Protection of Alcoholic Hydroxy Groups as Crotonate and Related Esters

By RENÉ ARENTZEN and COLIN B. REESE*
(*Department of Chemistry, King's College, Strand, London* WC2R 2LS)

Summary The thymidine 5′-esters (**2a**—**e**) have been prepared; the acrylyl, crotonyl, 4-methoxycrotonyl, and 4-phenoxycrotonyl derivatives (**2a**, **2b**, **2c**, and **2d**, respectively), unlike the cinnamoyl derivative (**2e**), are readily deacylated by treatment with dilute hydrazine in methanol–pyridine.

THE protection of alcoholic hydroxy groups as esters is a widely used procedure[1] especially in carbohydrate (including nucleoside) and steroid chemistry. Acetyl and benzoyl protecting groups, which may be removed by alkaline hydrolysis or ammonolysis, have been used most frequently for this purpose. However, ester protecting groups which may be removed under milder basic or even under neutral conditions are also of considerable value. For example, we have found the base-sensitive methoxy- and aryloxyacetyl groups[2] to be useful in nucleoside and nucleotide chemistry and other workers have reported the use of the 2,2,2-tribromoethoxycarbonyl[3] and 3-benzoylpropionyl[4] protecting groups which may, respectively, be removed by reduction (Zn–Cu couple) and by treatment with hydrazine. More recently, the use of the laevulinyl group, which may be removed either by treatment with sodium borohydride in aqueous dioxan[5] or with hydrazine in pyridine–acetic acid,[6] has been proposed.

We now report that crotonate and other substituted acrylate esters may also be deacylated by treatment with

hydrazine under mild conditions. Treatment of 3′-*O*-methoxytetrahydropyranylthymidine[7] (**1b**) with the appropriate acid anhydride,† followed by acidic hydrolysis of the products, gave 5′-*O*-acrylyl-, 5′-*O*-crotonyl-, 5′-*O*-(4-methoxy)crotonyl-, and 5′-*O*-(4-phenoxy)crotonyl-thymidines (**2a**, **2b**, **2c**, and **2d**, respectively) as crystalline compounds‡ in high yields except in the case of the previously reported acrylyl derivative[8] (**2a**) which was isolated in only 61% yield. 5′-*O*-Cinnamoylthymidine (**2e**) was obtained directly, in 59% yield, from unprotected thymidine (**1a**) and cinnamoyl chloride. The approximate half and complete (>98%) reaction times for the deacylation of the latter compounds (**2a**—**e**) with 0·05 M hydrazine hydrate [2·5 mol. equiv. with respect to (**2**)] in methanol–pyridine (4 : 1 v/v) at 20 °C are indicated in the Table.

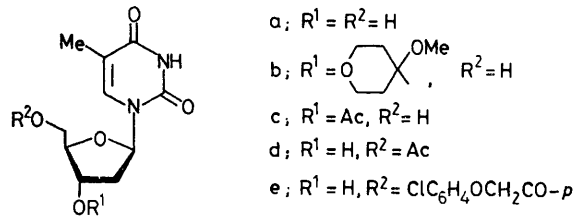
TABLE. Rates of deacylation of thymidine 5′-esters at 20 °C

Compound	Reaction with hydrazine[a] Half-time /h	Complete reaction time[c]/h	Reaction with K_2CO_3[b] Half-time /h	Complete reaction time[c]/h
(**2a**)	*ca.* 0·5[d]	4	4	30
(**2b**)	1·25	10	30	—
(**2c**)	0·3	2	6	45
(**2d**)	0·4	3[e]	8	60
(**2e**)	—[f]	—	45	—
(**1d**)	35	—	3	22
(**1e**)	0·3	3	0·05	0·5

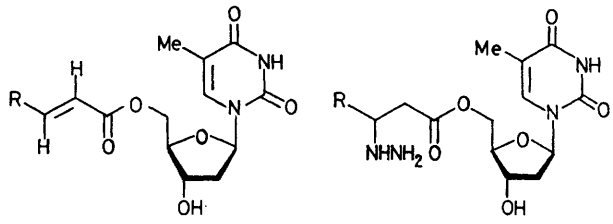
[a] 0·062 M Hydrazine hydrate–absolute methanol (0·4 ml) was added to a solution of substrate (0·01 mmol) in anhydrous pyridine (0·1 ml). [b] 0·5 M Aq. K_2CO_3 (0·1 ml) was added to a solution of substrate (0·01 mmol) in dioxan–water (0·4 ml; 5 : 3 v/v). [c] Reactions were monitored by t.l.c. on silica gel in the solvent system $CHCl_3$–MeOH (85 : 15 v/v). Reactions were deemed to be complete when (**1a**) accounted for >98% of the total nucleoside components. [d] The half-time of the reaction of (**2a**) with hydrazine [to give presumably (**3a**)] was *ca.* 2 min. [e] This is the time for *ca.* 90% conversion of (**2d**) into thymidine. [f] *ca.* 15% conversion of (**2e**) into thymidine occurred in 70 h.

It can be seen that the 4-methoxycrotonyl protecting group may be completely removed from (**2c**) by hydrazine under these mild conditions in 2 h; it is noteworthy that it is even more readily removable than the acrylyl group [Table, compound (**2a**)]. The crotonyl and 4-phenoxycrotonyl protecting groups [Table, compounds (**2b**) and (**2d**), respectively] are also relatively easily removable under the same conditions. However, the cinnamoyl group [compound (**2e**)] is comparatively resistant to attack by hydrazine. Not unexpectedly, 5′-*O*-*p*-chlorophenoxyacetylthymidine[7] (**1e**) undergoes hydrazinolysis much more rapidly than 5′-*O*-acetylthymidine (**1d**).

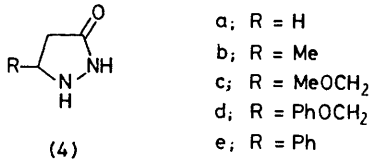
Ethyl cinnamate is reported[9] to react with hydrazine hydrate to give 5-phenylpyrazolidin-3-one (**4e**). We anticipated that the reactions of (**2a**—**e**) with hydrazine would proceed first by addition to give intermediate 3-hydrazinopropionate derivatives (**3a**—**e**) which would then cyclize to give (**1a**) and the corresponding 5-substituted pyrazolidin-3-ones (**4a**—**e**). The reactions between hydrazine and (**2a**—**c**) were investigated by ^1H n.m.r. spectroscopy. The latter compounds (0·10 mmol) were dissolved in [$^2H_5$]pyridine (0·1 ml) and [$^2H_4$]methanol (0·4 ml) and the solutions were treated with hydrazine hydrate (0·015 ml, 0·30 mmol). By monitoring the progress of these reactions by n.m.r. spectroscopy at 25 °C, the approximate half-times



(1)



(2) (3)



(4)

for the disappearance of the protons attached to the sp^2-hybridized carbon atoms of the acyl groups ($t_{\frac{1}{2}}$) and for the release of thymidine ($t_{\frac{1}{2}}'$) were estimated to be as follows: (**2a**), $t_{\frac{1}{2}}$ very short, $t_{\frac{1}{2}}'$ 16 min; (**2b**), $t_{\frac{1}{2}}$ 3, $t_{\frac{1}{2}}'$ 6 min; and (**2c**), $t_{\frac{1}{2}}$ 1, $t_{\frac{1}{2}}'$ 4 min. Thus, in this more concentrated solution [0·2 M with respect to substrate (**2**) and 0·6 M with respect to hydrazine], (**2b**) and (**2c**) were virtually completely converted into (**1a**) in 45 and 30 min, respectively. It thus appears that the addition step is faster than the second step for all three compounds and that this is especially so for (**2a**). It is also interesting to note that the rapidly formed intermediate (**3a**) appears to cyclize less rapidly than either (**3b**) or (**3c**).

The use of the 4-methoxycrotonyl protecting group in synthesis was demonstrated by the conversion of (**2c**) into

† Prepared by treating the corresponding carboxylic acid with 0·5 mol. equiv. of *NN*′-dicyclohexylcarbodi-imide in tetrahydrofuran except for acrylic anhydride which was prepared in benzene. 4-Phenoxycrotonic acid was prepared by a slight modification of the literature procedure (T. Podmanalthan and M. U. S. Sultanbawa, *J. Chem. Soc.*, 1963, 4210) and 4-methoxycrotonic acid was prepared by a superior procedure to that reported previously (L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.*, 1949, 3098; M. U. S. Sultanbawa, P. Veeravagu, and T. Padmanathan, *ibid.*, 1960, 1262). Treatment of thymidine with crotonyl chloride in the presence of 2,6-lutidine gives mainly 5′-*O*-vinylacetylthymidine. This is presumably due to the intermediacy of vinylketene in the acylation process (R. W. Holder, H. S. Freiman, and M. F. Stefanchik, *J. Org. Chem.*, 1976, **41**, 3303).

‡ Satisfactory spectroscopic and microanalytical data have been obtained for (**2a**—**e**). All of these derivatives except (**2a**) appear to be stable.

(**1c**) in 94% isolated yield; (**2c**) was allowed to react with an excess of acetic anhydride in pyridine and the products then treated with 0·05 M hydrazine hydrate in methanol–pyridine (4 : 1 v/v) for 2 h at 20 °C. It is clear from the Table that such selective de-acylation would be expected to proceed efficiently. It can also be seen from the Table that, unlike *p*-chlorophenoxyacetates, crotonates and 4-methoxycrotonates are relatively stable to alkaline hydrolysis. This suggests that, if a trihydroxy compound were protected with *p*-chlorophenoxyacetyl, 4-methoxycrotonyl, and acetyl groups, it should be possible to remove these groups in order by treatment first with K_2CO_3–aq. dioxan, followed by N_2H_4 in MeOH–pyridine and finally with NH_3–MeOH.

In conclusion, we believe that the 4-methoxycrotonyl and crotonyl (derived from the more accessible crotonic acid) protecting groups are likely to prove to be valuable additions to the armoury of ester groups available[1] for the protection of alcoholic hydroxy functions.

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