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MODIFICATION OF GUANINE BASES : REACTION OF GUANINE NUCLEOSIDES WITH ARYL AND CHLOROSULFONYL ISOCYANATES

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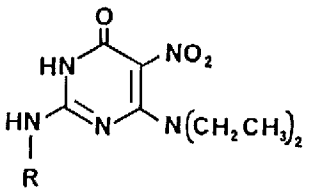
Summary : Aryl and chlorosulfonyl isocyanates react with suitably protected guanine nucleosides to afford the corresponding triazinoannelated nucleosides.

In a recent publication (1), N.J. Leonard et al. have described the use of chlorocarbonyl isocyanate to add an unsaturated six-membered ring onto the purine and pyrimidine residues of various nucleosides. Thus, suitably protected cytidine, adenosine, and guanosine afforded new 2,4-dioxo-1,3,5-triazinyl-substituted ribonucleosides. Their report prompts us to disclose now our results concerning the reactions of aryl and chlorosulfonyl isocyanates with various guanine derivatives, which provide a convenient route to the triazino ring systems 6 and 10.

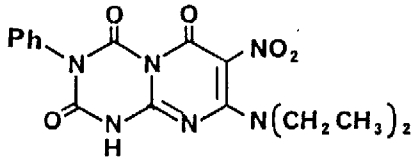
The reaction of aryl isocyanates with the amino-oxo-pyrimidine 1, a convenient and easily accessible model for the pyrimidine ring of guanine, was first explored. Treatment of 1 with an excess of phenyl isocyanate in acetonitrile in the presence of triethylamine yielded the pyrimidinotriazine 4 (2). The N-acyl derivatives 2 and 3 under the identical reaction conditions also provided 4. Adduct 4 is quite sensitive to nucleophilic reagents. Warming 4 in methanol resulted in the opening of the dioxo-triazinyl ring to yield the crystalline ureido derivative 5, the structure of which was determined by X-ray crystallography (3)(which serves, by extension, to confirm the structure of 4). An identical reaction sequence was observed on using p-tolyl isocyanate as the reagent.

The reaction of guanine nucleosides with aryl isocyanates has also been examined under similar reaction conditions. The hydroxyl groups in deoxyguanosine were first protected by silyl derivatisation (4). The resulting t-butyldimethylsilyl derivative afforded the tricyclic nucleoside 6 after treatment with excess phenyl isocyanate in acetonitrile in the presence of triethylamine. The structure of 6 could be unambiguously assigned by comparison of its spectroscopic data with that of the model 4. Removal of the silyl protecting groups was accomplished by using HF in pyridine (5) to give 7 (6). Again, the dioxotriazino ring



Ph NCO

NEt_3/CH_3CN



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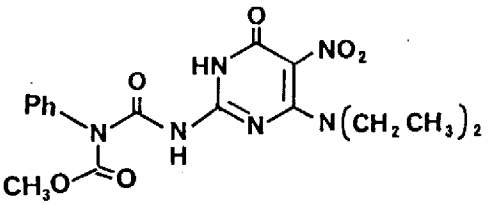
MeOH

1 R = H

2 R = $COCH_3$

3 R = $COPhOCH_3$(para)



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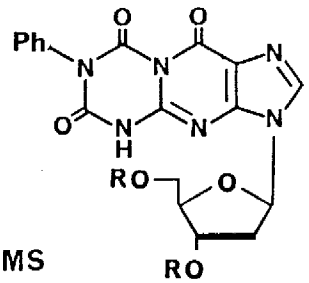
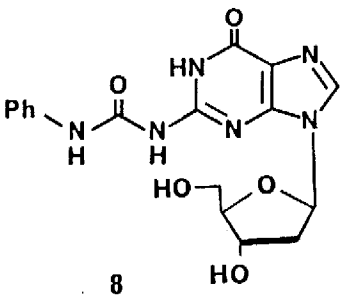


6 R = TBDMS

7 R = H



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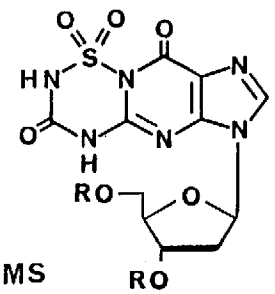
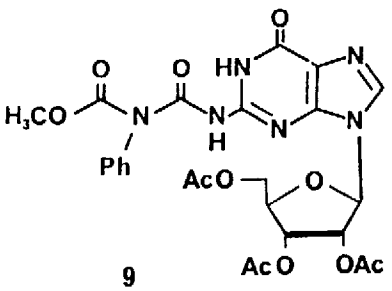


10 R = TBDMS



9

proved labile. Ring opening of 7 to give the ureido compound 8 was observed after only 5 min in the present of dilute sodium hydroxide at room temperature. In a comparable sequence of reactions, tetra-acetyl guanosine (7) added phenyl isocyanate to yield an adduct, which opened in the presence of methanol during column chromatographic purification (8) to afford the nucleoside 9.

The study of isocyanates in this type of reaction was extended to the more reactive chlorosulfonyl isocyanate (9). An instantaneous reaction was observed at 0°C on addition of this isocyanate to the silyl-protected deoxyguanosine in the presence of triethylamine. The thiatriazinopurine nucleoside 10 could be isolated in 41 % yield after chromatographic purification on silica gel (10).

The reactions of the guanine bases with isocyanates as described herein provide a new series of guanine nucleoside analogues. These results are fully consistent with those found by N.J. Leonard et al. (1). In addition, the isocyanate adducts may be regarded as potential N-O bifunctional protective groups for guanine nucleosides. In preliminary experiments we have found that the phenyl isocyanate adduct 7 is quantitatively transformed to deoxyguanosine by treatment with 0.1 M sodium hydroxide at 90°C for 24 h. Studies are in progress to extend these reactions to other nucleosides.

References and Notes

(1) S. Kumar and N.J. Leonard, J. Org. Chem. 1988, 53, 3959.

(2) 1,2,3,4-Tetrahydro-2,4,6-trioxo-3-phenyl-7-nitro-8-diethylamino-6H-pyrimidol,2-a-triazine (4): mp: 195-197°C; ^{1}HNMR (DMSOd$_6$)δ: 12.70 (s,1H), 7.45-7.25 (m,5H), 3.41 (q,4H, = 7.0 Hz), 1.12 (t,6H, J = 7.0 Hz); ^{13}CNMR (DMSOd$_6$)δ: 152.7, 150.5, 145.8, 143.3, 142.5, 132.2, 127.0, 126.8, 111.7, 42.1, 10.9; MS: 371 $(M-H)^-$, 252; IR (KBr): 3060, 2960, 1800, 1780, 1730, 1700, 1620, 1580, 1490, 1390, 1320, 1280, 770 cm^{-1}; UV (ethanol): 362 (4190), 265 (20400), 243 (19300) nm; $C_{16}H_{16}N_6O_5$: Calcd.: C, 51.61; H, 4.33; N, 22.57; O, 21.48. Found: C, 51.39; H, 4.43; N, 22.06; O, 21.71.

(3) 2-(N'-methoxycarbonyl-N'-phenylureido)-5-nitro-6-diethylamino-4-pyrimidinone-3H (5):mp: 208-210°C; ^{1}HNMR (DMSOd$_6$)δ: 11.35 (s,1H), 11.15 (s,1H), 7.42-7.29 (m,5H), 3.66 (s,3H), 3.34 (q,4H, J = 7.2 Hz), 1.09 (t,6H, J = 7.2 Hz); ^{13}CNMR (DMSOd$_6$)δ: 155.6, 155.1, 154.9, 151.8, 147.0, 136.0, 128.9, 128.6, 128.5, 114.9, 54.8, 44.0, 12.7; MS: $(M-H)^-$: 403 $(M+H)^+$, 405; IR (KBr): 3100, 2950, 1250, 1120, 1100, 960, 770, 720, 690 cm^{-1}; UV (methanol): 368 (3550), 286 (8940); $C_{17}H_{20}N_6O_6$: Calcd.: C, 50.49; H, 4.98; N, 20.78; O, 23.74. Found: C, 50.25; H, 5.01; N, 21.15; O, 24.31.
Crystals for X-ray analysis could be obtained from methanol solution and by vapor diffusion at 4°C. The crystals were monoclinic; space group P2 a = 9.072 (2), b = 28.877 (8), c = 7.450 (7); ß = 100.82 (5); $\bar{\lambda}$ = 1,54178 A; Z = 4; R = 0,086 for 1192 observed reflexions. The structure was solved by direct methods (MITHRIL, Gilmore 1984).

(4) K.K. Ogilvie, Can. J. Chem. 1973, 51, 3799.

(5) R.E. Ireland and M.D. Varney, J. Org. Chem. 1986, 51, 635.

(6) 3,5,6,7,8,10-Hexahydro-6,8,10-trioxo-3-2-deoxy-ß-D-ribofuranosyl-7-phenyl-(1,3,5- triazino) [1,2-a] purine (7): mp: > 260°C; ^{1}HNMR (DMSOd$_6$)δ: 12.45 (s,1H), 7.50-7.30 (m,5H), 6.15 (t,1H), 5.15 (s,1H), 4.75 (s,1H), 4.36 (m,1H), 3.80 (m,1H), 3.50 (m,2H), 2.55 (m,1H), 2.25 (m,1H), 0.5 DMF: 7.89, 2.83, 2.67; MS: 413 $(M+H)^+$; IR (KBr): 3400, 2940, 1780, 1720, 1650, 1560, 1420, 1050, 780 cm^{-1}; UV (methanol): 261 (11600) nm; $C_{18}H_{16}N_6O_6$, 0.5 DMF, 0.5 H_2O: Calcd.: C, 51.15; H, 4.51; N, 19.88. Found : C, 51.08; H, 4.55; N, 19.62.

(7) C.B. Reese and R. Saffhill, J. Chem. Soc. Chem. Commun. 1972, 2937.

(8) 1,6-Dihydro-2-(N'-methoxycarbonyl-N'-phenylureido)-6-oxo-9-(2,3,5-tri-O-acetyl-ß-D- ribofuranosyl)-9H purine (9): Oil; ^{1}HNMR (DMSOd$_6$)δ: 11.50 (s,2H), 8.20 (s,1H), 7.40-7.31 (m,5H), 6.06 (d,1H), 5.79 (t,1H), 5.50 (m,1H), 4.33 (m,3H), 3.67 (s,3H), 2.07 (s,3H), 2.00 (s,3H), 1.98 (s,3H); ^{13}CNHR (DMSOd$_6$)δ: 167.9, 167.3, 167.1, 154.5, 151.9, 151.8, 149.0, 137.0, 133.5, 126.6, 120.2, 116.1, 114.8, 82.3, 77.5, 70.0, 68.2, 61.0, 49.5, 18.5, 18.3, 18.1; MS: 609 $(M+Na)^+$, 587 $(M+H)^+$.

(9) (a) A.R. Katrizky, K.C. Caster, T.H. Maren, C.W. Conroy and A.B. Ilan, J. Med. Chem. 1987, 30, 2058.
(b) D.N. Dhar and K.S.K. Murthy, Synthesis, 1986, 437.

(10) : 1,1,3,9-Tetraoxo-2,3,4,6-tetrahydro-6-2-deoxy-3,5-Di-O-(tert-butyldimethylsilyl)-ß- D-ribofuranosyl-9H-(1,2,4,6-thiatriazino)[1,2-a]purine (10): mp:>260°C; ^{1}HNMR (DMSOd$_6$)δ: 10.40 (s,1H), 8.00 (s,1H), 6.15 (t,1H), 4.50 (m,1H), 3.80 (m,1H), 3.70 (m,2H), 2.75 (m,1H), 2.25 (m,1H), 0.90 (s,18H), 0.01 (s,6H), 0.00 (s,6H); MS: 599 $(M-H)^-$; IR (KBr): 3480, 2930, 1690, 1640, 1560, 1330, 1200, 1120, 1090, 840, 780 cm^{-1}; UV (methanol): 287 (7400) nm.

(11) : Satisfactory microanalyfical, UV, FAB MS, and ^{1}H and ^{13}CNMR data have been obtained for all new compounds.

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