ON THE STEREOCHEMISTRY OF CARBONYL SUBSTITUENTS AT THE 8-POSITION IN THE LYSERGIC ACID DERIVATIVES AND THEIR DESPYRROLE ANALOGS

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Abstract ——— The isomerization of the carbonyl substituents at the 8-position in some despyrrololysergic acid derivatives was discovered and stereochemical studies on the configuration of the 8-substituents and on the conformation of ring D in the lysergic acid derivatives and their despyrrole analogs were also carried out.

Potent pharmacological activity of ergot alkaloids, particularly lysergic acid derivatives, such as vasoconstriction, serotonin antagonism and hallucinogenic activity, has been considered as relying on the configuration of their carbonyl group at the 8-position[1], thus triggered many extensive studies[2-8] on their stereochemistry. In the course of our synthetic study on ergot alkaloids, we have succeeded in the synthesis of a number of despyrrole analogs of ergot alkaloids[9a-c] of which the compounds (5) and (6) were regarded as the lysergic acid analogs. This paper deals with our finding on the isomerization of the carbonyl substituents at the 8-position in some despyrrololysergic acid derivatives and stereochemical study on the configuration of the 8-substituents and on the conformation of ring D[1] in the lysergic acid derivatives and their despyrrole analogs.

The Preparation and Structure of Despyrrololysergic Acid Derivatives (5 and 6)

The compounds (5a), (6a), and (5b) having the structures analogous to lysergic acid and its derivatives (1a), (2a), and (1b) lacking only a pyrrole ring (ring B) were prepared and separated as follows. Two epimeric hydroxy esters (3) and (4), which were synthesized and separated as described in the previous paper[9b], were dehydrated by treatment with phosphorus oxychloride and phosphoric acid in pyridine[10a] to give a mixture of two unsaturated esters (5a) and (6a), epimeric with respect to the configuration of an ester group, with a ratio of about 2 : 1

in favor of the former (5a). The separation of (5a) and (6a) was performed successfully by the use of hplc[11]. A mixture of (5a) and (6a) was converted into the corresponding dimethylamide (5b) upon acid hydrolysis with 10% hydrochloric acid followed by amidation with imidazole, triphenyl phosphite, and dimethylamine[12]. However, the dimethylamide (5b) was found to be homogeneous on its isolation from its nmr spectrum. The stereochemistry of these separated despyrrole analogs (5a), (6a), and (5b) were determined from their nmr spectra upon comparison with those of the corresponding lysergic acid derivatives (1a), (2a), and (1b) as summarized in the Table. In the nmr spectra of the despyrrole analogs (5a) and (5b), the signal patterns of their 9-protons resemble very closely with those of lysergic acid derivatives (1a) and (1b), thus suggesting the β-configuration of the 8-substituents in (5a) and (5b). On the other hand, the signal pattern of the 9-proton in the despyrrole analog (6a) resembles well with that of (2a), established the α-configuration at the 8-position.
Next, we investigated the conformation of ring D in the lysergic acid derivatives and their despyrrole analogs by the comparisons of the nmr spectra of two epimeric pairs of (5a) and (6a), and (1a) and (2a). In the nmr spectra of the compounds (5a) and (1a) having an 8β-substituent, the 9-proton appears as a broad singlet and the 8-proton is coupled with the 7ax-proton (J= ca 11 Hz) and with the 7eq-proton (J=5-6 Hz). On the other hand, in the nmr spectra of the compounds (6a) and (2a) having an 8α-substituent, the 9-proton appears as a broad doublet with J=4-5 Hz and the couplings of the 8-proton with the geminal protons at the 7-position are very small ($\sim$5 Hz). Therefore, it is assumed from these nmr spectra that the conformation of ring D in the compounds (5a), (1a), (6a), and (2a) would take a half chair form irrespective of the configuration of the 8-substituent. All the other proton signals also coincide well with the above stereochemistry. Thus, it is now concluded that the 8-substituents in (5a) and (1a) are in a β-equatorial orientation while an α-axial orientation in (6a) and (2a) as shown in the Chart. In addition, the stereochemistry of the compouds (5b) and (1b) having a dimethylamido group at the 8-position, which have very resembled nmr spectra with those of the 8-substituted derivatives (5a) and (1a), could be determined as having a 8β-equatorial substituent as also shown in the Chart.

The Isomerization and Equilibration of the Substituents at the 8-Position

As described, dehydration of the hydroxy esters (3) and (4) afforded a mixture

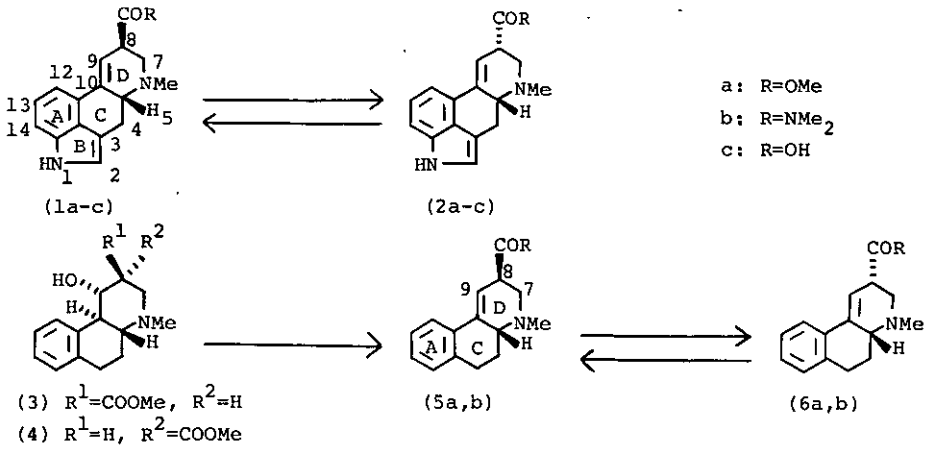

Table ^{1}H nmr Data for Benzo[f]quinoline Group and Ergoline Group in $CDCl_3$ (200 MHz).

Compds.	9-H	8-H	7eq-H	7ax-H	5-H	NMe	COOMe
			[Benzo[f]quinoline Group]				
(5a) 8β-COOMe	6.42 (br s)	3.66 (m)	3.22(br dd, J=11.5, 6)	2.56(t, J=11.5)	2.80(dq, J=12, 3)	2.53 (s)	3.78 (s)
(6a) 8α-COOMe	6.39 (br d, J=5)	3.21 (m)	3.37(br d, J=12)	2.62-2.44 (m)	2.77(br d, J=13)	2.50 (s)	3.74 (s)
(5b) 8β-$CONMe_2$	6.20 (br s)	3.94 (m)	3.04(br dd, J=11, 5)	2.73(t, J=11)	2.90 (m)	2.54 (s)	-
			[Ergoline Group]				
(1a)* 8β-COOMe	6.64 (br s)	3.77** (m)	3.31(br dd, J=11, 5)	2.72(t, J=11)	3.24 (m)	2.64 (s)	3.80 (s)
(2a)* 8α-COOMe	6.58 (br d, J=4)	3.32 (m)	3.37(br d, J=12)	2.84-2.64** (m)	3.22** (m)	2.59 (s)	3.74 (s)
(1b)*** 8β-$CONMe_2$	6.36 (br s)	3.98 (m)	3.08(br dd, J=11.2, 5.3)	2.89(dd, J=11.2, 10.4)	3.20 (m)	2.59 (s)	-

* Samples gifted from Dr. P. A. Stadler, SANDOZ LTD.

** Different values were reported[6].

*** The values reported by K. Bailey and A. A. Grey[7].

Chart

of two unsaturated esters (5a) and (6a) which were successfully separated.
The oily unsaturated esters (5a) and (6a) were found to isomerize to an equilibrium mixture of these two esters with the ratio of 2 : 1 when standing at room temperature neat for 2 days or in methanol for 5 h respectively. Furthermore, when the nmr spectrum was measured right after refluxing this equilibrium mixture in deuterium methoxide for 3 h, a signal for 8-proton at δ3.66 disappeared while the peaks due to 7eq-proton at δ3.22 and peak due to 7ax-proton at δ2.56 were changed to doublets with the coupling constants of 11.5 Hz in (5a) while the proton signal for the 8-position at δ3.21 also disappeared in (6a). These facts revealed that the 8-protons both in (5a) and (6a) are active and exchangeable hydrogens even in methanol as in the cases of lysergic acid (1c) and isolysergic acid (2c), each of which was also known[4] to form an equilibrium mixture in protic solvent.
Ethanolysis of this equilibrium mixture of two unsaturated esters (5a) and (6a) afforded a mixture of two ethyl esters which was shown to be an equilibrium mixture with a ratio of 5 : 2 in favor of the 8β-ethyl ester from the result of their behavior on hplc and the nmr spectrum[10].
Next, we investigated the isomerization of the oily dimethylamide (5b) which was obtained homogeneously from a mixture of two epimers (5a) and (6a) and was found not to isomerize in methanol. These results suggest that the compound (6b) having an amide group at the 8α-position would be very unstable and susceptible to isomerization to the stable isomer (5b). This coincides well with the fact that in the lysergic acid derivatives, methyl lysergate (1a) and methyl isolysergate (2a) afford a 3 : 2 equilibrium mixture[13], while their dimethylamides (1b) and (2b) yield an equilibrium mixture with the ratio of 84 : 16[3]. Further, the fact that complete hydrogen-deuterium exchange at the 8-position with deuterium methoxide was observed in the case of (5a) and (6a) whereas no such exchange was detected in the amide (5b) clearly showed marked difference in their reactivity of hydrogen at the 8-position.

In conclusion, although the isomerization of substituents at the 8-position in the lysergic acid derivatives has been explained in terms of activation of hydrogen at the 8-position by the double bond conjugated with indole nucleus[2], it is now provided the fact that the double bond conjugated with benzene ring such as in the benzo[f]quinoline analogs also has an activation effect on the hydrogen at the 8-position for isomerization.

ACKNOWLEDGEMENT

We warmly thank Dr. P. A. Stadler, SANDOZ LTD., for a sample of lysergic acid derivative.

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13 We found that methyl lysergate (1a) and methyl isolysergate (2a) underwent isomerization in methanol to afford a 3 : 2 equilibrium mixture. This ratio coincides with that reported by J. Rebek, et al. (see ref. 6).

Received, 23rd April, 1984