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TRANSFORMATION OF NUCLEOSIDES INTO THEIR 5′-DEOXY DERIVATIVES

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Dimethylformamide acetals (I) have been widely used in nucleoside[1-3] and nucleotide chemistry[3,4] as alkylating agents of the acidic amide group of heterocyclic bases. Their ability to esterify carboxylic acids[5] and phosphoric acid monoesters[4,6] and to alkylate phenols[7] has been also demonstrated. Compounds I react with various heterocyclic mercapto derivatives in boiling benzene or acetonitrile giving rise to the corresponding alkylthio derivatives in excellent yields :

$$(CH_3)_2N\text{-}CH(OR)_2 + R'\text{-}SH \longrightarrow R'\text{-}SR + ROH + (CH_3)_2N\text{-}CH{=}O$$

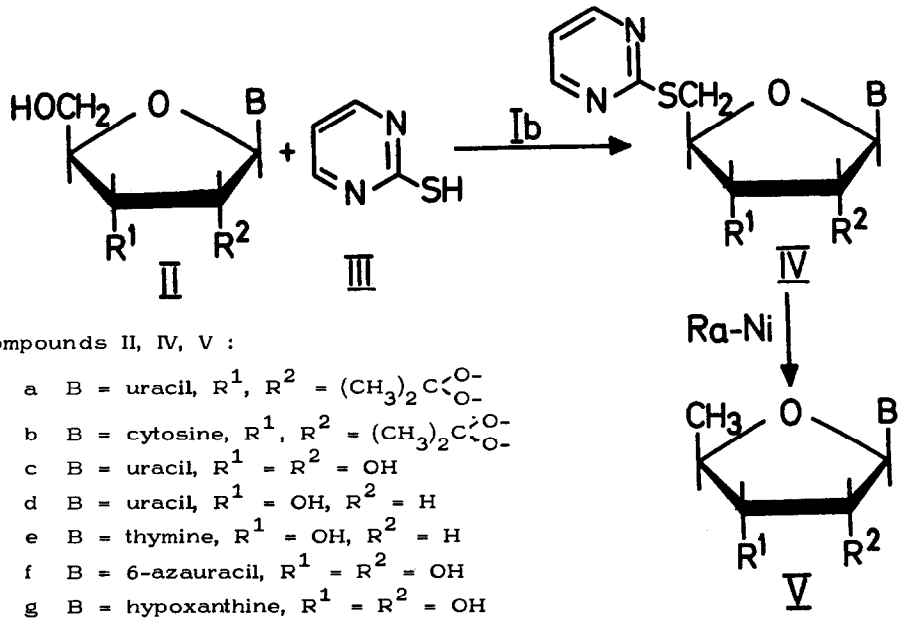
Ia R = methyl; Ib R = neopentyl

Thus, 2-mercaptopyrimidine (5 mmol) and dimethylformamide dimethylacetal (Ia) (cf.[8]) in benzene (20 ml) were refluxed for 1 hour, the mixture evaporated and distilled under diminished pressure to yield 2-methylthiopyrimidine (86%), b.p. 96°C/13 Torr. Similarly, 4-mercaptopyrimidine afforded the 4-methylthio derivative (76%), b.p. 115°C/13 Torr and 2-mercaptobenzoxazole gave the 2-methylthio derivative (82%), b.p. 90°C/0.05 Torr. The reaction of 2-thiouracil with Ia in boiling acetonitrile resulted in 2-methylthio--3-methyluracil (isolated by silica chromatography and crystallization from ethanol) in 70% yield, m.p. 121-122°C. 6-Mercaptopurine gives 6-methylthio-9-methylpurine, m.p. 201°C in 57% yield. (The two last mentioned examples include an additional methylation of the NH-group.)

Dimethylformamide ethyleneacetal (2-dimethylamino-1,3-dioxolane, I, R = $-CH_2CH_2-$, cf.[3]) reacts with 2-mercaptopyrimidine on prolonged heating in benzene to give 2-(2-hydroxyethylthio)pyrimidine, b.p. 145°C/0.05 Torr, in 60% yield.

Dimethylformamide dineopentylacetal (Ib) cannot alkylate the mercapto derivatives, in agreement with its failure to alkylate acidic amides[2] or to esterify carboxylic acids[5]. Its autocatalyzed "reacetalisation" by other alcohols, however, affords intermediates capable of the alkylation reactions mentioned. This principle was used for esterification of sterically hindered carboxylic acids or, for the synthesis of some amino acid esters[5]; similarly, the heating of xanthosine with Ib led to an intramolecular alkylation of the heterocyclic amide group by the sugar alkyl group originating from the C^4-hydroxymethyl group, under the formation of N^3,5′-anhydro derivative[9]. This principle together with the high affinity of 2-mercaptopyrimidine to the alkylation process mentioned can be used for transformation of the primary hydroxylic group of nucleoside sugar moieties to nucleoside

5′-(pyrimidin-2-yl-thio)-5′-deoxy derivatives. The reaction proceeds on brief refluxing the mixture of nucleoside (II) with small excess 2-mercaptopyrimidine (III) and acetal Ib in acetonitrile or other solvents (benzene, dimethylformamide). Compounds IV usually can be obtained from the reaction mixture by crystallization or, silica thin-layer chromatography :



In compounds II, IV, V :

a B = uracil, R^1, R^2 = $(CH_3)_2C$<O-, O-
b B = cytosine, R^1, R^2 = $(CH_3)_2C$<O-, O-
c B = uracil, R^1 = R^2 = OH
d B = uracil, R^1 = OH, R^2 = H
e B = thymine, R^1 = OH, R^2 = H
f B = 6-azauracil, R^1 = R^2 = OH
g B = hypoxanthine, R^1 = R^2 = OH

Thus, a mixture of 2′,3′-O-isopropylideneuridine (IIa) (2 mmol), 2-mercaptopyrimidine (III, 4 mmol) and Ib (2 ml) in benzene (20 ml) was refluxed under exclusion of moisture till the thin-layer chromatography (silica, ethanol-chloroform, 5:95) revealed a complete reaction. The mixture was evaporated in vacuo and compound IVa isolated on a loose layer of silica in the same system (the product was extracted with methanol). Yield, 0.55 g (73%), white foam. $C_{16}H_{18}N_4O_5S$ (378.4) calc. 50.78% C, 4.79% H, 14.81% N, 8.47% S; found 50.80% C, 4.49% H, 15.06% N, 8.38% S. UV-Spectrum (methanol) : λ_{max} 253 nm, λ_{min} 232 nm. NMR-Spectrum ($CDCl_3$, HMDS as internal standard) : 3.60 ppm (d, 2H) (-S-CH_2-), $J_{5',4'}$ = 6.0; 4.48 ppm (2 x t, 1 H) (C_4′-H), $J_{4',5'}$ = 6.0, $J_{4',3'}$ = 3.6; 6.98 ppm (d, 1 H) (pyrimidine C_5-H), $J_{vic-cis}$ = 5; 8.52 ppm (d, 2H) (pyrimidine C_4-H), C_6-H, $J_{vic-cis}$ = 5; other signals as for IIa. Similarly, compound IVb was prepared from IIb in 65% yield, as yellow foam (in this and other cases of compounds II containing amino groups on heterocyclic nuclei, the mixture prior to purifying by chromatography was treated with 10% triethylamine in 50% ethanol to decompose the N-dimethylaminomethylene derivatives of IV).

On treatment of 5′-O-trityl-2′-deoxythymidine with compounds III and Ib no appreciable reaction was observed, even when prolonged. Therefore, the reaction with Ib seems to take place on primary hydroxylic groups of the sugar moiety only. Consequently, unprotected nucleosides can be used for the above transformation to afford selectively the

5′-substituted derivatives IV. Thus, uridine (IIc) (8 mmol), III (10 mmol) and Ib (5 ml) in acetonitrile (40 ml) were refluxed 6 hours. After evaporation in vacuo, the residue was co-evaporated with 50% ethanol and crystallized from ethanol to yield 1.1 g (41%) pure IVc, m.p. 176°C. Another crop was obtained from the mother liquor by chromatography on silica loose layer in ethanol-chloroform (2:8). The overall-yield was 62%. $C_{13}H_{14}N_4O_5S$ (338.3), calc. 46.17% C, 4.17% H, 16.57% N, 9.48% S; found 46.04% C, 4.37% H, 16.79% N, 9.55% S. NMR-Spectrum (see above): 3.63 ppm (d, 2H) (-S-CH_2-) $J_{5',4'}$ = 5.0; 7.02 ppm (t, 1H) (pyrimidine C_5-H) J = 5; 8.53 ppm (d, 2H) (pyrimidine C_4-H, C_6-H J = 5, other signals as for IIc. 2′-Deoxyuridine (IId) was treated with compounds III and Ib under the above conditions to give, on direct crystallisation of the residue 72% of analytically pure IVd, m.p. 142°C. Analogously, 2′-deoxythymidine derivative IVe was obtained in 85% yield on a 25 mmol scale. M.p. 187°C. Finally, 6-azauridine (IIIf) afforded compound IVf in 62% yield (in this case, the work-up was effected by silica column chromatography and elution with ethanol-chloroform mixture, 1:9). Noncrystalline yellow foam, analytically pure. As a rule, the presence of 5′-(pyrimidin-2-yl-thio) group does not significantly influence the properties of the heterocyclic base, as demonstrated with compound IV possesing the same electrophoretic mobility as IIf.

In bacteriostatic activity assays of compounds IV with E. coli B in a synthetic medium with glucose, none of the test substances was found to be active up to 1 mg/ml (this estimation was performed by Mr. I. Votruba of This Institute).

Compounds IV are sufficiently stable even in strongly alkaline or acidic solutions. Thus, on boiling in 0.5 M sodium hydroxide, 50% IVa was recovered after 3 hours. In 1 N hydrochloric acid, 50% of IVe did not change after 1 hours at boiling temperature. The attempted acidic or alkaline hydrolysis of compounds IV were so far unsuccessful, leading rather to degradation of the nucleoside than to hydrolysis of the pyrimidine-S-linkage.

On the other hand, the treatment of compounds IV with Raney-Ni (W 4) in ethanol affords 5′-deoxynucleosides V as the sole products. As a general procedure, compound IV (2 mmol) was refluxed with 2-3 g of the catalyst in 100 ml ethanol for 30 min. After filtration through Celite and washing with hot ethanol (100 ml), the filtrate was evaporated to dryness in vacuo and the residue purified (removal of traces of salts) on a loose silica layer in chloroform-ethanol. On eluting with methanol and evaporation the residue of V was crystallized from ethanol. In this way, 5′-deoxyuridine (Vc) m.p. 177°C was obtained in 60% yield. $C_9H_{12}N_2O_5$ (228.2), calc. 47.36% C, 5.30% H, 12.28% N; found 47.51% C, 5.35% H, 12.02% N. Similarly, 2′,3′-O-isopropylidene derivative Va was isolated in 70% yield; white, non-crystalline foam. $C_{12}H_{16}N_2O_5$ (268.3), calc. 53.72% C, 6.01% H, 10.44% N; found: 54.01% C, 6.29% H, 10.36% N. 2′,5′-Dideoxyuridine (Vd) was obtained from IVd in 48% yield, m.p. 157°C (ethanol); $C_9H_{12}N_2O_4$ (212.2), calc. 50.94% C, 5.70% H, 13.20% N; found 50.78% C, 5.72% H, 13.21% N. Compound IVe gave 2′,5′-dideoxythymidine (Ve) in 70% yield; m.p. 193°C; $C_{10}H_{14}N_2O_4$ (226.2), calc. 53.09% C, 6.19% H, 12.38% N; found 53.38% C, 6.30% H, 12.07% N. In addition to analytical data, the structure of compounds V was confirmed by mass-spectra revealing the corresponding

molecular peaks and characteristic molecular fragments and, moreover, by their NMR-spectra which, in addition to the typical signals of the parent nucleoside contained characteristic doublet of the C_4'-methyl group at 1.30 - 1.40 ppm ($J_{4',5'}$ = 6.5 Hz). At the same time, the signals corresponding to the C_4'-hydroxymethyl group disappeared.

The method described above represents a useful synthetic tool for the conversion of primary hydroxylic group into a substituted thio derivative and then to the corresponding deoxy derivative. In nucleoside chemistry, this procedure is comparable with the older one, using 5'-deoxy-5'-iodo derivatives as intermediates. In comparison with the latter, the present method does not require any specific protecting of the polyfunctional molecule, taking place on primary hydroxylic functions selectively. The intermediates IV may serve as starting materials for other interesting nucleoside derivatives, such as the corresponding sulfones or nucleoside 5'-deoxy-5'-sulfonic acids. This topics will be described elsewhere. Furthermore, the reaction is not limited to nucleoside chemistry. Its principle may prove useful in other fields, such as amino acid derivatives[10] and related compounds.

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