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Oxygen to Nitrogen Alkyl Migration in the Cross Alkylation of 1-Alkoxyadenines : 1-Alkoxy-9-alkyladenine Salts as Possible Alkylating Reagents

An interest in searching for a new class of cytotoxic alkylating agent[1] has focused our efforts on studying chemical and biological properties of the 1-alkoxyadenines (I) and 1-alkoxy-9-alkyladenine salts (V) which have been synthesized in our laboratory.[2] We now wish to record the cross alkylation of I to form 1-alkoxy-9-alkyladenine salts (II), in which two alkyl groups are different, accompanied by $O \rightarrow N_{(9)}$ alkyl migration.

As might be expected from the result of our previous work,[2a] 1-ethoxyadenine (I : $R=C_2H_5$) underwent alkylation almost exclusively at the 9-position when treated with methyl iodide and benzyl bromide in N,N-dimethylacetamide at room temperature, furnishing the corresponding 1-ethoxy-9-alkyladenine salts (type II) in good yields: 1-ethoxy-9-methyladenine hydriodide (II: $R=C_2H_5$; $R'=CH_3$; X=I), m.p. 204°(decomp.);[2b] 1-ethoxy-9-benzyladenine hydrobromide dihydrate (II: $R=C_2H_5$; $R'=C_6H_5CH_2$; X=Br), m.p. *ca.* 130°(decomp.),*1 picrate, m.p. 212°(decomp.).[2b] Similar reaction of 1-methoxyadenine (I: $R=CH_3$) with benzyl bromide gave, after treatment with sodium iodide, 1-methoxy-9-benzyladenine hydriodide (II: $R=CH_3$; $R'=C_6H_5CH_2$; X=I) of m.p. 213~215°[2b] in 61% yield.

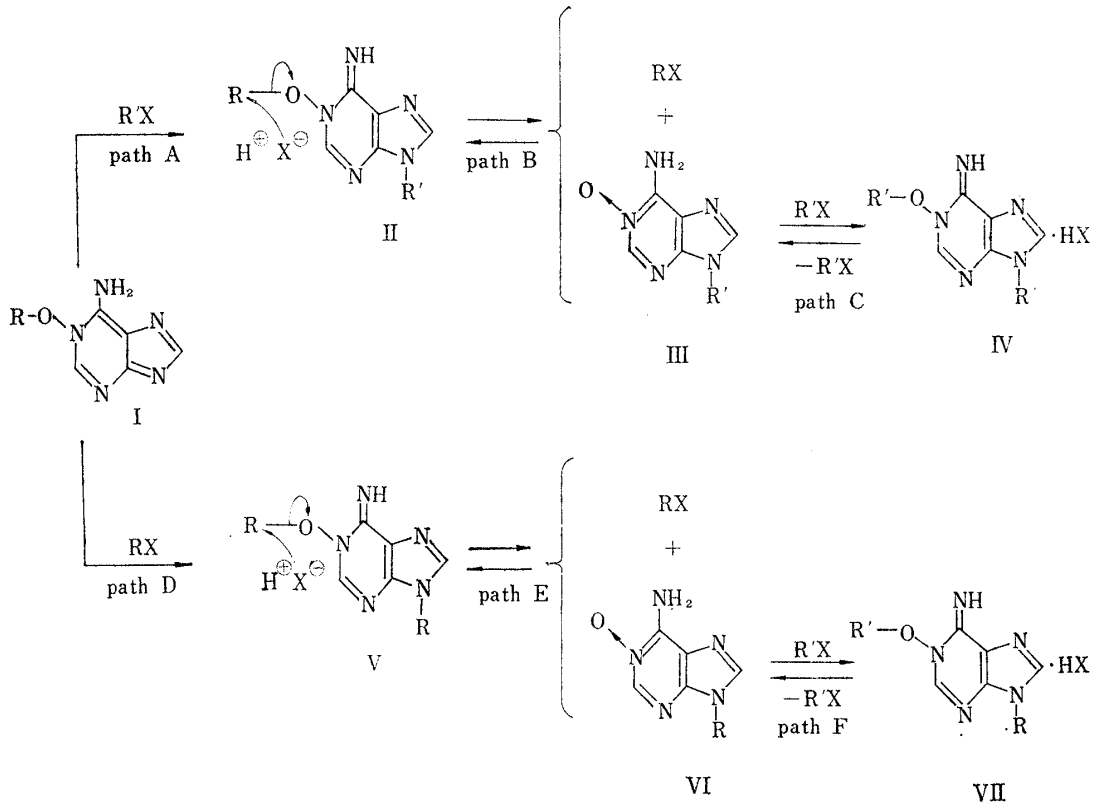


Chart 1.

*1 Elemental analytical data in good accord with theory were obtained for this substance.

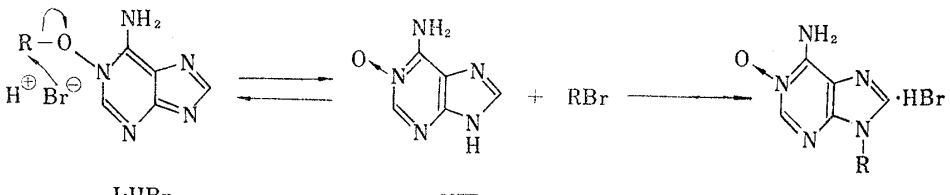
1) G. P. Wheeler : Cancer Research, **22**, 651 (1962).
2) *a*) T. Fujii, T. Itaya, S. Yamada : This Bulletin, **13**, 1017 (1965); *b*) T. Fujii, C. C. Wu, T. Itaya, S. Yamada : Chem. & Ind. (London), **1966**, 1598.

On the other hand, alkylation of I with the alkyl halides (R'X) less reactive than those (RX) whose alkyl groups were same as in I resulted in the formation of a mixture of at most four possible 1-alkoxy-9-alkyladenine salts (II, IV, V, and VII), two 9-alkyladenine 1-oxides (III and VI), and RX. Thus, treatment of 1-benzyloxyadenine (I: R=$C_6H_5CH_2$) with an excess of ethyl iodide in N,N-dimethylacetamide at room temperature gave a mixture, in which the presence of seven products, namely, 1-benzyloxy-9-ethyladenine hydriodide (II: R=$C_6H_5CH_2$; R'=C_2H_5; X=I), 9-ethyladenine 1-oxide (III: R'=C_2H_5), 1-ethoxy-9-ethyladenine hydriodide (IV: R'=C_2H_5; X=I), 1-benzyloxy-9-benzyladenine hydriodide (V: R=$C_6H_5CH_2$; X=I), 9-benzyladenine 1-oxide (VI: R=$C_6H_5CH_2$), 1-ethoxy-9-benzyladenine hydriodide (VII: R'=C_2H_5; R=$C_6H_5CH_2$; X=I), and benzyl iodide, was indicated by paper chromatographical comparison with the known samples.[2] The displacement of the benzyl group from the oxygen atom of I (R=$C_6H_5CH_2$) and migration to the 9-position were evidenced by isolation (15% yield) of 1-ethoxy-9-ethyladenine hydriodide[2a] from the reaction mixture and by hydrogenolysis, using hydrogen and Raney nickel, of the mixture after converted to the corresponding free bases, which led to the formation of 9-benzyladenine and 9-ethyladenine. Ethylation of 1-methoxyadenine (I: R=CH_3) with ethyl iodide under similar reaction condition was also found to involve the migration of the methyl group from the oxygen to nitrogen atom at the 9-position.

The complicated pattern of the reaction products described above could be understood, as illustrated in Chart 1, by slow reaction of I with less reactive R'X (path A) to form the normally alkylated product (II), which undergoes nucleophilic attack by $X^{\ominus}$ at the α-carbon of the alkoxy group, analogous to that of 1-alkoxypyridinium salts,[3] to give an equilibrated mixture with RX and III (path B). The N-oxide (III) thus formed would further react with the excess of R'X to provide IV (path C)[2b] and the more reactive RX produced by path B should alkylate, competitively with R'X, the unaltered I to give V (path D), which is further converted to VI and VII through paths E and F similar to paths B and C.

In the case of reaction of 1-benzyloxyadenine (I: R=$C_6H_5CH_2$) with methyl iodide, the products detected were only four, namely, 1-benzyloxy-9-methyladenine hydriodide (II: R=$C_6H_5CH_2$; R'=CH_3; X=I), 9-methyladenine 1-oxide (III: R'=CH_3), 1-methoxy-9-methyladenine hydriodide (IV: R'=CH_3; X=I), and benzyl iodide. The absence of the 9-benzylated products in the reaction mixture is probably due to the fast 9-methylation in path A to have consumed I (R=$C_6H_5CH_2$) before II (R=$C_6H_5CH_2$; R'=CH_3; X=I) equilibrates with III (R'=CH_3) and benzyl iodide, rendering path D virtually impracticable.

A more evident O→$N_{(9)}$ benzyl migration was demonstrated by the reaction of 1-benzyloxyadenine (I: R=$C_6H_5CH_2$) with 0.1 mole equivalent of benzyl bromide in



I·HBr VIII VI·HBr

(R=$C_6H_5CH_2$)

Chart 2.

3) For recent reviews, see *a*) T. Okamoto: Yūki Gōsei Kagaku, **19**, 790 (1961); *b*) R. Eisenthal, A.R. Katritzky: Tetrahedron, **21**, 2205 (1965); *c*) S. Takahashi, H. Kanō: This Bulletin, **14**, 375 (1966).

N,N-dimethylacetamide at 60~70° for 58 hr. to give 0.57 mole equivalent of 9-benzyladenine 1-oxide (Ⅵ: R=$C_6H_5CH_2$),*2 and by thermal degradation of 1-benzyloxyadenine hydrobromide (Ⅰ·HBr: R=$C_6H_5CH_2$) in N,N-dimethylacetamide at 90~100° leading to the formation of 9-benzyladenine 1-oxide (Ⅵ: R=$C_6H_5CH_2$)[2] (22% yield) and adenine 1-oxide (Ⅷ)[4] (35% yield). In the postulated mechanism for the latter reaction as indicated in Chart 2, the α-carbon of the benzyloxy group in Ⅰ·HBr (R=$C_6H_5CH_2$) would undergo nucleophilic attack by $Br^{\ominus}$ to give a mixture of Ⅷ and benzyl bromide, which provides thermodynamically stable Ⅵ·HBr (R=$C_6H_5CH_2$).*3

The O→$N_{(9)}$ alkyl migration described above has been suggestive of the use of the 1-alkoxyadenine derivatives as possible alkylating reagents. Thus, treatment of 1-benzyloxy-9-benzyladenine hydrobromide (Ⅴ: R=$C_6H_5CH_2$; X=Br)[2] with boiling ethanol gave both benzyl ethyl ether and 9-benzyladenine 1-oxide hydrobromide (Ⅵ·HBr: R=$C_6H_5CH_2$)[2a] in good yields.*4 Similarly, 1-methoxy-9-benzyladenine hydriodide (Ⅱ: R=CH_3; R′=$C_6H_5CH_2$; X=I)[2b] afforded benzyl methyl ether when treated with hot benzyl alcohol.

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*2 For a mechanism of this reaction, paths D and E where the RX formed recycles would be postulated. A similar use of a catalytic amount of methyl iodide in the synthesis of 1-methyl-4-pyridone from 4-methoxypyridine has been reported.[5]

*3 Such a dissociation-recombination mechanism of the benzyl group would be closely related to the recently reported benzyl (or allyl or glycosyl) migrations of 1,3-dibenzylhypoxanthine bromide to both 7- and 9-positions[6] and of N-acyl-3-benzyl (or allyl or 3-methyl-2-butenyl or glycosyl)adenine hydrobromides to the 9-position.[7]

*4 An analogous reaction of 1-benzyloxypyridinium bromide with ethanol has been reported recently.[8]

4) *a*) M. A. Stevens, D. I. Magrath, H. W. Smith, G. B. Brown : J. Am. Chem. Soc., **80**, 2755 (1958); *b*) M. A. Stevens, G. B. Brown : *Ibid.*, **80**, 2759 (1958).
5) *a*) P. Beak, J. Bonham : Tetrahedron Letters, **1964**, 3083; *b*) *Idem* : J. Am. Chem. Soc., **87**, 3365 (1965).
6) J. A. Montgomery, H. J. Thomas, K. Hewson : Chem. & Ind. (London), **1965**, 1596.
7) *a*) B. Shimizu, M. Miyaki : Tetrahedron Letters, **1965**, 2059; *b*) M. Miyaki, K. Iwase, B. Shimizu : This Bulletin, **14**, 87 (1966); *c*) B. Shimizu, M. Miyaki : Chem. & Ind. (London), **1966**, 664.
8) R. M. Titkova, V. A. Mikhalev : Zhur. Obshcheĭ Khim., **34**, 4126 (1964) (C.A., **62**, 9098 (1965)).