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THE REACTION OF 2',3',5'-TRI-O-ACYL-6-AZAURIDINES WITH DIMETHYLCHLOROMETHYLENEAMMONIUM CHLORIDE A SYNTHESIS OF 6-AZACYTIDINE

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DIMETHYLCHLOROMETHYLENEAMMONIUM chloride (II), readily available by reaction of phosgene or thionyl chloride with dimethylformamide,[1,2] is a highly reactive compound which has proved a versatile reagent in many fields of organic synthesis.[3-8] The recently developed method for the preparation of acid chlorides by treatment of carboxylic acids or their salts with inorganic acid halides in the presence of catalytic amounts of dimethylformamide[2] gives an interesting illustration of the action of (II) as a chlorinating reagent. This property of dimethylchloromethyleneammonium chloride (II) has also been exploited in the preparation of chlorinated derivatives of 1,3,5-triazine and of quinazoline.[8]

We have now found that compound (II) will also react with a number of

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1 Z. Arnold, Coll. Czech. Chem. Comm. 24, 4048 (1959).

2 H.H. Bosshard, R. Mory, M. Schmid and H. Zollinger, Helv. Chim. Acta 42, 1653 (1959).

3 Z. Arnold and F. Šorm, Coll. Czech. Chem. Comm. 23, 452 (1958).

4 M. Zaoral and Z. Arnold, Tetrahedron Letters No. 14, 9 (1960).

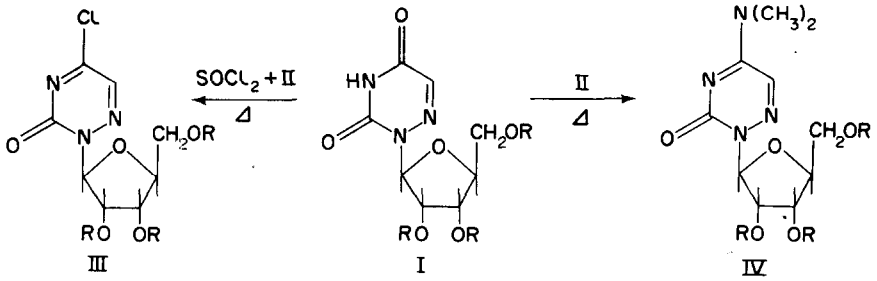
5 Z. Arnold, Coll. Czech. Chem. Comm. 26, 1723 (1961).

6 K. Morita, S. Noguchi and M. Nishikawa, Chem. Pharm. Bull. 7, 896 (1959).

7 J. Žemlička and Z. Arnold, Coll. Czech. Chem. Comm. 26, 2838 (1961).

8 H. Eilingsfeld, M. Seefelder and H. Weidinger, Angew. Chem. 72, 836 (1960).

further heterocyclic systems containing the grouping -CO.NH-, for instance with nucleosides in which the sugar moiety has been acylated to protect it against the formylating action[5,6,9] of dimethylchloromethyleneammonium chloride (II). In the case of 2',3',5'-tri-O-benzoyl-6-azauridine[10] (I) we have been able to direct reaction with the compound II along two distinct courses. Reaction of (I) with less than one equivalent of (II) - by treatment with thionyl chloride in boiling chloroform in the presence of a catalytic amount of dimethylformamide - readily gives a practically quantitative yield of the chloro derivative III, m.p. 149.5°-151.5° (Found: C, 60.70; H, 3.77; Cl, 5.90; N, 7.42. Calc.: C, 60.47; H, 3.85; Cl, 6.16; N, 7.30). On the other hand, treatment of the tribenzoyl derivative (I) with more than one equivalent of the reagent (II) in boiling chloroform leads to an interesting reaction resulting in a high yield of the dimethylamino derivative (IV), m.p. 177°-179°, undepressed on admixture of the product obtained by the action of dimethylamine on the chloro compound III (Found: C, 63.43; H, 4.77; N, 9.56; Calc.: C, 63.69; H, 4.82; N, 9.58).



9 J. Zemlicka, J. Beranek and J. Smrt, Coll. Czech. Chem. Comm. in press.

10 V. Cerneckij, S. Chladek, F. Sorm and J. Smrt, Coll. Czech. Chem. Comm. 26, 87 (1962).

The chlorine in (III) is very reactive. Thus the compound reacts with ammonia at low temperature to give a practically quantitative yield of 2',3',5'-tri-O-benzoyl-6-azacytidine, m.p. 218° (Found: C, 62.77; H, 4.51; N, 10.07. Calc.: C, 62.58; H, 4.35; N, 10.07). Removal of the benzoyl groups afforded 6-azacytidine, m.p. 222°-224° (decomp.), undepressed on admixture of an authentic sample.[10] This procedure offers considerable advantages over the current method[10-12] for the preparation of 4-amino derivatives of the pyrimidine nucleosides through the corresponding thio compounds.

The reaction of dimethylchloromethyleneammonium chloride (II) with further heterocyclic systems is being examined, as is the detailed course of the reaction and the possibility of using the products in other syntheses.

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[11] J.J. Fox, D. van Praag, I. Wempen, I.L. Doerr, L. Cheong, J.E. Knoll, M.L. Eidinoff, A. Bendich and G.B. Brown, J. Amer. Chem. Soc. 81, 178 (1959).

[12] I. Wempen, R. Duschinsky, L. Kaplan and J.J. Fox, J. Amer. Chem. Soc. 83, 4755 (1961).