Comparative Study of Carbonyl Protecting Groups in the Synthesis of Hydrocortisone-21-Acetate

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Summary:Hydrocortisone acetate can be synthesized from cortisone acetate by selectively reducing the 11- keto group. For this purpose, carbonyl groups present at C-3 and C-20 are protected by various groups. After reduction of carbonyl group at C-11 by a suitable reagent, carbonyl groups are deprotected. In the course of our synthetic work on the synthesis of hydrocortisone acetate from cortisone acetate [16, 38], we came across numerous protection and deprotection methods in the literature. Herein, we present a review of comparative study of these methods along with our own work.

Introduction

Cortisone and hydrocortisone acetate belong to a class of organic compounds known as steroids [1,2]. The steroids [3, 4, 5] are organic compounds, which have per hydro-1, 2-cyclo pentanophenanthrene nucleus (1) in their structure. This basic skeleton consists of four rings fused together, three of which are six membered, while the forth one is five membered, being fused together by 1,2 linkage as shown in the fig.1

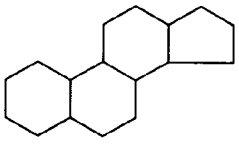


Fig 1: Per hydro-1, 2- cyclo pentanophenanthrene (1)

All the evidence obtained so far has revealed that all the cyclohexane rings in the steroid nucleus are in the chair form. The groups lying below the plane of steroid nucleus are assigned the α-configuration and those lying above are assigned β-configuration and it is in well accordance with the Barton's Auwers-Skita rule of catalytic hydrogenation which state: "Catalytic hydrogenation of ketones in strongly acid media (rapid hydrogenation) produces axial hydroxyl compounds whereas hydrogenation in neutral media (slow hydrogenation) produces the equatorial alcohol, if ketone is very much hindered". [5, 6].

Cortisone acetate (II) has three carbonyl groups at C-3, C-11, C-20 and an acetate group at C-21 (fig.2). It has a hydroxyl group at C-17 lying below the plane and therefore its chemical name is Δ^4-Pregnene-17α, 21-diol- 3, 11, 20-trione-21-acetate (II).

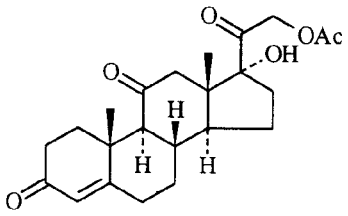


Fig 2: Cortisone Acetate (II)

Its conversion to hydrocortisone acetate involves selective reduction of the carbonyl group present at C-11 to hydroxyl group, which necessitates the protection of the remaining carbonyl groups at C-3 and C-20. The carbonyl group present at C-11 is least reactive among all the three because of the steric hindrance due to the presence of large methyl groups at C-18 and C-19. The carbonyl group located at C-20 is also sterically hindered due to the neighbouring bulky acetate group. Hence it is the C-3 carbonyl group, at which substitution takes place easily [7], C-20 is attacked with difficulty [8] and C-11 gets substituted very rarely. Only smaller groups under extreme reaction conditions can be substituted here [9].

In this review, we intend to present a comparative study of various methods of protection and deprotection involved in the synthesis of hydrocortisone acetate from cortisone acetate cited in the literature so far along with our own work for the convenience of future researchers.

Table-1:Comparison Chart of Various Protections

No.	Reactant	Product	Protecting agent/ reaction conditions.	Yield %	Ref.
1	Cortisone	3, 20- bisketal	Ethylene glycol/ *p*-toluene sulphonic acid/ benzene/ 5 hrs. reflux	73	13
2	Cortisone acetate	3- mono ketal	Ethylene glycol/ *p*-toluene sulphonic acid/ benzene/ 4 hrs. reflux	64	13
3	Cortisone acetate	3, 20- bisketal	Ethylene glycol (excess)/ *p*-toluene sulphonic acid 1.0 mm Hg/ 45°C/ 9 hrs. distillation.	90	16
4	Cortisone	3, 20- bisoxime	Hydroxylamine hydrochloride/ sodium acetate/ 80% methanol/ 15 hrs. reflux.	77	22
5	Cortisone acetate	3, 20- bis oxime	Hydroxylamine hydrochloride/ sodium acetate/ 80% methanol/ 18 hrs. reflux.	88	33
6	Cortisone acetate	3, 20- bis hydrazone	Hydrazine hydrate (85%), 80% EtOH/ 18 hrs. reflux.	95	33
7	Cortisone acetate	3,20- bis phenyl hydrazone	Phenyl hydrazine hydrochloride, 80% EtOH/ 20 hrs. reflux.	60	39
8	Cortisone acetate	3,20-bis 2,4 dinitro phenyl hydrazone	2, 4- dinitro phenyl hydrazine hydrochloride, hydrochloric acid, THF.	>20	39
9	Cortisone	3,20- bis-semicarbazone	Semicarbazide acetate/ acetic acid/ 70- 75 °C/ 2- 3 hrs. reflux.	70	17
10	Cortisone acetate	3,20- bis-semicarbazone	Semicarbazide hydrochloride/ pyridine/ water/ methanol/ 15 hrs reflux.	91	33
11	Cortisone acetate	3- mono-semicarbazone	Semicarbazide acetate/ acetic acid/ 70- 75 °C/ 2- 3 hrs. reflux.	80	17

Methods of Protection

Various protecting groups have been used in order to protect the carbonyl groups in cortisone or cortisone acetate at C-3 and C-20 (table 1). The choice of a specific protecting group depends on a number of factors. The group must be stable to the reaction conditions of subsequent reactions and be readily removable without causing unacceptable losses of the product. In addition, the substrate must be stable to the reaction conditions required for the introduction of the protecting groups. For example, Protecting groups, which require strong acids, or dehydrating agents for their formation should be avoided with substrate bearing the 11-hydroxyl group (e.g.; hydrocortisone). When only one carbonyl or hydroxyl group is to be blocked in multifunctional organic compounds, the choice of the protecting group is determined by the ease with which the group can be introduced selectively into the parent molecule.

Carbonyl Protection as Ketal

Salmi [10, 11] introduced ketal formation, a method of protection of carbonyl group for the first time. He refluxed the ketones using a mixture of benzene and ethylene glycol. *p*-Toluene sulphonic acid was used as a catalyst to effect ketal formation. (fig.3)

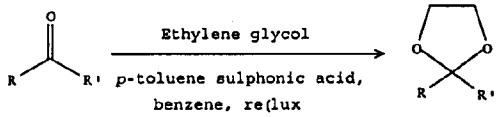


Fig 3: Ketal formation of carbonyl group.

Ketal protecting groups are generally formed by nucleophilic attack on carbonyl group and the rate of this process is determined by steric and electronic factors associated with the steroidal ketone. Steric effects are usually more important due to the rigid tetracyclic skeleton [12].

Antonucci *etal* applied the Salmi's method to 17α-Hydroxy-11-deoxy corticosterone- 21-acetate (Reichstein's substance S acetate) (III). Acetate was treated with an excess of ethylene glycol in benzene to yield 3-monoethylene ketal (IV) [13]. (fig. 4) *p*-Toluenesulphonic acid was used as a catalyst.

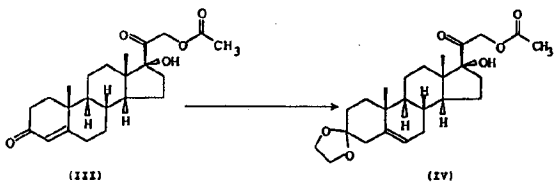


Fig 4: 3-Monoethylene ketal formation of Rechstein's substance S acetate.

Moreover, a coincident rearrangement of the double bond from C-4 to C-5 position during the formation of ethylene ketals of Δ^4- 3- keto steroids (III, IV) was noted by Antonucci *et al* [14] as depicted in fig 4.

The same steric effect was observed when only 3- monoethylene ketal (V) at C-3 was obtained from cortisone acetate in 60% yield under harsh conditions; reaction mixture was refluxed for longer times (fig 5). However, cortisone (VI) gave 3, 20-bisketal (VII) on the same treatment revealing that the carbonyl group at C-20 of cortisone acetate is sterically hindered by the neighbouring acetate group at C-21 (fig 6).

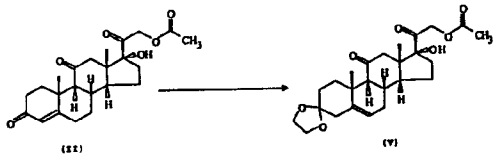


Fig 5: 3- Monoethylene ketal formation of cortisone acetate

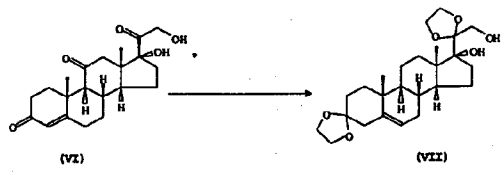


Fig 6: 3, 20-Bisketal formation of cortisone

The steric hindrance due to an acetate group at C-21 of cortisone acetate to the condensation of carbonyl group at C-20 with ethylene glycol was further confirmed when reduction of C-20 carbonyl group of cortisone-21- acetate-3-monoketal (V) gave the corresponding hydroxy derivative. The later underwent acetylation to form cortisone-20, 21-diacetate-3-monoketal (VIII) because the hydroxy derivative is less sterically hindered on account of free rotation around the signally bonded C-20 atom (fig 7).

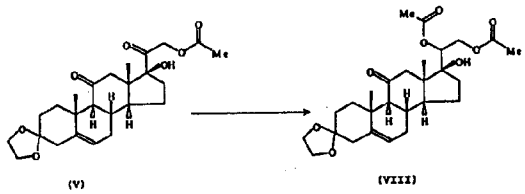


Fig 7: Acetylation of cortisone-21-acetate-3-monoketal

Allen *et al* [15] synthesized steroidal cyclic ketals in a modified way and got better yield. A mixture of steroid, ethylene glycol, (in large excess to serve both as reactant and solvent) and *p*-toluene sulphonic acid was stirred and distilled under reduced pressure (2.0 mm Hg) at a slow rate for about 5 hours as otherwise water formed during the reaction hinders it to proceed due to unfavourable equilibria.

We [16] converted cortisone acetate to cortisone acetate-3, 20-bisethylene ketal in excellent yields using the modified procedure [15]. Pressure was further reduced to 0.5 mm Hg and the duration of the reaction was increased to 9 hours leading to the conclusion that ketal formation can be achieved both at C-3 and at C-20 simultaneously by forcing the reaction forward under harsh conditions. Excellent yield was obtained by avoiding the decomposition products (Allen's method) by reducing the pressure and thus decreasing the reaction temperature. However, a large quantity of ethylene glycol was used as the rate of distillation was enhanced.

Carbonyl Group Protection as Imine Derivatives

Carbonyl group can also be protected by converting it into its imine derivatives. Most commonly used imine derivatives are oxime, hydrazone, phenyl hydrazone, semicarbazone, and 2, 4-dinitro phenyl hydrazone (table 1). These are formed by substitution of a nitrogen atom of protecting reagent for the carbonyl oxygen atom.

Wendler *et al* [17] selectively protected C-3 and C-20 carbonyl groups of cortisone (VI) by treating it with an excess of semicarbazide acetate in acetic acid solution at 70-75°C for two to three hours to get the corresponding bissemicarbazone (IX). However, cortisone acetate (II) on the same treatment gave only 3-mono derivative (X) again leading to the conclusion that the 21-acetate group sterically hinders the formation of a derivative at C-20 carbonyl group (fig 8).

Hopper *et al* [18] used pyridine in methanol as a solvent for semicarbazone formation. Pyridine is used here as a tertiary base, solvent and as a catalyst. Tertiary base such as pyridine might be expected to effect condensation of carbonyl group with hydroxylamine, semicarbazide or O-methyl hydroxylamine differently in as much as they would favour the production of NH_2O^- ion; in practice such differences if they exit, are of small account [19].

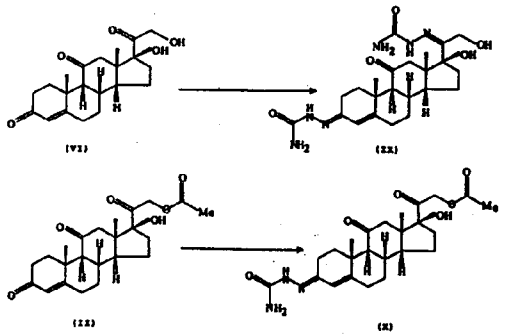


Fig 8: Semicarbazone formation of cortisone and cortisone 21- acetate.

Blatt [20] has shown that the base catalysed oximation favours the most strongly hydrogen bonded forms of the derivatives of O-hydroxy ketones in the aromatic series and Schmidt-Thome [21] suggested that 20-hydroxy imino–steroids assume a configuration allowing the strongest hydrogen bonding with the substituent at the 21- position. Brooks *et al* [22] protected the C-3 and C-20 carbonyl groups of cortisone and cortisone acetate by semicarbazone and oxime formation using semicarbazide hydrochloride and hydroxylamine hydrochloride respectively in the presence of a tertiary base (pyridine) and got better yields (90-98%).

Jones *et al* [23] protected carbonyl groups at C-3 and C-20 of cortisone acetate by semicarbazone and oxime formation using semicarbazide hydrochloride and hydroxylamine hydrochloride respectively in the presence of sodium bicarbonate but the yields were low.

Oliveto *et al* [24] converted cortisone into the corresponding 3, 20-bishydrazone, 3, 20-bisoxime and 3, 20-bissemicarbazone by refluxing the reaction mixture for 12-18 hours with hydrazine hydrate, hydroxyl amine hydrochloride and semicarbazide hydrochloride respectively.

The authors converted cortisone acetate to its oxime, hydrazone, phenyl hydrazone, 2, 4-dinitro phenyl hydrazone and semicarbazone derivatives [16, 38, 39]. For 3, 20-bisoxime, hydroxylamine hydrochloride was used in the presence of sodium acetate and tetra hydro furan and got almost quantitative results. 3, 20-bis hydrazone and 3, 20-bis phenyl hydrazone were synthesized by reacting cortisone acetate with 70% hydrazine hydrate and phenyl hydrazine hydrochloride respectively in the presence of sodium acetate and 80% ethyl alcohol. Yield with hydrazine was 95-96% but with phenyl hydrazine hydrochloride, only 60% could be achieved. Loss in the yield by 34-35% in case of phenyl hydrazone with respect to hydrazone was thought to be due to steric reasons as phenyl ring is much bulky than hydrogen. 2,4 - Dinitro phenyl hydrazine hydrochloride was also tried to form cortisone acetate 3,20-bis 2,4- dinitro phenyl hydrazone but it was not proved to be a good protecting reagent in this very case. Firstly, acetate group at C-21 was hydrolyzed as acidic conditions were used in the reaction. Secondly, due to huge size of the reagent major product was 3-mono derivative along with the minor amount of 3,20- bis derivative. There was also a problem in the isolation of the products from the reaction mixture. 3, 20- Bis semicarbazone was synthesized in the usual way [24]. Cortisone acetate was treated with semicarbazide hydrochloride in pyridine along with methyl alcohol and water to get cortisone acetate 3, 20- bis semicarbazone in 80% yield.

Reduction of C-11 Carbonyl Group

The second step in the synthesis is the reduction of C-11 carbonyl group to C-11β hydroxyl group. A number of reagents have been used so far for this purpose. These are lithium aluminium hydride, lithium borohydride, and sodium borohydride. One mole of each of these reagents is capable of reducing 4 moles of ketone.

A mechanistic picture of reduction by $LiAlH_4$ includes the lithium ion as a Lewis acid catalyst . This is conceptually similar to the role of a proton in catalysing nucleophilic addition to a carbonyl group. The better Lewis acid, aluminium hydride (AlH_3), ultimately ends up bonded to the oxygen atom [25]. The lithium aluminium alkoxide formed initially provides the hydride for a subsequent step until all the four hydrogen atoms are utilized. Final hydrolysis yields the alcohol. The mechanism of reduction of the keto group with the lithium aluminium hydride in tetera hydro furan is given in fig. 9.

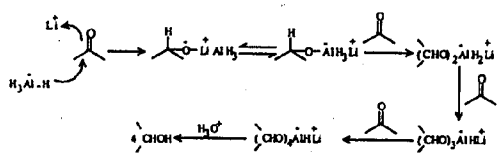


Fig 9: Mechanism of reduction with lithium aluminium hydride.

The reaction of $NaBH_4$ is conceptually similar to $LiAlH_4$ except that sodium ion does not coordinate to carbonyl oxygen as strongly as lithium ion does [26]. For this reason, $NaBH_4$ reductions are carried out in protic solvent such as alcohols or even water, if the solution is not acidic.

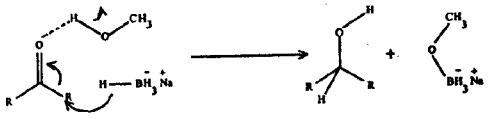


Fig 10: Mechanism of reduction with sodium borohydride.

Reduction of carbonyl groups with $LiAlH_4$, $NaBH_4$ and related metal hydrides are stereospecific and mainly give 11-β hydroxyl group [27-29]. An 11-β substituent (polar conformation) is considered less stable than the corresponding 11-α substituent (equatorial conformation) [30]. Thus, one would anticipate that reduction of a C-11 carbonyl group would yield primarily the equatorial 11-α hydroxyl compound (frontal attack). But with metal hydrides of the type mentioned, steric effects prevail over energetic factors and rear attack (11-β conformation) is favoured [31]. However, it is found in some cases that 11-α hydroxyl group has also been isolated in low yields, e.g., when diethylene ketal of cortisone in tetra hydrofuran was reduced with lithium aluminium hydride, 11-α hydroxy compound (8%) was formed in addition to 11-β hydroxy compound (58%). It is ascribed to the overall size of the e.g.; aluminium hydride or, the species participating in the nucleophilic reduction [32].

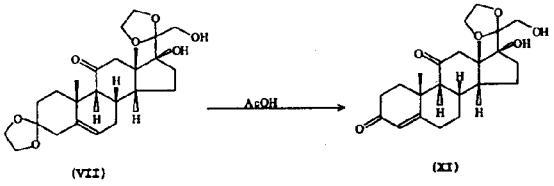


Fig 11: Hydrolysis of C-3 ketal with acetic acid.

For the reduction of 3, 20-bisketal of cortisone acetate, the use of sodium borohydride is recommended. It has following advantages over lithium aluminium hydride.

1. It is relatively selective and moderate reducing agent and does not reduce esters (acetate group at C-21in cortisone acetate.)

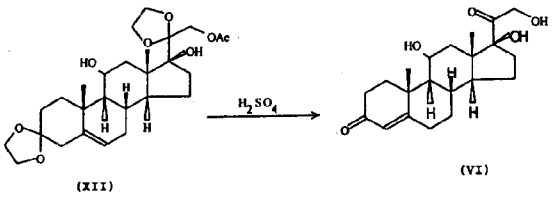


Fig 12: Hydrolysis of C-3 and C-20 ketals with sulphuric acid.

2. It can be used in alcohol or even in water, where, lithium aluminium hydride must be used in a non- hydroxylic solvent and must be rigorously protected from moisture.

3. The reductions with $NaBH_4$ yield almost exclusively 11-β hydroxyl group in the case of cortisone acetate.

Methods of Deprotection:

Various agents of deprotection of carbonyl protecting group have been used in the synthesis of hydrocortisone acetate (table 2). Ketals are generally hydrolysed by acidic hydrolysis and for the purpose, dilute sulphuric acid, hydrochloric acid or acetic acid is used. Antonucci *et al* [14] used aqueous acetic acid for the ketal hydrolysis. Application of 90% acetic acid to cortisone 3, 20-bisketal (VII) removed selectively the C-3 ketal, and afforded the C-20 mono ethylene ketal (XI) of cortisone.

However, aqueous sulphuric acid or hydrochloric acid is used for the hydrolysis of 3 and 20 bisethylene ketals of hydrocortisone or hydrocortisone acetate (XII).

Wendler *et al* [17] hydrolyzed semicarbazone with a mixture of glacial acetic acid, water, anhydrous sodium acetate and 90% aqueous pyruvic acid under an atmosphere of nitrogen at 75°C. After a period of 4 hours, mixture was concentrated in vacuum nearly to dryness; water was added and the product was extracted with ethyl acetate.

Oliveto *et al* [33] found that the use of nitrous acid give better results (65%) for the fission of the semicarbazone group. They hydrolysed 3, 20 bis-semicarbazone of cortisone (IX) by dissolving it in dilute hydrochloric acid and by treating the resulting solution with a excess of sodium nitrite at 0- 5°C.

Table-2: Comparison Chart of Various Deprotections

No.	Compound	Deprotection agent/ reaction conditions	Product	Yield %	Ref.
1	Hydrocortisone acetate 3,20-bis ketal	AcOH/ 2 hrs./ 25 °C	Hydrocortisone acetate 3-monoketal	62	15
2	Hydrocortisone acetate 3,20-bis ketal	H_2SO_4(80%)MeOH/50 min./ 25 °C	Hydrocortisone	60	16
3	Hydrocortisone acetate 3,20-bis oxime	$NaNO_2$/ dil. HCl/ 0- 5°C/ 4-5hrs.	Hydrocortisone	78	33
4	Hydrocortisone acetate 3,20-bis oxime	Levulinic acid/ HCl(9:1v/v)/ 60°C/ 3 hrs.	Hydrocortisone	97	38
5	Hydrocortisone acetate 3,20-bis oxime	$NaNO_2$/ dil. HCl/ 0- 5°C/ 4-5hrs.	Hydrocortisone	81	33
6	Hydrocortisone acetate 3,20-bis oxime	Levulinic acid/ HCl(9:1v/v)/ 60°C/ 3 hrs.	Hydrocortisone	95	38
7	Hydrocortisone acetate 3,20-bis hydrazone	Levulinic acid/ HCl(9:1v/v)/ 60°C/ 3 hrs.	Hydrocortisone	97	16
8	Hydrocortisone acetate 3,20-bis phenylhydrazone	Levulinic acid/ HCl(9:1v/v)/ 60°C/ 3 hrs.	Hydrocortisone	92	39
9	Hydrocortisone acetate 3,20-bis semicarbazone	$NaNO_2$/ dil. HCl/ 0- 1°C/ 4-5hrs.	Hydrocortisone	69	33
10	Hydrocortisone acetate 3,20-bis semicarbazone	Levulinic acid/ HCl(9:1v/v)/ 60°C/ 3 hrs.	Hydrocortisone	98	38

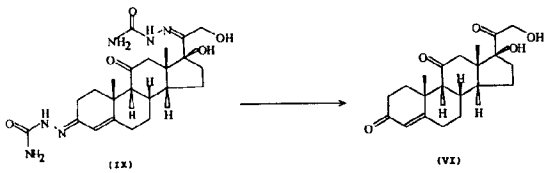


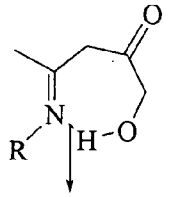
Fig 13: Hydrolysis of cortisone 3, 20 bissemicarbazone with nitrous acid.

Keeney *et al* [34] used a mixture of sodium nitrite and hydrochloric acid in order to hydrolyse various oximes. Oliveto *et al* [33] splitted 3, 20 bisoxime of cortisone acetate to the parent ketone by this method but the overall yields were low.

Mattox and Kendall [35, 36] hydrolysed oximes and hydrazones of various steroids with a mixture of pyruvic acid and acetic acid but the yields were low. Various decomposition products were also isolated along with the required products. (Table 2)

Depuy *et al* [37] found levulinic acid as an excellent agent for hydrolysing oximes of acetone, benzaldehyde, benzophenone, di benzyl ketone and 2, 4 – dinitrophenyl hydrazones of cholesterol. He also found that the conjugated oximes hydrolyse much more slowly than the non- conjugated ones. 64-99 % yields were reported for these reactions.

We [16, 38] used the same procedure to hydrolyze 3, 20- bis oxime, 3, 20- bishydrazone, 3, 20- bis phenyl hydrazone and 3, 20- bis semicarbazone of cortisone acetate and achieved excellent results. Each of the protected derivatives was mixed with 30 parts of a solution of levulinic acid and 1N hydrochloric acid (9:1 v/v); the reaction mixture was stirred for three hours at room temperature and the product was extracted with methylene chloride. Extracted products were washed with bicarbonate solution and water respectively to remove the acid; all the products were found to be free of any decomposition products and in almost quantitative yields. Besides, the higher yields obtained from levulinic acid, it is cheaper, more easily purified and more stable. It can be recovered, too, if used in excess. Higher yields with levulinic acid may be attributed to the shift of equilibrium towards the levulinic acid derivatives (Oxime, hydrazone, semicarbazone etc.) due to internal hydrogen bonding as depicted in fig 14.



Hydrogen bonding

Fig 14: Stabilization of levulinic acid derivatives by internal hydrogen bonding.

However, use of acid in aqueous medium hydrolyzed the acetate group at C-21. Therefore, after deprotection, acetylation of hydrocortisone acetate

gave the required product (hydrocortisone acetate). Acetylation was achieved by treating the hydrocortisone with a mixture of acetic anhydride and pyridine for a period of six hours at room temperature.

Conclusions

Tables 1 and 2 highlight the comparative study of protection and deprotection methods involved in the synthesis of hydrocortisone from cortisone/cortisone acetate. Cortisone acetate can be converted into hydrocortisone acetate by selectively reducing the 11- keto group. Reduction is preceded by the selective protection at C-3 and C-20. This is attributed to the fact that the nucleophilic attack of the protecting agents at C-11 carbonyl group is sterically hindered due to the 1,3 interactions with neighbouring methyl groups at C-18 and C-19. Moreover, protection at C-20 is also sterically hindered due to neighbouring bulky acetate group (at C-21). However, the third carbonyl group (at C-3) is free from all steric hindrances and is easily substituted. Hence, it is C-3 at which protection takes place easily [7]; C-20 is attacked with difficulty [8] and C-11 gets substituted very rarely [9].

As for as protection by ketal formation is concerned, cortisone/ cortisone 21-acetate 3, 20-bisketal can be prepared in almost quantitative yield in less duration (9 hours) [16] in comparison with other methods i.e. by imine derivative formation methods [16, 38,39]. However, the reaction mixture is to be continuously distilled under reduced pressure of 1 mm Hg, as otherwise, water formed during ketal formation hinders the reaction to proceed due to unfavourable equilibrium. Hence, a large quantity of anhydrous ethylene glycol is required [16]. Formation of imine derivative of cortisone/cortisone acetate such as bisoxime [16], bissemicarbazone [38], bishydrazone and bisphenyl hydrazone [39] also takes place in nearly quantitative yields but takes 15-18 hours. However, limited quantities of solvents are required here (as compared to ketal formation).

As for as reduction is concerned, sodium borohydride in THF is proved to be a better reducing agent as it is relatively less reactive than lithium aluminium hydride. Moreover, it does not reduce C-2 acetate group. Also, as compared to $LiAlH_4$, it produces 11-α epimer in negligible amounts [27-32].

For the hydrolysis of ketals, sulphuric acid is the best one (AcOH hydrolyzes ketal group at C-3), levulinic acid- HCl mixture (9:1v/v) is proved to be the best one for the hydrolysis of oximes, hydrazones and semicarbazones of cortisone acetate [37, 38].

Deprotection process involving the use of levulinic acid as a deprotecting agent has several advantages over other acids. Higher yields are obtained with levulinic acid. It is cheaper, more easily purified and more stable. No decomposition products are obtained with it. It can be recovered, too, if used in excess. Higher yields with levulinic acid may be attributed to the shift of equilibrium towards the levulinic acid derivatives (Oxime, hydrazone and semicarbazone) due to an internal hydrogen bonding as depicted in Fig. 14. Finally, acetylation using usual methods (with acetic anhydride/pyridine) afforded the hydrocortisone acetate [16].

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