

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 H₂O and the precipitates were collected by filtration. Recrystallization from DMF gave 0.25 g (80.4%) of colorless crystals, mp >320°. *Anal.* Calcd. for C₁₅H₁₃O₃N₅: 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 K₂CO₃ 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 H₂O, 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 NH₄OAc in 15 ml of sulfolane was heated under mild reflux for 11 hr. After cooling, the reaction mixture was diluted with 30 ml of H₂O 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 reported³⁾ 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 that⁴⁾ proposed for the aldehyde formation of 1-alkoxyppyridinium 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.

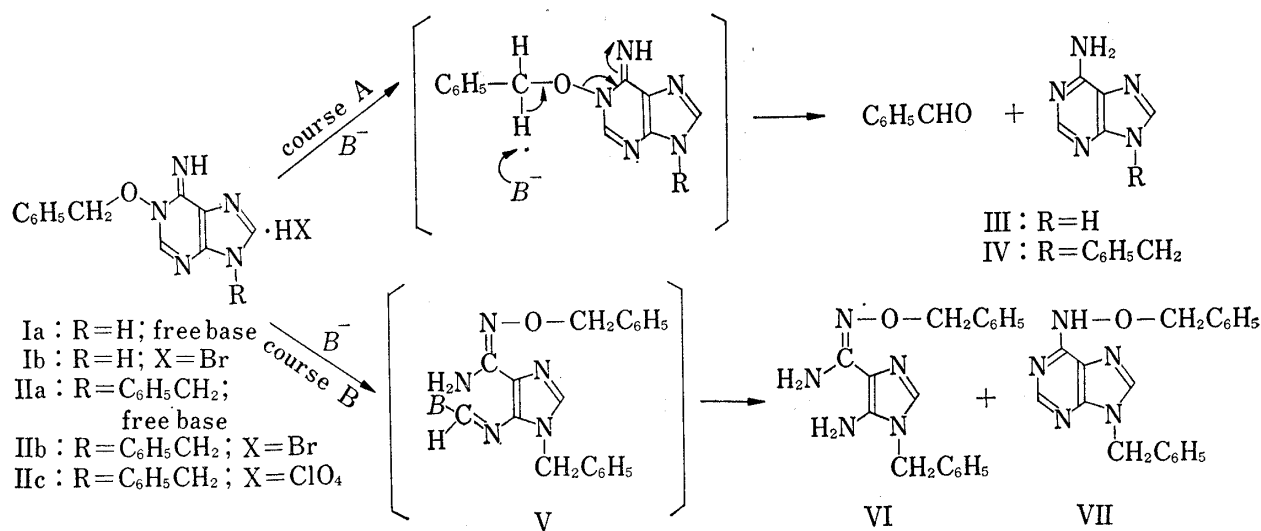
One phase of the work began with deoxygenation of 1-benzyloxyadenine derivatives using Raney nickel alone. When Ia and its hydrobromide (Ib) were separately treated with Raney nickel W-2 catalyst in 2-methoxyethanol under conditions similar to those³⁾ employed for the hydrogenolysis of Ia but without 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.

Chart 1^a

a) For convenience of illustration, 1-benzyloxyadenine (Ia) and its salt (Ib) are represented by one of the tautomeric forms, which is not favored.

Chart 1 could be operative to some extent in competition with course B, which has been found to proceed most readily⁵⁻⁷⁾ in the alkaline region.

Thus, attention was directed to the reaction with strong base. On being heated with sodium ethoxide in ethanol, perchlorate IIc furnished 9-benzyl-N-benzyloxyadenine (VII)^{5b)} (61%), 5-amino-1-benzyl-N'-benzyloxyimidazole-4-carboxamide (VI)^{5b)} (9%), and small amounts of 9-benzyladenine (IV) and benzaldehyde. It is reasonable to assume that VI and VII were derived from the common intermediate (V: $B=OC_2H_5$) as in the case of the Dimroth rearrangement caused by hydroxide ion.^{5,7)} The occurrence of the deoxygenation (course A in Chart 1) only to a slight extent was not surprising in view of the recently reported facile rearrangement of 1-methoxy-2',3'-O-isopropylideneadenosine in ethanol to the N-methoxy isomer.⁸⁾ The reaction of hydrobromide IIb with boiling 0.1N aq. sodium hydroxide was found to give a similar result but with an increased yield of VI. Treatment of the 9-unsubstituted derivative (Ia) with ethanolic sodium ethoxide also afforded benzaldehyde in a very low yield.

In order to increase the extent of the aldehyde formation, we may now consider the use of bromide ion for abstracting a benzylic proton from the 1-benzyloxy group. This ion has served to convert the N-phenacyloxy group in other heterocyclic systems⁹⁾ into phenylglyoxal and should be unfavorable for either occurrence of the course B reaction or its nucleophilic attack on the benzylic carbon atom^{10a,c)} which is equilibrated with the benzylation of the N-oxide group by the generated benzyl bromide.^{10a,b)} Thus, hydrobromide IIb was heated in N,N-dimethylacetamide (DMAC) at 120° for 6 hr, and it was found that benzaldehyde was formed in at least 18% yield. The yield of benzaldehyde decreased as the water content of solvent DMAC was increased. On the other hand, treatment of a mixture of

- 5) a) T. Fujii, T. Itaya, C.C. Wu, and S. Yamada, *Chem. Ind. (London)*, **1966**, 1967; b) T. Fujii, T. Itaya, C.C. Wu, and F. Tanaka, *Tetrahedron*, **27**, 2415 (1971).
- 6) T. Fujii, T. Sato, and T. Itaya, *Chem. Pharm. Bull. (Tokyo)*, **19**, 1731 (1971).
- 7) T. Itaya, F. Tanaka, and T. Fujii, *Tetrahedron*, **28**, 585 (1972).
- 8) A. Yamazaki, I. Kumashiro, and T. Takenishi, *Chem. Pharm. Bull. (Tokyo)*, **17**, 1128 (1969).
- 9) a) T. Kato, Y. Goto, and Y. Yamamoto, *Yakugaku Zasshi*, **84**, 287 (1964); b) M. Yanai, T. Kinoshita, and M. Yamaguchi, *ibid.*, **86**, 81 (1966).
- 10) a) T. Fujii, T. Itaya, and S. Yamada, *Chem. Pharm. Bull. (Tokyo)*, **14**, 1452 (1966); b) T. Fujii and T. Itaya, *ibid.*, **19**, 1611 (1971); c) T. Fujii, T. Itaya, and S. Moro, *ibid.*, **20**, 985 (1972).

9-benzyladenine 1-oxide^{3,11)} and benzyl bromide in DMAC at 120° for 6 hr produced the same aldehyde in 20% yield. It is most likely that this reaction proceeds through the facile formation¹¹⁾ of hydrobromide IIb followed by the breakdown as discussed.

In conclusion, the present results confirm that 1-benzyloxyadenine derivatives are capable of undergoing deoxygenation at any rate to form benzaldehyde in spite of their keen susceptibility to the Dimroth rearrangement and related reactions. The deoxygenation described must be corresponding to reaction path A of 1-alkoxypyridinium salts according to the Katritzky's classification.^{4b)}

Experimental¹²⁾

Reaction of 1-Benzyloxyadenine Derivatives (I and II) with Raney Nickel—The experiment with Ia is described in detail as a typical example.

A stirred mixture of the monohydrate³⁾ (550 mg, 2.12 mmoles) of Ia in 2-methoxyethanol (50 ml) and Raney Ni W-2 catalyst (*ca.* 1.5 ml) was kept at 50–55° for 3 hr. The catalyst was filtered off, and the filtrate was evaporated at 50° and 18 mm Hg to give a colorless distillate and a light greenish residual solid. The residue was triturated with ether (10 ml), and an insoluble solid was removed by filtration. The ethereal filtrate was combined with the distillate described above, and the mixture was concentrated at ordinary pressure. To the resulting residue was added a solution¹³⁾ of 2,4-dinitrophenylhydrazine—H₃PO₄ in ethanol, giving orange minute crystals (23 mg), mp 235° (with previous sintering). Recrystallization from ethanol yielded orange micro-needles, mp 240–241°, undepressed upon mixture with authentic benzaldehyde 2,4-dinitrophenylhydrazone. The infrared (IR) spectra of both samples were also identical.

The separate experiments with Ib, IIa, IIb, and IIc were conducted in the same way and brought similar results.

Reaction of 1-Benzyloxyadenine Derivatives (Ia, IIb, and IIc) with Base—The procedure employed for IIc is described below in detail.

A solution of perchlorate IIc^{10c)} (2.16 g, 5 mmoles) in 0.1N ethanolic sodium ethoxide (55 ml) was heated at reflux for 10.5 hr. Since it was found that a considerable amount of the starting IIc remained unchanged, 1N ethanolic sodium ethoxide (5 ml) was added, and the mixture was refluxed for 2 hr and allowed to stand at room temp. for 48 hr. The precipitates that formed were collected by filtration and washed with a little ethanol to give a first crop (630 mg) of VII as a faintly pink leaves. The filtrate and the washings were combined and evaporated *in vacuo* to dryness, leaving a solid, which was triturated with ether (100 ml). The mixture was filtered to remove an insoluble solid (fraction A). The ethereal filtrate was evaporated to dryness to leave a partially crystallized oil. Trituration of this residue with ether (10 ml) and filtration of the resulting mixture gave crude VI, which was recrystallized from 70% aq. ethanol to produce almost colorless plates (140 mg, 9%), mp 131–133°, identical [by thin-layer chromatography (TLC) and IR spectrum] with authentic 5-amino-1-benzyl-N'-benzyloxyimidazole-4-carboxamide (VI).^{5b)}

The ethereal filtrate, which was obtained when crude VI was filtered off, was evaporated to leave a very small amount of an oil, from which the odor of benzaldehyde was perceptible. The oil was dissolved in a little ethanol, and a small volume of 2,4-dinitrophenylhydrazine—H₃PO₄ reagent¹³⁾ was added to yield yellow precipitates (7 mg). They were recrystallized from ethanol as orange minute needles, mp 240–241°, identified with authentic benzaldehyde 2,4-dinitrophenylhydrazone by means of mixed melting-point test and IR spectrum.

Next the solid of fraction A described above was chromatographed on silica gel (100 g). Elution with chloroform—ethanol (9:1, v/v) and evaporation of the eluate furnished a crystalline mass, which was washed with a little ethanol to give a second crop (380 mg) of VII, total yield, 1.01 g (61%). Recrystallization of the combined first and second crop of crystals of VII from ethanol afforded colorless plates, mp 210–211° (decomp.), undepressed in melting point on admixture with authentic 9-benzyl-N-benzyloxyadenine (VII).^{5b)} Identification was further established by TLC and IR spectrum.

Isolation of 9-benzyladenine (IV) was carried out in the following manner: The mother liquor of the recrystallization of crude VI was combined with the ethanolic washings which were obtained when the second crop of VII was isolated. The mixture was concentrated to a small volume and subjected to preparative TLC [silica gel GF₂₅₄, chloroform—ethanol (8:1, v/v)]. A zone whose *R_f* value was corresponding to that of authentic IV was located under UV rays and was extracted with chloroform—ethanol (9:1,

11) a) T. Fujii, C.C. Wu, T. Itaya, and S. Yamada, *Chem. Ind. (London)*, 1966, 1598; b) T. Fujii, C.C. Wu, and T. Itaya, *Chem. Pharm. Bull. (Tokyo)*, 19, 1368 (1971).

12) All melting points are corrected.

13) G.D. Johnson, *J. Am. Chem. Soc.*, 73, 5888 (1951).

v/v). The extracts were evaporated *in vacuo*, and the residue was again chromatographed on a preparative TLC plate [silica gel GF₂₅₄, ethanol-ethyl acetate (1:6, v/v)], giving IV (4 mg), mp 233—236°. Identity was confirmed by means of mixed melting-point test, TLC, and IR spectrum.

In the reaction of Ia·H₂O³⁾ (2.59 g, 10 mmoles) with boiling 0.1N ethanolic sodium ethoxide (50 ml) for 10 hr, the formation of a minute amount of benzaldehyde was confirmed by the same procedure as described above.

Treatment of the monohydrate³⁾ (4.30 g, 10 mmoles) of IIb with boiling 0.1N aq. NaOH (300 ml) for 30 min also produced benzaldehyde in a very low yield.

Deoxygenation of 9-Benzyl-1-benzoyloxyadenine Hydrobromide (IIb) in N,N-Dimethylacetamide (DMAC)—A stirred mixture of IIb·H₂O³⁾ (2.00 g, 4.65 mmoles) and DMAC (5 ml) was kept at 120° in a stream of nitrogen for 6 hr. After cooling, the mixture was diluted with H₂O (20 ml) and extracted with ether. The extracts were combined, washed with H₂O, dried over anhyd. Na₂SO₄, and evaporated to leave an oily residue. This oil was allowed to react with 2,4-dinitrophenylhydrazine—H₃PO₄ reagent,¹³⁾ and 240 mg (18%) of benzaldehyde 2,4-dinitrophenylhydrazone, mp 240—241°, was obtained.

In this reaction, replacement of the solvent by 90% or 50% aq. DMAC resulted in reduction in yield of the hydrazone derivative to 3 or 0.5%.

When a stirred mixture of 9-benzyladenine 1-oxide^{3,11)} (1.13 g, 4.68 mmoles), benzyl bromide (800 mg, 4.68 mmoles), and DMAC (5 ml) was heated at 120° for 6 hr, the formation of benzaldehyde in 20% yield was evidenced by isolating it as the corresponding 2,4-dinitrophenylhydrazone in a manner similar to that described above.

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Reaction of N-Haloamide. XIV.¹⁾ Reaction of N,N-Dichlorophenylacetamide with Cyclohexene

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It has been reported that the reactions of N,N-dihalobenzenesulfonamide and N,N-dichlorobenzamide with cyclohexene gave adducts, 2-halo-1-benzenesulfonamidocyclohexane and 2-chloro-1-benzamidocyclohexane, respectively.³⁾

This report deals with the reaction of N,N-dichlorophenylacetamide (I) with cyclohexene (II) which gives adducts different from that expected from above reactions.

N-Chlorophenylacetamides were prepared by the modified procedure of the synthesis of N,N-dichlorourethane.⁴⁾ Passage of chlorine through a heterogeneous mixture of acetic acid-sodium acetate buffer solution and phenylacetamide in chloroform for one hour resulted in the formation of crystalline N-monochlorophenylacetamide (III), mp 126—127°. When the chlorine-passage was continued for three hours more, a yellow oil was obtained. It was likely N,N-dichlorophenylacetamide (I) on the basis of measurement of active chlorine (iodometry) and infrared spectrum.

The dichloroamide (I) was relatively unstable, decomposed on distillation, while monochloroamide (III) was very stable. No change was observed on refluxing of III with cyclohexene (II). Upon storage at 0°, dichloroamide (I) could be kept without decomposition for several weeks.

1) Part XIII: S. Takemura, H. Niizato, and Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **19**, 1606 (1971).

2) Location: *Kowakae, Higashi-Osaka*.

3) Y. Ueno, S. Takemura, Y. Ando, and H. Terauchi, *Chem. Pharm. Bull.* (Tokyo), **15**, 1193 (1967); K. Otsuki, S. Takemura, K. Okamoto, and Y. Ueno, *ibid.*, **17**, 528 (1969).

4) T.A. Foglia and B. Swern, *J. Org. Chem.*, **31**, 3625 (1966).