signals at δ 2.5–2.8, and (2) the absence of an AcO-1 and a H-1 signal at δ 2 and 6, respectively. The remaining absorptions closely resembled those of **3**. A careful analysis of the 400-MHz spectrum with the aid of decoupling experiments therefore established the structure **5** for this product. The elementary analysis and mass spectrum supported the structure. The mechanism for the formation of such a further reduced P sugar is, however, currently under investigation.

The values of the geminal P—C—H coupling constants ($J_{1,P}$) of the presently described phosphinyl coompounds apparently depend upon the magnitude of their approximate O=P—C—H dihedral angles illustrated in the Newman projections (Figure 1). Thus the anti conformation of the O=P—C—H group exhibited a lower magnitude of coupling than the gauche conformation, providing a quick method for assignment of configuration of the P sugars. A similar dependance of the geminal P—C—H coupling constant of the O=P—C—H dihedral angle has been reported for a linear and cyclic phosphonyl compound.[5] The large values of the H—C-5—P geminal coupling constants ($J_{5,P}$ = 20-21.7 Hz for **3–5** and 15.7 Hz for **6, 7**) appear to be compatible with gauche coupling, although the exact $J_{5,P}$ value of anti coupling has not been obtained for a D-gluco-type P sugar[6] (**9**) because of the poor resolution of its ^{1}H NMR spectrum at 60 MHz. There have been reported some examples of more reliable angular dependance of P—C—C—H vicinal coupling constants upon the dihedral angles in the case of phosphonate compounds.[7] However, because of the small differences in the magnitude of the vicinal coupling ($J_{2,P}$ and $J_{4,P}$) of the present (*S*)-phosphinyl-*ido*-hexopyranose (**3, 4**) and its *R* isomer (**6, 7**), these values do not seem to have been utilized as a decisive method for assignment of the *R,S* configuration to the ring P atom.

It is not certain at present whether the predominant formation of L-ido-type P sugars from the D-*xylo*-hexofuranoses (**1, 2**) is due to a steric requirement of an intermediate. The above mechanistic study is being continued and an effective preparative method for gluco-type P sugars is currently in progress. Nevertheless, this initial work clearly demonstrates the utility of 400-MHz ^{1}H NMR studies for the effective determination of configuration and conformation of sugars containing phosphorus in the ring.

Experimental Section

^{1}H NMR spectra were obtained with a Bruker WH-400 cryospectrometer at 27 °C. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Spin decoupling was performed for each proton signal to confirm the coupling constants. The NMR spectra of all compounds were completely interpretable in a first-order analysis at 400 MHz. The materials used for the measurements were prepared as described in ref 2.

Registry No. **1**, 79917-67-2; **2**, 79917-68-3; **3**, 79917-69-4; **4**, 79917-70-7; **5**, 79917-71-8; **6**, 79917-72-9; **7**, 79917-73-0.

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Stereospecific Synthesis of Muscarines and Allomuscarines in D and L Series

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Received July 18, 1981

D(−)-(1*R*,3*S*,4*R*)-Muscarine iodide (**4**) and L(+)-(1*S*,3*S*,4*R*)-allomuscarine iodide (**2**) were synthesized from 2-deoxy-D-ribose (**5**). Treatment of the β cyanide **6a** with a methanolic hydrogen chloride solution gave a mixture of methyl esters **7a** and **8a**. These esters reacted with dimethylamine at 90 °C to yield the corresponding deprotected dimethyl amide **10a**. Selective tosylation in dry pyridine of **10a** and reduction of the tosylamide **11a** with lithium aluminum hydride in refluxing tetrahydrofuran, followed by quaternization of the crude amine with methyl iodide, gave D(−)-muscarine iodide (**4**). The same procedure with the α cyanide **6b** gave L(+)-allomuscarine iodide (**2**). L(+)-(1*S*,3*R*,4*S*)-Muscarine iodide (**1**) and D(−)-(1*R*,3*R*,4*S*)-allomuscarine iodide (**3**) were analogously prepared from 2-deoxy-L-ribose (**13**). The anomeric purity of these compounds was established by spectroscopic data.

The interesting physiological activity of L(+)-muscarine (**1**), isolated from *Amanita muscaria*, has generated much interest over the years. Its structure elucidation[1] showed the presence of three asymetric centers (Scheme I), which implied the existence of four pairs of enantiomers in both the D and L series. All stereoisomers have been synthesized.[2]

The majority of the published syntheses afford a racemic or an isomeric mixture of natural muscarine with different stereoisomers. A few elegant stereospecific syntheses have been reported: starting from an α-amino acid as the chiral precursor, L(+)-muscarine (**1**) and L(+)-allomuscarine (**2**) were obtained after an enzymatic resolution.[3] D(−)-allomuscarine (**3**) was synthesized from an optically active diol.[4]

Among the easily accessible chiral products used as starting materials for the synthesis of muscarines, carbohydrates are the most obvious: L(+)-muscarine (**1**) has been obtained from L-arabinose, via L-chitaric acid,[5] and also from D-mannitol;[6] D(−)-muscarine (**4**) has been prepared from D-glucosamine[7] and from 2-deoxy-D-ribose.[8]

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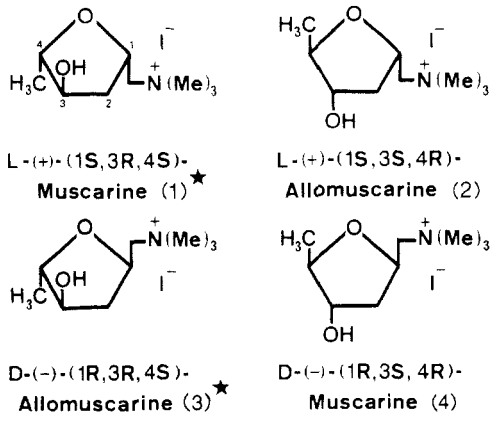
Scheme I[a]



[a] The star indicates natural compounds isolated from *Amanita muscaria* by Eugster, C. H.; Schleusener, E. *Helv. Chim. Acta* **1969**, *52*, 708 (the numbering of the carbohydrate ring was adopted for all compounds).

D(−)-epiallomuscarine has been recently synthesized from D-glucose.[9,10]

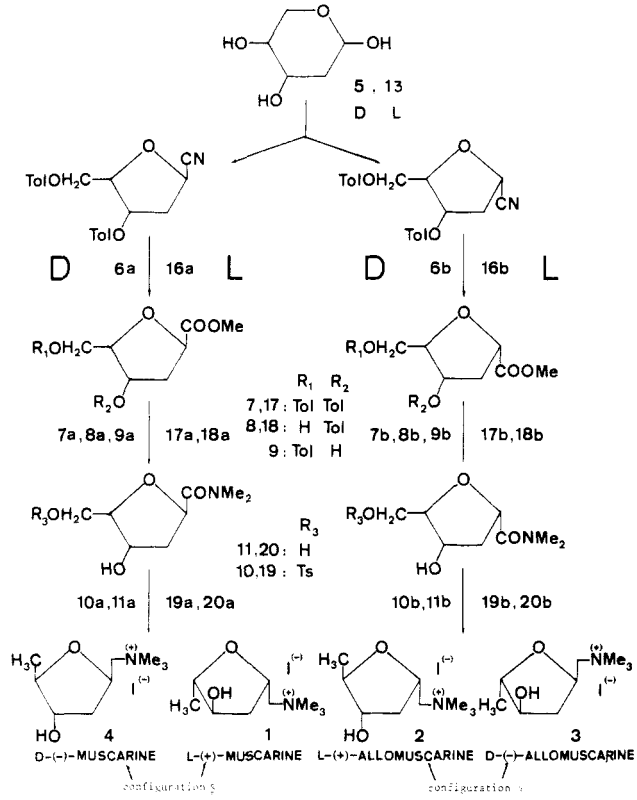
However, these different stereospecific syntheses required either an enzymatic resolution[3] or a chromatographic separation from intermediate 3-hydroxy isomers,[4,6,9,10] and simple stereospecific syntheses of muscarines and their analogues are still in demand.

The structure of L-(+)-muscarine (1), or one of its stereoisomers from a carbohydrate, requires two conditions: (1) a skeleton, already containing the different asymetric centers and (2) a reactive function at C-1 to allow construction of the quaternary ammonium salt. Among the functional groups needed as precursors, an aldehyde[9,10] or an acid[5-8] have been most commonly used. Another appropriate precursor, well-known in *C*-nucleoside chemistry,[11] is the cyanide function. Our choice of 2-deoxyerythropentofuranosyl 1-cyanides as key intermediates was based on their availability from 2-deoxyriboses and on the existence of the three needed chiral centers in the carbohydrate moiety.

We first tested our synthetic scheme with 2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-erythropentofuranosyl 1-cyanide (**6a**), a compound previously prepared in our laboratories.[12] As shown in Scheme II, the β cyanide **6a** was treated with methanolic hydrogen chloride to afford the expected β ditoluoyl ester **7a**, with two β monotoluoyl esters: **8a** (3-*O*-*p*-toluoyl) and **9a** (5-*O*-*p*-toluoyl; 63% overall yield). The ratio of isomers depended on the normality of the methanolic hydrogen chloride solution, with predominance of **7a** and **8a**. The structure and configuration of these esters were determined by ^{1}H NMR. The anomeric proton H-1 appeared on these spectra as a sharp triplet with $J_{1-2} + J_{1-2'} = 16$ Hz, characteristic of a β configuration.[13]

When α cyanide **6b** was subjected to the same conditions, the ^{1}H NMR spectra of the product showed a doublet of doublet with a smaller peak width $J_{1-2} + J_{1-2'} = 10$ Hz for H-1. This absorption is characteristic of the α configuration,[13] thereby further confirming the preservation of chirality at the anomeric center. As anticipated, the chirality of the anomeric carbon was also preserved during the mild alcoholysis of the nitrile into ester.

Scheme II



The different β methyl esters **7a**, **8a**, and **9a** were treated in a steel bomb at 90 °C with 50% methanolic dimethylamine to give amide **10a**[8] (70%). The ^{1}H NMR spectrum indicated the β configuration. Selective tosylation at −15 °C afforded the 5-*O*-*p*-tosyl compound **11a**[8] (70%). Reduction with lithium aluminum hydride in refluxing THF, followed by quaternization with an excess of methyl iodide, gave D(−)-(1*R*,3*S*,4*R*)-muscarine iodide (**4**).[8,14] The physical and spectroscopic properties of this synthetic alkaloid were identical with those previously described: mp 145–146 °C (acetone–petroleum ether); $[\alpha]^{25}_D$ −6.1° (*c* 0.45, H_2O).

The same methodology was employed with the α anomer **6b** to yield L(+)-(1*S*,3*S*,4*R*)-allomuscarine iodide (**2**):[3,14] mp 127–128 °C (acetone–petroleum ether); $[\alpha]^{25}_D$ +36.8° (*c* 0.75, H_2O).

We further adapted this convenient synthetic route to the L series, as shown in Scheme II. However, 2-deoxy-L-ribose (**13**) was not immediately accessible and had to be prepared in five steps from L-arabinose (**12**), as described in the literature.[15] As in the D series, **13** afforded the β and α cyanides **16a** and **16b**, in three steps, after separation by column chromatography.

The β cyanide **16a**, gave L(+)-(1*S*,3*R*,4*S*)-muscarine iodide (**1**):[3,14,16] mp 145–147 °C; $[\alpha]^{25}_D$ +5.9° (*c* 0.41, H_2O).

Analogously, the α anomer yielded D(−)-(1*R*,3*R*,4*S*)-allomuscarine iodide (**3**):[17] mp 125–126 °C; $[\alpha]^{25}_D$ −37.7° (*c* 0.65, H_2O).

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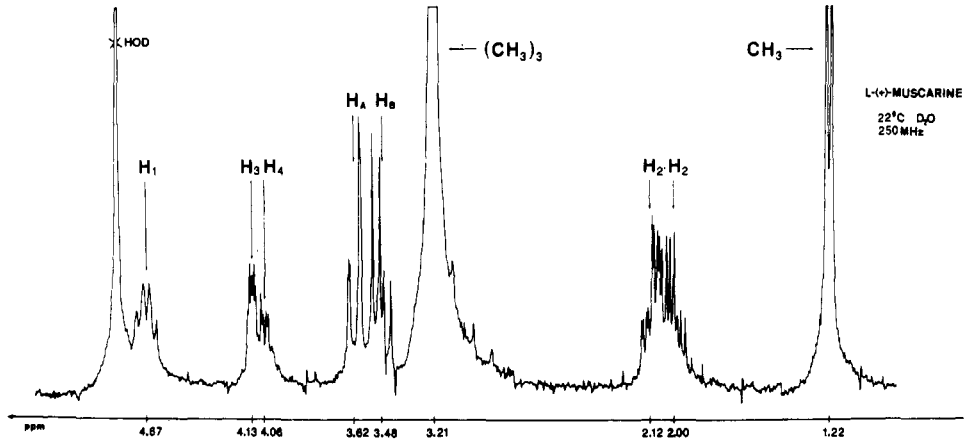

Figure 1. NMR spectrum of L(+)-muscarine at 250 MHz in D_2O. Coupling constants (Hz): J_{A-B} = 14.0, J_{1-A} = 2.3, J_{1-B} = 9.1, J_{1-2} = 9.4, $J_{1-2'}$ = 6.2, J_{2-3} = 5.5, $J_{2'-3}$ = 2.8, J_{3-4} = 2.9, J_{4-CH_3} = 6.4.

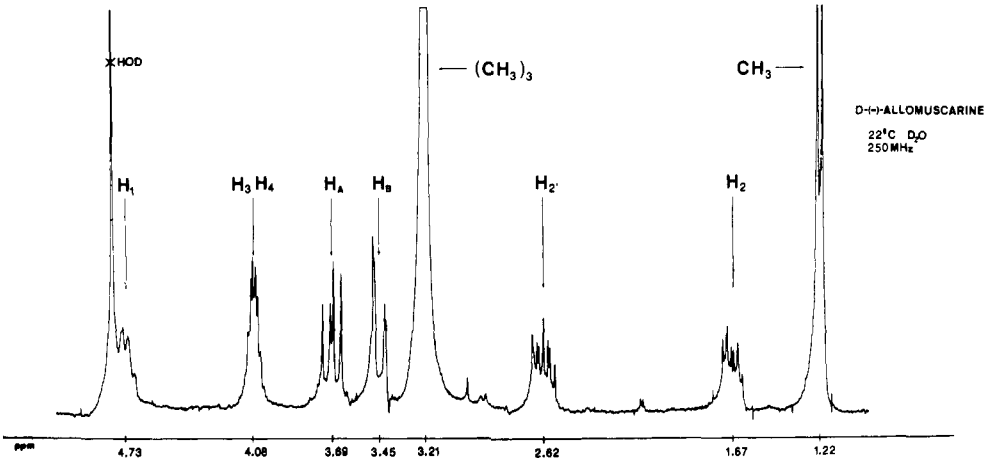

Figure 2. NMR spectrum of D(−)-allomuscarine at 250 MHz in D_2O. Coupling constants (Hz): J_{A-B} = 14.0, J_{1-A} = 9.8, J_{1-B} = 1.5, J_{1-2} = 5.25, $J_{1-2'}$ = 8.0, J_{2-3} = 5.25, $J_{2'-3}$ = 6.0, J_{4-CH_3} = 6.5.

Discussion

The structure and the configuration of all the described compounds have been assigned unequivocally by ^1H NMR and mass spectra. The value and sign of the optical rotations allowed us to confirm these assignments.

Some of the intermediates with the β configuration obtained in the D series were previously described by Hardegger[8] (amide **10a** and tosylamide **11a**). Comparison of our optical rotation values to the literature values presented some disagreement: $[\alpha]^{25}_D$ −2.0° for **10a** (lit.[8] $[\alpha]^{25}_D$ +13.9°) and $[\alpha]^{25}_D$ −7.0° for **11a** (lit.[8] $[\alpha]^{25}_D$ +7.0°). Having synthesized the corresponding enantiomers in the L series, we could verify and confirm our results: thus, for amide **19a**, $[\alpha]^{25}_D$ +1.0° and for tosylamide **20a**, $[\alpha]^{25}_D$ +6.3°.

As the ^1H NMR spectra unequivocally assigned the β configuration of amides **10a**, **11a**, **19a**, and **20a** (and the α configuration for the corresponding **10b**, **11b**, **19b**, and **20b**), the discrepancy between the optical rotations could be attributed to epimerization during the cyclization of the furan ring.[8] We must point out that it is difficult to record small optical rotations values and that uncertainties are observed even in recent investigations.[9,10]

The mass spectra of our compounds also afforded valuable information on their structure and configuration.

Both anomers β and α of a same compound exhibited similar fragmentations (characteristic of 2-deoxyribose) with different peak intensities.[18]

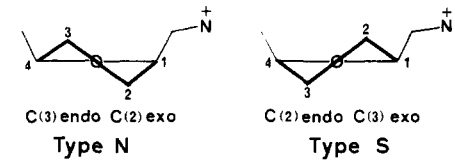

Figure 3.

^1H NMR spectroscopy was the most powerful technique for unequivocal determination of anomeric identity. First, the spectra of both enantiomers in the D and L series are superimposable. Moreover, in accord with previous investigations, the signal and multiplicity of the proton H-1 depended on its configuration:[13] the β anomer exhibited a sharp triplet and the α anomer a doublet of doublets, with a coupling constant $J_{1-2} + J_{1-2'}$ always greater for β than for α (Table I).

The ^1H NMR spectra at 250 MHz of L(+)-muscarine iodide (1, Figure 1) and D(−)-allomuscarine iodide (3, Figure 2) allowed us to make structural assignments and to measure the different coupling constants. Moreover the anomeric purity could be immediately ascertained by the chemical shifts of protons H-2 and H-2′: δ 2.00 (H-2), 2.10 (H-2′) for L(+)-muscarine iodide and δ 1.67 (H-2), 2.62 (H-2′) for D(−)-allomuscarine iodide. Various studies[19] on the conformation of furanose sugars have established a relationship between the coupling constants and the relative percentage of the *N* or *S* preferred conformations:

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(19) Davies, D. B.; Danyluk, S. S. *Biochemistry* **1975**, *13*, 4417 and references cited therein.

Table I. Chemical Shifts (ppm) at 60 MHz (Solvent, $CDCl_3$)

compd D (L)	H-1	H-2,2′	H-3	H-4, H-5,5′	aromatic H	$J_{1-2} + J_{1-2'}$ Hz	other
7a (**17a**)	4.85 (t)	2.45-2.65 (m)	5.60 (m)	4.60 (m)	7.30 (m, 4 H), 8.00 (m, 4 H)	8 + 8	2.50 (s, 6 H, CH_3 arom), 3.80 (s, 3 H, CH_3 ester)
7b (**17b**)	4.90 (dd)	2.55-2.80 (m)	5.55 (m)	4.45-4.75 (m)	7.25 (m, 4 H), 7.95 (m, 4 H)	7.2 + 4	2.50 (s, 6 H, CH_3 arom), 3.80 (s, 3 H, CH_3 ester)
8a (**18a**)	4.90 (t)	2.60-2.75 (m)	5.60 (m)	4.45 (m) 3.85-4.00 (m)	7.35 (m, 2 H), 8.05 (m, 2 H)	8.5 + 8.5	2.50 (s, 3 H, CH_3 arom), 3.90 (s, 3 H, CH_3 ester)
8b (**18b**)	4.95 (dd)	2.65-2.80 (m)	5.60 (m)	4.60 (m) 3.90-4.05 (m)	7.40 (m, 2 H), 8.05 (m, 2 H)	7 + 4.5	2.50 (s, 3 H, CH_3 arom), 3.90 (s, 3 H, CH_3 ester)
10a (**19a**)	5.05 (t)	2.30 (dd)	4.50 (m)	4.05 (m) 3.70 (m)		7.5 + 7.5	3.00 (s, 3 H, NCH_3), 3.05 (s, 3 H, NCH_3)
10b (**19b**)	5.10 (dd)	2.30 (m)	4.20 (m)	3.70 (m)		7 + 3.5	3.05 (s, 3 H, NCH_3), 3.20 (s, 3 H, NCH_3)
11a (**20a**)	4.95 (t)	2.30 (m)	4.45 (m)	4.10 (m)	7.45 (m, 2 H), 7.85 (m, 2 H)	7.25 + 7.25	2.50 (s, 3 H, CH_3 arom), 3.00 (s, 3 H, NCH_3), 3.15 (s, 3 H, NCH_3)
11b (**20b**)	5.05 (dd)	2.25-2.40 (m)	4.60 (m)	4.10-4.40 (m)	7.45 (m, 2 H), 7.90 (m, 2 H)	5.6 + 4	2.55 (s, 3 H, CH_3 arom), 3.05 (s, 3 H, NCH_3), 3.20 (s, 3 H, NCH_3)

% $S = J_{1-2}/J_{1-2} + J_{3-4}$ (Figure 3).

For L(+)-muscarine iodide (β configuration) we observed the predominance of the *S* conformation (76%). For D-(−)-allomuscarine iodide (α configuration), we observed the equal presence of the two conformers *S* and *N* (45% and 55%, respectively). These conformations were confirmed in the other enantiomeric pairs: D(−)-muscarine iodide (**4**) and L(+)-allomuscarine iodide (**2**) and could be attributed to the steric hindrance of the site quaternary ammonium chain in the β configuration. The different flexibilities of these molecules in solution, as shown by their ^1H NMR spectra, coupled with biological data at the molecular level should expand our knowledge of the topology of the muscarinic receptor.

The described investigations will permit easy access to numerous analogues of muscarines which are of potential interest for their pharmacological activities or use as labeled probes for receptor studies in neurobiology.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus. All reported values are uncorrected. Optical rotations were determined on a Perkin-Elmer 241-MC polarimeter. Microanalyses were carried out in our laboratories and in Paris VI University Laboratories. Infrared spectra were obtained on a Perkin-Elmer 137 spectrometer. Nuclear magnetic resonance spectra were obtained on a Varian EM-360 (60 MHz) and a Cameca (250 MHz). Low-resolution mass spectra were obtained on a VG-Micromass spectrometer (70 70 F). Analytical thin-layer chromatography (TLC) was performed on precoated silical gel plates (Merck, 60 F_{254}) and visualized under UV light (254 nm) or with iodine and sprayed with a sugar reagent (anisaldehyde/sulfuric acid + heating). Column chromatography was performed with silica gel 60 (70–230 mesh, Merck). Tetrahydrofuran and ether were distilled from sodium metal or calcium hydride.

1-(Carbomethoxy)-2-deoxy-3,5-di-*O*-*p*-toluoyl- and -3-*O*-*p*-toluoyl-β-D-erythropentofuranose (7a and 8a). A mixture of 4.15 g (10.9 mmol) of β cyanide **6a**[11] and 40 mL of anhydrous methanolic hydrogen chloride (3 N) was stirred overnight at room temperature. The solvent was evaporated under reduced pressure. The crude product was diluted with dichloromethane and an insoluble material was removed by filtration. After column chromatography (dichloromethane, dichloromethane-methanol, 99:1), we isolated 248 mg (5.5 yield) of ditoluoyl ester **7a** and 1.43 g (46.5% yield of monotoluoyl ester **8a**. **7a**: oil; $[\alpha]^{25}_D$ +28.6° (*c* 1.44, $CHCl_3$); R_f 0.47 (petroleum ether–ethyl acetate, 5:3); mass spectrum, *m/e* 353 (1.3, M–COOMe), 276 (7, M − TolOH), 263 (12.6, M − CH_2OTol), 140 (35.2, M − 2 TolOH), 119 (100, Tol), 91 (38.3, C_7H_7). Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.43; H, 6.04. **8a**: oil; $[\alpha]^{25}_D$ −16.2° (*c* 1.08, $CHCl_3$); R_f 0.51 (petroleum ether–ethyl acetate, 1:1); IR (neat) 1755–1720 cm^{-1}; mass spectrum, *m/e* 264 (1.3, M − 30), 263 (5.9, M − 31), 235 (1.1, M − COOMe), 158 (2.4, M − TolOH), 140 (6.0), 136 (3.8, TolOH), 119 (100, Tol), 91 (20.7, C_7H_7). Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.21; H, 6.11.

A third compound **9a** with R_f 0.67 (petroleum ether–ethyl acetate, 1:1) was also isolated and identified as the 5-*O*-*p*-toluoyl ester by its NMR spectra.

1-(*N*,*N*-Dimethylcarboxamido)-2-deoxy-β-D-erythropentofuranose (10a). A solution of 1.48 g (5.05 mmol) of the monotoluoyl ester **8a** in 30 mL of 50% methanolic dimethylamine was heated at 90 °C in a steel bomb for 24 h. The solution was evaporated and the crude amine was purified by column chromatography (dichloromethane–methanol, 96:4) to yield 730 mg (77%) of amine **10a**: mp 100 °C (methanol, petroleum ether); $[\alpha]^{25}_D$ −2.0° (*c* 0.63, $CHCl_3$); R_f 0.70 (dichloromethane–methanol, 90:10); IR 1650 cm^{-1}; mass spectrum, *m/e* 190 (1.3, M + 1), 159 (15, M − 30), 129 (4.4, $CONMe_2$ + 57), 117 (100, M − $CONMe_2$), 100 (98.2, $CONMe_2$ + 28), 73 (59.1, $CONMe_2$ + 1), 72 (63.6, $CONMe_2$). Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.64; H, 8.20; N, 7.17.

1-(*N*,*N*-Dimethylcarboxamido)-2-deoxy-5-*O*-tosyl-β-D-erythropentofuranose (11a). A solution of 725 mg (3.83 mmol) of **10a** in 10 mL of dry pyridine was cooled to −10 °C. After a few minutes, 730 mg (3.83 mmol) of recrystallized *p*-tosyl chloride was added. The mixture was kept at −15 °C for 48 h. After addition of 30 mL of water and extraction with 50 mL of dichloromethane, the organic phase was washed with 1 N hydrochloric acid, sodium bicarbonate, and then water. The dichloromethane layer was dried with sodium sulfate and evaporated under reduced pressure. The crude amine was purified by column chromatography (dichloromethane–methanol, 99:1) to give 880 mg (67% yield) of monotosylamide **11a** [mp 116–117 °C (methanol–petroleum ether); $[\alpha]^{25}_D$ −7° (*c* 0.67, $CHCl_3$); R_f 0.56 (dichloromethane–methanol, 95:5); mass spectra, *m/e* 343 (4.5, M), 271 (6.3, M − $CONMe_2$), 172 (17.7, TsOH), 155 (14.1, Ts), 100 (5.9, $CONMe_2$ + 28), 91 (40.3, C_7H_7), 81 (100, furan=CH_2) 72 (20.5, $CONMe_2$)] and 106 mg (5.6% yield) of ditosylamide [R_f 0.46; petroleum ether–ethyl acetate, 1:2]. Anal. Calcd for $C_{15}H_{21}NO_6S$: C, 52.47; H, 6.17; N, 4.08. Found: C, 52.63; H, 6.45; N, 3.98.

D(−)-Muscarine Iodide (4). A mixture of 25 mL of anhydrous tetrahydrofuran and 360 mg (9.25 mmol) of lithium aluminum hydride was cooled at 0 °C in a two-necked round-bottomed, 100-mL flask with a condenser protected with a calcium chloride drying tube. A solution of 645 mg (1.85 mmol) of tosylate **11a** in 70 mL of anhydrous tetrahydrofuran was added dropwise under stirring. Upon completion of the addition, the reaction mixture was heated under reflux for 1 h. The cooled mixture was hydrolyzed with 5 mL of 30% aqueous potassium hydroxide and filtered. The solvent was removed by evaporation. The aqueous layer was extracted by ethyl acetate several times. The organic

extracts were dried with sodium sulfate, filtered, and concentrated under reduced pressure to give 115 mg of crude amine (39% yield) as an oil: R_f 0.28 (dichloromethane–methanol, 70:30).

To a solution of 90 mg of amine in 5 mL of anhydrous ether was added an excess of methyl iodide. After a few minutes, a white precipitate appeared. The supernatant ether was decanted. After several coevaporations with anhydrous ether, 110 mg of crystalline solid was obtained.

Recrystallizations from acetone–petroleum ether gave 70 mg (42% yield) of D(−)-muscarine iodide (4) as white flakes: mp 145–146 °C; $[\alpha]^{25}_D$ −6.1° (c 0.45, H_2O) [lit.[8] $[\alpha]^{25}_D$ −7.8° (c 1, H_2O)]. Anal. Calcd for $C_9H_{20}INO_2$: C, 35.89; H, 6.69; N, 4.64. Found: C, 35.86; H, 6.67; N, 4.71.

The same procedure described for the transformation of cyanide **6a** to D(−)-muscarine iodide (4) was used for the synthesis of the three other isomers.

1-(Carbomethoxy)-2-deoxy-3,5-di-*O*-*p*-toluoyl- and -3-*O*-*p*-toluoyl-α-D-erythropentofuranose (7b and 8b). A mixture of 3.24 g (8.54 mmol) of **6b** with 40 mL of 2.5 N methanolic hydrogen chloride gave 380 mg (11% yield) of ditoluoyl ester **7b** and 1.32 g (52% yield) of 3-toluoyl ester **8b**. **7b**: mp 69 °C; $[\alpha]^{25}_D$ +55.4° (c 0.43, $CHCl_3$); R_f 0.45 (petroleum ether–ethyl acetate, 5:3). Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.78; H, 6.05. **8b**: mp 95 °C; $[\alpha]^{25}_D$ +28.7° (c 0.69, $CHCl_3$); R_f 0.41 (petroleum ether–ethyl acetate, 1:1); IR (KBr) 1750, 1720 cm^{-1}; mass spectrum, *m/e* 264 (1.7, M–30), 263 (9.9, M − 31), 235 (5.6, M − COOMe), 158 (10.6, M − TolOH), 140 (30.4), 137 (13.7, TolOH + H), 119 (100, Tol), 91 (31.4, C_7H_7). Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.10; H, 6.16.

1-(*N*,*N*-Dimethylcarboxamido)-2-deoxy-α-D-erythropentofuranose (10b). A mixture of 300 mg (0.14 mmol) of **7b** and 1.31 g (0.84 mmol) of **8b** gave 765 mg (78% yield) of amide **10b**: oil; $[\alpha]^{25}_D$ +83° (c 0.67, $CHCl_3$); R_f 0.70 (dichloromethane–methanol, 90:10); IR 1640 cm^{-1}; mass spectrum, *m/e* 190 (14.1, M + 1), 159 (3.9, M − 30), 129 (12.8, $CONMe_2$ + 57), 117 (93, M − $CONMe_2$), 100 (100, $CONMe_2$ + 28), 73 (71.2, $CONMe_2$ + 1), 72 (84.4, $CONMe_2$). Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.89; H, 8.04; N, 7.69.

1-(*N*,*N*-Dimethylcarboxamido)-2-deoxy-5-*O*-tosyl-α-D-erythropentofuranose (11b). Amide **10b** (0.69 g, 3.65 mmol) treated with 0.695 g of *p*-tosyl chloride gave 820 mg (66% yield) of monotosylamide **11b** and 170 mg (9% yield) of ditosylamide [R_f 0.32 (petroleum ether–ethyl acetate, 1:2)]. **11b**: mp 99–100 °C; $[\alpha]^{25}_D$ +49.5° (c 0.44, $CHCl_3$); R_f 0.81 (dichloromethane–methanol, 95:5); mass spectrum, *m/e* 343 (2.0, M), 271 (6.5, M − $CONMe_2$), 172 (1.7, TsOH), 171 (7.7, TsO), 155 (12.7, Ts), 100 (22.2, $CONMe_2$ + 28), 91 (23.2, C_7H_7), 81 (100, furan=CH_2), 72 (23.7, $COMe_2$). Anal. Calcd for $C_{15}H_{21}NO_6S$: C, 52.47; H, 6.17; N, 4.08. Found: C, 52.30; H, 6.39; N, 4.41.

L(+)-Allomuscarine Iodide (2). 5-*O*-Tosylamide **11b** (815 mg, 2.37 mmol) gave 195 mg of L(+)-allomuscarine iodide (**2**) as white crystals: mp 127–128 °C (acetone–petroleum ether); $[\alpha]^{25}_D$ +36.8° (c 0.74, H_2O); $[\alpha]^{25}_D$ +37.8° (c 0.56, EtOH) [lit.[3] $[\alpha]^{25}_D$ for the synthetic alkaloid, +29° (EtOH)]. Anal. Calcd for $C_9H_{20}INO_2$: C, 35.89; H, 6.69; N, 4.64. Found: C, 36.18; H, 6.49; N, 4.70.

2-Deoxy-L-ribose (13). L-Arabinose (**12**) was manipulated as described in the literature[14] with some modifications: the transformation of 3,4-di-*O*-acetyl-L-arabinal into L-arabinal was carried out with 3 N sodium hydroxide, followed by neutralization with an acidic cation-exchange resin (Dowex-W 50); hydration of L-arabinal with 1 N sulfuric acid at 0 °C (2 h) was followed by neutralization with an anion-exchange resin (AG 2 X-10) to give 2-deoxy-L-ribose (**13**) as a hard colorless oil (10% overall yield): $[\alpha]^{25}_D$ +49° (c 1.06, H_2O).

2-Deoxy-3,5-di-*O*-*p*-toluoyl-β- and -α-L-erythropentofuranosyl 1-Cyanide (16a and 16b). The procedure described in the D series for the transformation of **5** to **6a** and **6b**[11] was used herein. Compound **13** (11.45 g, 85.36 mmol) afforded in the first step a mixture of the two anomers β- and α-*O*-methyl **14a** and **14b**, which were separated by column chromatography (70% yield). **14a**: mp 75–76 °C; $[\alpha]^{25}_D$ +8.8° (c 0.52, $CHCl_3$). Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.37; H, 6.64. **14b**: mp 82–83 °C; $[\alpha]^{25}_D$ −126.7° (c 0.62, $CHCl_3$). Anal. Found: C, 68.20; H, 6.62.

Treatment of **14a** and **14b** with hydrogen chloride in acetic acid gave **15** (70% yield): mp 119 °C; mass spectrum, *m/e* 353 (1.5, M − Cl), 216 (13.5, M − Cl − TolOH), 136 (26.5, TolOH), 119 (100, Tol), 91 (48.8, C_7H_7), 81 (73, furan=CH_2).

Compound **15** was treated with dry sodium cyanide in freshly distilled monoglyme to afford after column chromatography the two anomers β and α **16a** and **16b** (70% yield), with predominance of the β anomer (80%).

16a: mp 109–110 °C (ethanol); $[\alpha]^{25}_D$ −25.3° (c 2.11, $CHCl_3$) [in the D series, $[\alpha]^{25}_D$ +24.6° (c 0.81, $CHCl_3$)]; mass spectrum, *m/e* 379.5 (0.1, M), 260 (0.3, M − Tol), 243 (6.1, M − TolOH), 230 (2.6, M − CH_2OTol), 137 (1.2, TolOH + H), 19 (100, Tol), 91 (17.6, C_7H_7). Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.67; H, 5.90; N, 4.03.

16b: mp 143–144 °C (ethanol); $[\alpha]^{25}_D$ −59.45° (c 1.44, $CHCl_3$) [in the D series, $[\alpha]^{25}_D$ +60.6° (c 0.65, $CHCl_3$)]; mass spectrum, *m/e* 243 (18.1, M − TolOH), 230 (4.8, M − CH_2OTol), 137 (5.0, TolOH + H), 136 (6.1, TolOH), 119 (100, Tol), 91 (98.3, C_7H_7). Anal. Found for $C_{22}H_{21}NO_5$: C, 69.54; H, 5.99; N, 3.89.

1-(Carbomethoxy)-2-deoxy-3,5-di-*O*-*p*-toluoyl- and -3-*O*-*p*-toluoyl-β-L-erythropentofuranose (17a and 18a). Compound **16a** (1.3 g, 3.43 mmol) was treated with 50 mL of 1.5 N methanolic hydrogen chloride solution to afford 670 mg (47.5% yield) of ditoluoyl ester **17a** and 115 mg (11% yield) of 3-toluoyl ester **18a**. **17a**: oil; $[\alpha]^{25}_D$ −31.5° (c 1.26, $CHCl_3$); Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.75; H, 6.16. **18a**: mp 55–56 °C; $[\alpha]^{25}_D$ +15.3° (c 0.63, $CHCl_3$); mass spectrum, *m/e* 264 (1.7, M − 30), 263 (8.3, M − 31), 235 (0.9, M − COOMe), 158 (1.6, M − TolOH), 137 (6.1, TolOH + H), 136 (3.0, TolOH), 119 (100, Tol). Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.53; H, 6.46.

1-(*N*,*N*-Dimethylcarboxamido)-2-deoxy-β-L-erythropentofuranose (19a). Compound **17a** (0.67 g, 1.63 mmol) and compound **18a** (0.1 g, 0.34 mmol) yielded amine **19a** (71%): mp 103 °C (THF); $[\alpha]^{25}_D$ +1° (c 0.85, $CHCl_3$); mass spectrum, *m/e* 190 (4.0, M + 1), 159 (5.9, M − 30), 117 (100, M − $CONMe_2$), 100 (90.6, $CONMe_2$ + 28), 73 (71.2, $CONMe_2$ + 1), 72 (84.4, $CONMe_2$). Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.79; H, 8.31; N, 7.41.

1-(*N*,*N*-Dimethylcarboxamido)-2-deoxy-5-tosyl-β-L-erythropentofuranose (20a). Compound **19a** (250 mg, 1.32 mmol) reacted with 2.80 mg (1.45 mmol) of *p*-tosyl chloride to afford 300 mg (66% yield) of 5-tosyl amide **20a**: mp 116–117 °C; $[\alpha]^{25}_D$ +6.3° (c 0.73, $CHCl_3$); mass spectrum, *m/e* 343 (3.2, M), 271 (7.4, M − $CONMe_2$), 172 (2.5, TsOH), 171 (5.5, TsO), 155 (22.0, Ts), 100 (9.1, $CONMe_2$ + 28), 91 (37.8, C_7H_7), 81 (100, furan=CH_2), 72 (30.3, $CONMe_2$). Anal. Calcd for $C_{15}H_{21}NO_6S$: C, 52.47; H, 6.17; N, 4.08. Found: C, 52.73; H, 6.45; N, 4.27.

L(+)-Muscarine Iodide (1). 20a (270 mg, 0.78 mmol) gave after recrystallization 65 mg of L(+)-muscarine iodide (1) as white flakes: mp 145–147 °C (acetone–petroleum ether); $[\alpha]^{25}_D$ +5.9° (c 0.41, H_2O) [lit.[16] $[\alpha]^{25}_D$ for the chloride, +6.7° (H_2O); lit.[3] $[\alpha]^{22}_D$ for the iodide, +3.1° (EtOH)]. Anal. Calcd for $C_9H_{20}INO_2$: C, 35.89; H, 6.69; N, 4.64. Found: C, 35.76; H, 6.40; N, 4.64.

1-(Carbomethoxy)-2-deoxy-3,5-di-*O*-*p*-toluoyl- and -3-*O*-*p*-toluoyl-α-L-erythropentofuranose (17b and 18b). Compound **16b** (0.53 g, 1.4 mmol) was treated with 20 mL of 2 N methanolic hydrogen chloride solution to afford 155 mg (26% yield) of ditoluoyl ester **17b** and 260 mg (39%) of 3-toluoyl ester **18b**. **17b**: mp 71–72 °C; $[\alpha]^{25}_D$ −55.3° (c 0.49, $CHCl_3$); mass spectrum, *m/e* 353 (1.9, M − COOMe), 276 (6.7, M − TolOH), 263 (7.1, M − CH_2OTol), 140 (28.7, M − 2 TolOH), 119 (100, Tol), 91 (21.7, C_7H_7), 81 (61.1, furan=CH_2). Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.58; H, 6.01. **18b**: mp 98 °C; $[\alpha]^{25}_D$ −27.8° (c 0.46, $CHCl_3$); mass spectrum, *m/e* 264 (3.6, M − 30), 263 (13.2, M − 31), 235 (6.9, M − COOMe), 158 (9.8, M − TolOH), 140 (35.7), 137 (16.9, TolOH + H), 119 (100, Tol), 91 (49.4, C_7H_7). Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.11; H, 6.36.

1-(*N*,*N*-Dimethylcarboxamido)-2-deoxy-α-L-erythropentofuranose (19b). Compound **17b** (415 mg, 1 mmol) gave 135 mg (71% yield) of amide **19b** as an oil: $[\alpha]^{25}_D$ +85.0° (c 0.80, $CHCl_3$); mass spectrum, *m/e* 190 (7.3, M + 1), 159 (2.4, M − 30), 129 (9.1, $CONMe_2$ + 57), 117 (100, M − $CONMe_2$), 100 (99.9, $CONMe_2$ + 28), 73 (59.0, $CONMe_2$ + 1), 72 (75.9, $CONMe_2$). Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 51.66; H, 8.20; N, 6.58.

1-(*N*,*N*-Dimethylcarboxamido)-2-deoxy-5-*O*-tosyl-α-L-erythropentofuranose (20b). Compound **19b**, (225 mg, 1.2

mmol) was treated with 250 mg (1.32 mmol) of tosyl chloride to yield 250 mg (61%) of tosylamide **20b**: mp 100 °C; $[\alpha]^{25}_D$ -49.0° (c 0.76, $CHCl_3$); mass spectrum, m/e 343 (1.5, M), 271 (6.3, M - $CONMe_2$), 172 (1.1, TsOH), 171 (5.4, TsO), 155 (15.7, Ts), 100 (26.1, $CONMe_2$ + 28), 91 (27.7, C_7H_7), 81 (100, furan=CH_2), 72 (25.5, $CONMe_2$). Anal. Calcd for $C_{15}H_{21}NO_6S$: C, 52.47; H, 6.17; N, 4.08. Found: C, 52.67; H, 6.08; N, 4.15.

D(-)-Allomuscarine Iodide (3). Compound **20b** (185 mg, 0.54 mmol) gave after recrystallization 60 mg (37% yield) of D(-)-allomuscarine iodide (**3**) as white crystals: mp 125-126 °C (acetone-petroleum ether); $[\alpha]^{25}_D$ -37.7° (c 0.65, H_2O); $[\alpha]^{25}_D$ -39.1° (c 0.38, EtOH) [lit.[17] $[\alpha]^{22}_D$ for natural alkaloid, -32° (c 1.1, H_2O)]. Anal. Calcd for $C_9H_{20}INO_2$: C, 35.89; H, 6.69; N, 4.64. Found: C, 36.03; H, 6.56; N, 4.48.

Acknowledgment. We are grateful to Dr. J. Igolen for his support and helpful discussions and acknowledge the assitance of Dr. S. Tran Dinh, CEA Saclay for ^1H NMR spectra at 250 Hz. We thank Professor M. M. Joullié, University of Pennsylvania, for helping to improve this manuscript. One of us (S.P.) also acknowledges the Délégation Générale à la Recherche Scientifique for a grant.

Registry No. 1, 24570-49-8; 2, 79827-61-5; 3, 35119-38-1; 4, 79827-62-6; 6a, 50908-41-3; 6b, 50908-40-2; 7a, 79827-63-7; 7b, 79827-64-8; 8a, 79827-65-9; 8b, 79827-66-0; 9a, 79827-67-1; 10a, 79827-68-2; 10b, 79827-69-3; 11a, 79827-70-6; 11b, 79827-71-7; 11b ditosylamide, 79827-82-0; 12, 5328-37-0; 13, 18546-37-7; 14a, 22837-37-2; 14b, 22837-36-1; 15, 3056-12-0; 16a, 79827-72-8; 16b, 79827-73-9; 17a, 79827-75-1; 18a, 79827-76-2; 18b, 79827-77-3; 19a, 79827-78-4; 19b, 79827-79-5; 20a, 79827-80-8; 20b, 79827-81-9; 2,5-dideoxy-1-[(dimethylamino)methyl]-β-D-erythropentofuranose, 79827-82-0.

Degradation of Cloprednol in Aqueous Solution. The Enolization Step

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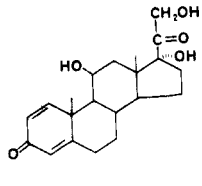
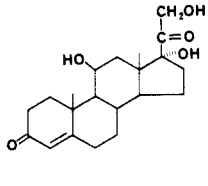
Received September 4, 1981

The degradation of the glucocorticoid cloprednol (**3a**) and its 21,21-dideuterio analogue (**3c**) was studied in aqueous solution at 60 °C. The kinetic deuterium isotope effect was found to vary from 5.5 under acidic conditions to 1.0 under alkaline conditions, indicating a change in rate-determining step as a function of pH. Incorporation of hydrogen into the C-21 position of cloprednol in partially degraded samples of **3c** occurred slowly or not at all under acidic conditions but occurred rapidly under alkaline conditions. These results are consistent with the formation of an obligatory enol intermediate in the degradation reaction of cloprednol and require a change in the rate-determining step from rate-determining enolization under acidic conditions to reversible enol formation under alkaline conditions. Prednisolone (**1**), hydrocortisone (**2**), and other glucocorticoids possessing the dihydroxyacetone group at C-17 are expected to behave similarly.

Many of the synthetic glucocorticoids used clinically share a common structural feature, namely, the dihydroxyacetone group at C-17. The degradation of two glucocorticoids, prednisolone (**1**) and hydrocortisone (**2**), has been studied in aqueous solution, and the reactivity observed was derived exclusively from transformations of the dihydroxyacetone group.[1-3]



1



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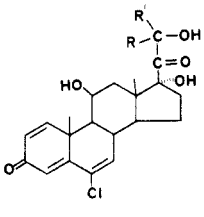

3a R=R'=H
3b R=H R'=D
3c R=R'=D

Kinetic and product studies of the degradation of both prednisolone (**1**) and hydrocortisone (**2**) have provided some insight into the reactivity of the dihydroxyacetone group, but elucidation of a detailed mechanism of decomposition has been frustrated by the complex nature of the reaction. Previous studies have shown that the degradation products are derived from both oxidative and solvolytic pathways. Both the type of degradation products formed and the rate of degradation have been shown to exhibit dependence on pH, trace metal ions, and oxygen.[1,4-11]

In every attempt to describe the mechanism of degradation of glucocorticoids an assumption has been made that enolization of the dihydroxyacetone group is the first step of the reaction.[4-6,8-10,12-14] There has been less agreement on the kinetic significance of enolization on the overall reaction rate. Pitman and co-workers presumed that enolization was the rate-determining step in the degradation of hydrocortisone in alkaline solution.[15] Recently, Hansen and Bundgaard have proposed a mechanistic scheme involving reversible enol formation and ionization to explain the observed pH-log k_{obsd} profile they obtained for hydrocortisone.[6] For an answer to some fundamental questions relating to the role enolization may play in the degradation of this class of steroids in aqueous solution,[16] kinetic isotope and exchange studies of deuterium at C-21 in a new systemic glucocorticoid, clopred-

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(16) Cloprednol (**3**) differs from prednisolone (**1**) and hydrocortisone (**2**) in rings A and B only, far from the reactive site. The reactivity of the dihydroxyacetone side chain in these steroids is expected to be nearly identical.

0022-3263/82/1947-0198$01.25/0