of 0.6 g (22.2%) of 8-(2-aminophenyl)theophylline[2] (III), mp >320°, and a mixture of tricycloquinazoline[3] (VI), mp 322°, which could be separated by fractional crystallization from DMF–$H_2O$.

The filtrate was diluted with 40 ml of $H_2O$ and allowed to stand overnight to precipitate 0.45 g (16.6%) of 1,3-dimethyl-11*H*-pyrimido[4,5-*b*][1,4]benzodiazepine-2,4,6(1*H*,3*H*,5*H*)-trione[2] (IV), which was filtered off and recrystallized from EtOH to give pale yellow needles, mp 260°. The filtrate was further diluted with a large amount of $H_2O$ and allowed to stand for several days. The separated crystals were collected by filtration and recrystallized from DMF to afforded 0.35 g (11.8%) of 2,4-dimethylpurino[7,8-*c*]quinazoline-3,5,6(2*H*,4*H*,7*H*)-trione (V) as colorless prisms, mp >320°. *Anal.* Calcd. for $C_{14}H_{11}O_3N_5$: C, 56.56; H, 3.73; N, 23.56. Found: C, 56.71; H, 3.72; N, 23.29.

**Reaction of 5,6-Diamino-1,3-dimethyluracil Bisulfite (I-Bisulfite) with II**——When 2.7 g (0.01 mole) of I-bisulfite and 1.6 g (0.01 mole) of II were similarly treated in 10 ml of sulfolane, 0.42 g (15.6%) of III, 0.23 g (21.5%) of VI, 0.57 g (21%) of IV, and 0.3 g (10.1%) of V were obtained.

**Reaction of I with 6-Chloroisatoic Anhydride**——A mixture of 1.7 g (0.01 mole) of I and 1.98 g (0.01 mole) of 6-chloroisatoic anhydride in 10 ml of sulfolane was heated under reflux for 30 min. After cooling, the precipitates were collected by filtration, washed with EtOH and recrystallized from DMF to give 2.0 g (64.5%) of 8-(2-amino-5-chlorophenyl)theophylline (XIV) as colorless prisms, mp>350°. *Anal.* Calcd. for $C_{13}H_{12}O_2N_5Cl$: C, 51.07; H, 3.96; N, 22.91. Found: C, 50.93; H, 4.04; N, 22.64.

The filtrate was diluted with $H_2O$ and the separated crystals were collected by filtration. Recrystallization from DMF gave 0.5 g (15.2%) of 10-chloro-2,4-dimethylpurino[7,8-*c*]quinazoline-3,5,6(2*H*,4*H*,7*H*)-trione (XV) as colorless leaflets, mp >350°. *Anal.* Calcd. for $C_{14}H_{10}O_3N_5Cl$: C, 50.69; H, 3.04; N, 21.12. Found: C, 50.43; H, 3.33; N, 21.37.

**2,4-Dimethylpurino[7,8-*c*]quinazoline-3,5,6(2*H*,4*H*,7*H*)-trione (V) by the Reaction of 8-(2-Aminophenyl)-theophylline (III) with Urea**——The throughly mixed 0.27 g (0.001 mole) of III and 0.46 g (0.01 mole) of urea was fused at 300° for 20 min. The reaction mixture was crushed in $H_2O$ and the precipitates were collected by filtration. The crude product was recrystallized from DMF to give 0.20 g (67.3%) of V, which was identical in all respects with the product (V) obtained from the reaction of I with II.

**10-Chloro-2,4-dimethylpurino[7,8-*c*]quinazoline-3,5,6(2*H*,4*H*,7*H*)-trione (XV) by the Reaction of 8-(2-Amino-5-chlorophenyl)theophylline (XIV) with Urea**——The throughly mixed 0.31 g (0.001 mole) of XIV and 0.46 g (0.01 mole) of urea were treated with analogously as described above to give 0.28 g (84.9%) of XV.

**8-(2-Methylaminophenyl)theophylline (XVI)**——A mixture of 1.7 g (0.01 mole) of I and 1.77 g (0.01 mole) of N-methylisatoic anhydride in 10 ml of sulfolane was heated under mild reflux for 20 min. After cooling, the separated crystals were collected by filtration, washed with EtOH, and recrystallized from DMF to give 1.15 g (40.4%) of pale yellow leaflets, mp >320°. *Anal.* Calcd. for $C_{14}H_{15}O_2N_5$: C, 58.93; H, 5.30; N, 24.55. Found: C, 58.77; H, 5.13; N, 24.62.

**7-Methyl-2,4-dimethylpurino[7,8-*c*]quinazoline-3,5,6(2*H*,4*H*,7*H*)-trione (XVII)**——A: A mixture of 0.29 g (0.001 mole) of XVI and 0.46 g (0.01 mole) of urea was fused at 300° for 20 min. The reaction mixture was crushed in $H_2O$ and the precipitates were collected by filtration. Recrystallization from DMF gave 0.25 g (80.4%) of colorless crystals, mp >320°. *Anal.* Calcd. for $C_{15}H_{13}O_3N_5$: C, 57.87; H, 4.21; N, 22.50. Found: C, 58.03; H, 4.14; N, 22.48.

B: To a mixture of 0.3 g (0.001 mole) of V and 0.3 g of $K_2CO_3$ in 10 ml of DMF was added 0.28 g (0.002 mole) of MeI and refluxed for 4 hr. The reaction mixture was diluted with $H_2O$, and the precipitates which separated were filtered. Recrystallization from DMF gave 0.21 g (67%) of colorless crystals, mp >320°, which was identical in all respects with the product obtained in A.

**Formation of Tricycloquinazoline (VI) by the Reaction of II with Ammonium Acetate**——A mixture of 3.2 g (0.02 mole) of II and 1.54 g (0.02 mole) of $NH_4OAc$ in 15 ml of sulfolane was heated under mild reflux for 11 hr. After cooling, the reaction mixture was diluted with 30 ml of $H_2O$ to precipitate the crude product, which was collected by filtration and extracted with hot EtOH several times. The combined EtOH-extracts were maintained in an ice-box to separate 0.05 g (2.3%) of VI.

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# Purines. IX.[1] Deoxygenation of 1-Benzyloxyadenine Derivatives: The Formation of Benzaldehyde

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It has previously been reported[3] that in the reduction of 1-benzyloxyadenine (Ia) or 1-benzyloxy-9-benzyladenine (IIa) with Raney nickel and hydrogen the hydrogenolytic cleavage of the N—O bond to form adenine (III) or 9-benzyladenine (IV) was accompanied by the nonreductive cleavage which produced a small amount of benzaldehyde. We have assumed that this aldehyde formation was probably caused by a trace of sodium aluminate and alkali included in the catalyst and is explainable by a mechanism analogous to that[4] proposed for the aldehyde formation of 1-alkoxypyridinium salts by base. The object of the present paper is to describe some confirmatory experiments together with the deoxygenation of Ia, IIa, and their salts by base or bromide ion.

One phase of the work began with deoxygenation of 1-benzyloxyadenine derivatives using Raney nickel alone. When Ia and its hydrobromide (Ib) were separately treated with Raney nickel W-2 catalyst in 2-methoxyethanol under conditions similar to those[3] employed for the hydrogenolysis of Ia but without applying external hydrogen, it was possible to isolate a small amount of benzaldehyde as its 2,4-dinitrophenylhydrazone. Likewise, IIa and the corresponding salts, hydrobromide IIb and perchlorate IIc, were also found to yield a minute quantity of benzaldehyde under similar reaction conditions. These facts suggest the possibility that in the reaction of 1-alkoxyadenine derivatives with base course A in

1) Paper VIII in this series, T. Fujii, S. Sakurai, and T. Uematsu, *Chem. Pharm. Bull.* (Tokyo), **20**, 1334 (1972).
2) Location: *13-1 Takara-machi, Kanazawa, 920, Japan.*
3) T. Fujii and T. Itaya, *Tetrahedron*, **27**, 351 (1971).
4) For reviews, see *a*) T. Okamoto, *Yuki Gosei Kagaku Kyokai Shi*, **19**, 790 (1961); *b*) A.R. Katritzky and J.M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York, N.Y., 1971, p. 448, pp. 550—551.