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THERMAL REARRANGEMENT OF 3-HYDROXY-2-(HYDROXYPHENYL)-3-METHYL-3H-INDOLE

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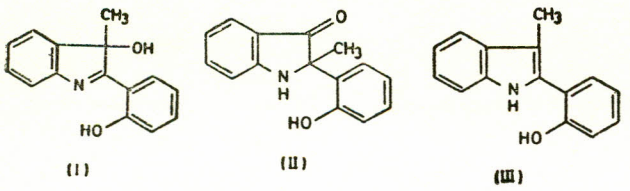
A variety of methods have been used for synthesising indoles.[1,2] The autoxidation of 2-(2-hydroxyphenyl)-3-methylindole(III) to afford 3-hydroxy-2-(2-hydroxyphenyl)-3-methyl-3*H*-indole (I) has already been reported.[3] We have found that sublimation of 3-hydroxy-2-(2-hydroxyphenly)-3-methyl-3*H*-indole (I) under reduced pressure yield a yellow amorphous powder, which on crystallisation gave a rearranged compound, 2-(2-hydroxyphenyl)-2-methyl-pseudoindodxyl (II). The structure of (II) was supported by its UV spectrum which remained unchanged upon acidification indicating the absence of 3*H*-indole nucleus, by its IR spectrum which showed the presence of a secondary amino group and a carbonyl function (ν 3415 and 1662 cm^{-1}) and by its NMR spectrum which in particular showed the presence of two exchangeable protons (corresponding to a hydroxyl and a secondary amino functions).



Experimental

UV spectra were recorded in ethanolic solution (95%) on a Perkin–Elmer model 137 spectrophotometer, and IR spectrum was recorded in nujol on a Perkin–Elmer model 237 spectrophotometer. Mass spectrum was recorded with an AEI MS-9. NMR spectrum was recorded with a Varian HA 100 instrument with $SiMe_4$ as internal standard.

2-(2-Hydroxyphenyl)-2-methyl-pseudoindoxyl (II). 3-Hydroxy-2-(2-hydroxyphenyl)-3-methyl-3*H*-indole[3] (I) (0.5 g) was sublimed at 180–185° (bath temp)/15 mm. The resulting yellow amorphous powder was crystallised from petroleum–ether (40–60°) to afford 2-(2-hydroxyphenyl)-2-methyl-pseudoindoxyl(II) (0.12 g, 24%) as yellow prisms, m.p. 120–121° (Found: C 75.4, H 5.4, N 5.9%, *m/e*, 239. $C_{15}H_{13}NO_2$ requires: C 75.3,H 5.4, N 5.8%; mol wt 239). The UV spectrum in ethanol λ_{max} 229 and 401 nm (log 4.32 and 3.35); λ_{infl} 259 and 283 nm (log 3.76 and 3.31); ν_{max} 3415 (NH), 1662 (C 0) cm^{-1}; NMR ($CDCl_3$) δ 1.77 (s, 3H, Me) 5.17 and 9.78 [2H(NH and OH), both protons removed by exchange with D_2O] and 6.60–7.80 (m, 8H,ArH.)

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SYNTHESIS OF SPONGOCYTIDINE

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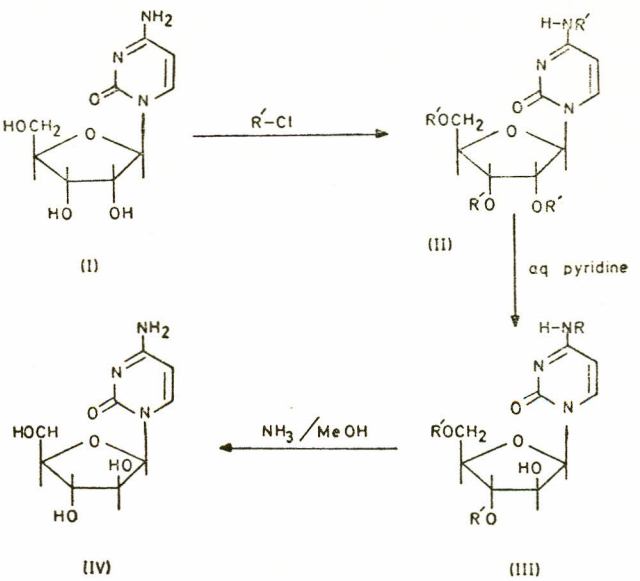
Spongocytidine has been found to be an antiviral and a carcinostatic agent[1]. Several approaches for the synthesis of this nucleoside have been achieved by various groups of workers.[2,3] We have investigated a new synthetic route for the synthesis of spongocytidine(IV) via nucleoside transformations. It was observed that cytidine (I) on treatment with 2,4-dinitrobenzoyl chloride in pyridine solution yielded the product (II) which was purified by absorption chromatorgaphy on silica and was obtained in a crystalline form (m.p. 187–89°). The NMR spectrum of (II) indicated the presence of the aromatic protons in the region of τ2.15–3.00. The IR spectvum showed the



R'-Cl=2, 4-Dinitrobenzoyl chloride

presence of the carbonyl group at 1740 cm^{-1} and nitro group at 1400 cm^{-1}. The product on treatment with aqueous pyridine solution and subsequent treatment with methanolic ammonia yielded spongocytidine (IV) and very little cytidine (I). Spongocytidine was separated from cytidine by making the 2′,3-*o*-isopropylidene derivative of eytidine using conventional methods.[4] Spongocytidine was isolated by preparative layer chromatography and was found to be identical with the authentic material supplied to us by Ichino.[2] The overall yield of the reaction was found to be 38%.

In this way it has been shown that 2,4-dinitrobenzyol group can be used as a suitable leaving group at position 2′- and as a protecting group at position 3′- and 5′- of the ribose moiety.

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REACTION OF STEROLS WITH DMSO AND ACETIC ANHYDRIDE: FORMATION OF 3β-ACETOXYMETHOXY CHOLEST-5-ENE

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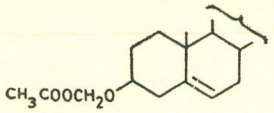
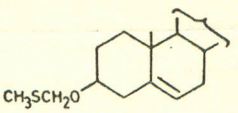
It was previously reported that, from experiments involving cholesteryl type ions in the reaction of of sterols with DMSO and acetic anhydride small yield of the product assigned the structure (I) have been obtained, the major product been the thioether having the structure (II).

The likely pathways for the formation of steroidal ketones, thioethers, acetates and olefines in DMSO–acetic anhydride medium have been discussed in details in the light of our previous results[1,2] and those of other workers[3] and can be summarised in case of formation of thioether and ketone respectivley as shown below[1] (scheme 1).



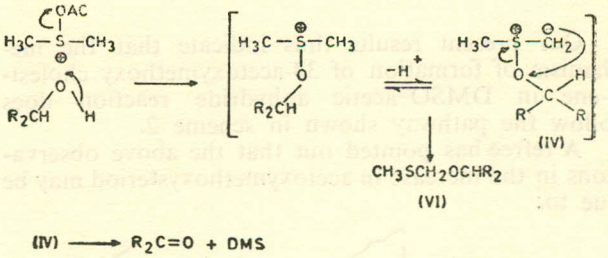
(I)



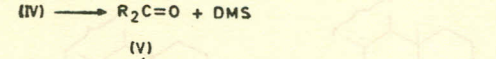
(II)

The alcohol intervenes in the above scheme by attack on the acetoxysulphonium ion(III), (formed by the reaction of acetic anhydride with DMSO[1]) to form alkoxydimethyl sulphonium ion which can lose a proton to yield the ylide (IV). The ylide may then collapse to give the carbonyl product (V) alongwith DMS or it may rearrange to give the methylthiomethyl ether (VI). During the course of the above investigations, we observed that alongwith the formation of thioethers of the type (II) from cholesterol, sitosterol and i-cholesterol, a minor side product acetoxymethoxy sterol (I) was also obtained. Its structure was determined on the basis of NMR, IR and mass spectra and its hydrolysis to cholesterol.

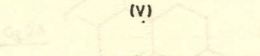
Scheme 1



(IV)



(VI)



(V)

One possibility in the formation of 3β-acetoxymethoxy cholest-5-ene during the reaction of cholesterol with DMSO/Ac_2O is that formaldehyde is involved as shown in the scheme 2 and proposed by us earlier.[2] Formaldehyde is known to be one of the decomposi tion product of DMSO.[4]

That the cholesteryl ion (VII) is involved in the above reaction is based on the fact that both cholesterol and i-cholesterol give the same product (II) on treatment with DMSO–acetic anhydride[1,2].

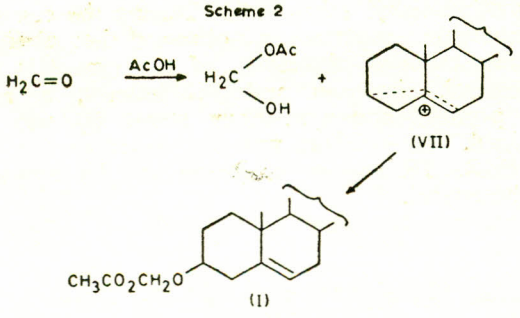
If formaldehyde is involved, then passing an excess of formaldeyhde in the reaction medium ought to increase the yield of the 3β-acetoxycholest-5-ene. This has been found to be true. On passing dry formaldehyde generated by heating para-formaldehyde in the reaction vessel containing cholesterol–DMSO– acetic anhydride, the yield of 3β-acetoxymethoxy cholest-5-ene increased from 5 to 15%, the major product still being thioether (II). Passing dry formaldehyde in reaction vessel containing cholesterol, DMSO and acetic acid–sodium acetate also gave 3β-acetoxymethoxy cholest-5-ene (5%) alongwith thioether. The major product was however, cholestryl acetate (3β-acetoxycholest-5-ene) (Table 1).

TABLE 1

Substrate	Reagents	Products(%)		
		Thioether	Acetoxymethoxy	Acetate
Cholesterol	DMSO + Ac_2O	90	2–5	—
Cholesterol	$H_2C{=}O$ + DMSO + Ac_2O	65	15	—
Cholesterol	$H_2C{=}O$ + CMSO + AcOH + NaOAc	20	5	70

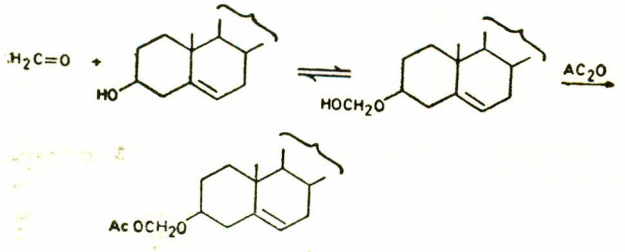
Products are quoted as "approximate composition of recovered steroid(%7)". The compsition is decided by considerationof spectral properties of the crude reaction products and also isolated yields. Recovered yields may have been affected by the presence in the reaction mixture of steroidal sulphonium salts that would be taken up into aqueous layer. A similar explanation has been advanced in another context.[5]

Scheme 2



Our present results thus indicate that the mechanism of formation of 3β-acetoxymethoxy cholest-5-ene in DMSO–acetic anhydride reaction does follow the pathway shown in scheme 2.

A refree has pointed out that the above observations in the increase in acetoxymethoxysteriod may be due to:



It is interestingas we are trying to prepare the intermediate, 3-β-hydroxymethoxycholest-5-ene for use in the synthesis of 3-β-acetoxymethoxysteroids. However if the above mechanism is a probable pathway than cho,lestan–3-β-ol and cyclohexanol should also give acetoxymethoxy compounds. No such compounds could be isolated by us or other workers[6] and the only products obtained were simple acetates[2,6] We are, therefore, led to believe that the double bond in cholesterol is in som way invovled giving rise to a stable cholestryl ion (VII).

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