

Circular Dichroism Studies of Some 13-Oxosparteines

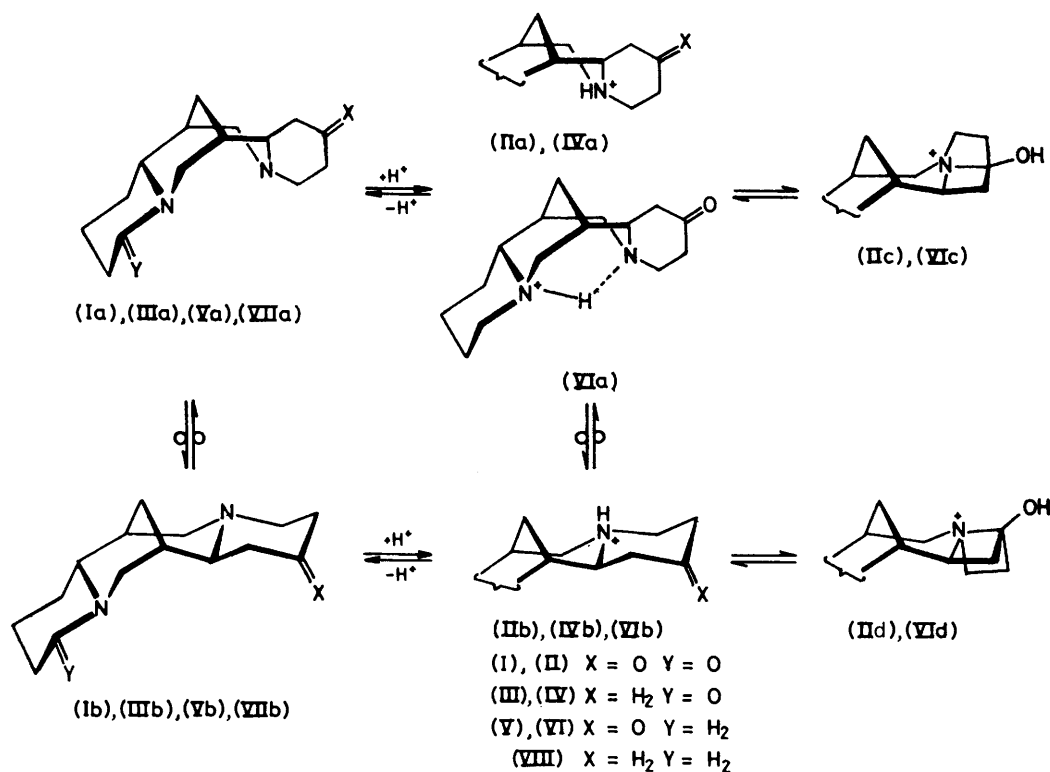
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C.d. data for 13-oxosparteines and related compounds provide direct evidence for the process of protonation, involving possible transannular interaction of the carbonyl and amine functions in the ring D boat form. Transannular interactions are found to occur both in the 11 α - and in the more rigid 11 β -series. In the 11 α -series transannular interaction in ring D requires ring C to adopt a boat conformation. The ring D bridged forms are evidently stabilized in water and presumably in other protic solvents. In the absence of a 2-oxo-function the process of transannular interaction upon acidification is retarded due to intramolecular hydrogen bonding between N(1) and N(16).

2,13-DIOXO-11 α -SPARTEINE (I) is an interesting alkaloid in which lactam, tertiary amine, and ketone functions are all included in a tetracyclic skeleton. This skeleton was found to exist in an equilibrium of the all-chair (Ia) and c boat (Ib) conformers, on the basis of both chemical and spectroscopic studies.¹ The equilibrium

the observation of conformational changes in this chiral molecule.

The c.d. studies reported here are extended to some related compounds, *i.e.* 13-oxo-11 α -sparteine (V), with no lactam function, and 2,13-dioxo-11 β -sparteine (VIII), with a *trans*-quinolizidine skeleton.



(Ia) \rightleftharpoons (Ib) is simply rationalized in terms of dipole-dipole interaction between the two nitrogen functions, destabilizing the otherwise energetically favoured all-*trans* conformation (Ia).

Recently, the results of catalytic hydrogenation of (I) suggested the formation of the D boat species (IId) in the presence of acid.² In this case, the D boat conformation would be stabilized by transannular interaction between carbonyl at C(13) and the protonated tertiary N(16) amine function.

These findings required, however, additional physico-chemical evidence for the postulated conformation. C.d. measurements were clearly the method of choice for

Some c.d. data for (I) have already been published in connection with chiroptical studies of various sparteine alkaloids.³

RESULTS AND DISCUSSION

C.d. data for (I), (V), and (VIII) in various solvents are reported in Tables 1–3, respectively. The concentrations of solutions (0.001–0.01M) correspond to those used in hydrogenation reactions.² There are four optically active transitions observed in the spectral region 200–300 nm, namely the well known ketone $n-\pi^*$ transition, the amide $n-\pi^*$ and $\pi-\pi^*$ bands, and another transition, here ascribed to a σ -bonded tran-

sition resulting from the interaction between the π -orbital of the 13-oxo-group and the amine n orbital. The variations of the magnitude of Cotton effects within these transitions are discussed below.

Ketone $n-\pi^*$ Transition.—This is easily observed in the c.d. spectra of (I) as a negative band at *ca.* 290 nm (Table 1) in accord with the predictions of the octant rule⁴ for either (Ia or b).

Not unexpectedly, the magnitude of the Cotton effect and the position of its maximum depend upon solvent polarity. Although this is a general feature of the c.d.

further addition of HCl (entries 7—9) has little influence on the c.d. spectra.

The disappearance of the ketone Cotton effect is unexpected, since ketones do not usually show a variation in the magnitude of $\Delta\epsilon$ with pH of an aqueous solution. However, the observed results can be rationalized if protonation of (I) at N(16) is followed by formation of the bridged quaternary salt (IIc), which has rings c and d in the boat form.

In acetonitrile, acidification of (I) with HClO₄ (entry 17) or the use of crystalline mono- and di-perchlorates of

TABLE 1
C.d. spectra of 2,13-dioxo-11 α -sparteine (I)

No.	Solvent	pH	Ketone $n-\pi^*$	σ coupled $n-\pi^*$	Lactam	
					$n-\pi^*$	$\pi-\pi^*$
1	H ₂ O + 1 equiv. NaOH	12.0	-1.85 (286.5)	+0.17 (252)	+5.6 (221)	-4.9 (202)
2	H ₂ O	7.7	-1.32 (286.5)	+0.17sh (250)	+6.3 (222)	-6.1 (202)
3	H ₂ O + 0.25 equiv. HCl	7.3	-1.06 (286.5)	+sh (253)	+7.5 (222)	-8.9 (202)
4	H ₂ O + 0.50 equiv. HCl	6.9	-0.82 (286.5)	+sh (255)	+8.1 (222)	-9.8 (202)
5	H ₂ O + 0.75 equiv. HCl	6.5	-0.55 (286.5)		+8.5 (222)	-11.1 (201)
6	H ₂ O + 1 equiv. HCl	5.6	-0.20 (286.5)		+9.2 (223)	-13.2 (201)
7	H ₂ O + 1.5 equiv. HCl	3.6	-0.11 (286.5)		+9.4 (223)	-13.4 (201)
8	H ₂ O + 2.5 equiv. HCl	1.8	-0.10 (287)		+9.7 (223)	-13.6 (201)
9	H ₂ O + 25 equiv. HCl	0.7	-0.10 (287)		+9.8 (223)	-13.8 (201)
10	MeOH		-1.51 (293)	+1.65 (244)		-1.9 (209)
11	MeOH + 2 equiv. 70% HClO ₄ ^a		-0.02 (295)		+10.1 (225)	-17.8 (201)
12	MeOH, (VI)·HClO ₄		-0.07 (293)		+7.5 (226)	-14.0 (201)
13	EtOH		-1.49 (293)	+2.3 (236)		-4.7 (206)
14	MeCN		-2.19 (296)	+3.4 (245)		-5.3 (214)
15	MeCN, (I)·HClO ₄		-0.87 (293) ^b		+10.5 (232)	-29.4 (204)
16	MeCN, (I)·2HClO ₄		-0.99 (294) ^b		+2.0 (231)	-5.2 (202)
17	MeCN + >2 equiv. 70% HClO ₄		-0.98 (295) ^b		+1.5 (232)	-3.2 (205)
18	MeCN, (VI)·HClO ₄		-1.05 (293) ^b		+11.4 (232)	-32.6 (204)
19	Dioxan		-2.05 (296)	+5.7 (241)		-10.6 (212)
20	CHCl ₃		-2.44 (297)			

^a Previous c.d. data³ for the salt of (I) in acidic methanol are evidently in error. ^b Shows vibronic structure.

TABLE 2
C.d. spectra of 2,13-dioxo-11 β -sparteine (VIII)

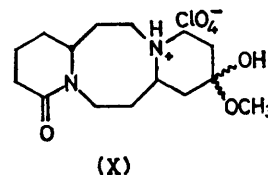
No.	Solvent	pH	Ketone $n-\pi^*$	σ -coupled $n-\pi^*$	Lactam	
					$n-\pi^*$	$\pi-\pi^*$
1	H ₂ O + 1 equiv. NaOH	11.9	+1.38 (283)	-0.11 (251)	+8.4 (223.5)	-10.4 (201)
2	H ₂ O	7.5	+0.94 (283.5)		+9.5 (223.5)	-15.3 (202)
3	H ₂ O + 0.25 equiv. HCl	7.2	+0.75 (283.5)		+10.1 (223.5)	-16.8 (202)
4	H ₂ O + 0.50 equiv. HCl	6.8	+0.555 (284)		+10.6 (224.5)	-19.2 (202)
5	H ₂ O + 0.75 equiv. HCl	6.2	+0.365 (284)		+11.0 (224.5)	-21.6 (202)
6	H ₂ O + 1 equiv. HCl	4.9	+0.21 (284)		+11.5 (225)	-22.9 (202.5)
7	H ₂ O + 1.5 equiv. HCl	3.4	+0.07 (286)		+11.8 (224)	-24.6 (202)
8	H ₂ O + 2.5 equiv. HCl	2.9	+0.07 (286)		+12.1 (223.5)	-24.6 (202)
9	H ₂ O + 25 equiv. HCl	1.7	+0.07 (286)		+12.1 (223.5)	-24.6 (202)

spectra of ketones, the variations of the magnitude of Cotton effects apparently also reflect the equilibrium between (Ia and b). In less polar solvents (Table 1, entries 14, 19, and 20) the equilibrium is shifted toward (Ib) and higher values of $\Delta\epsilon$ are expected for (Ib), according to the octant projection (Figure 1a and b) while in polar solvents (entries 2, 10, and 13) the all-chair conformation (Ia) dominates.

The influence of pH on the conformational equilibrium was studied in some detail. It was found that addition of HCl to aqueous solution of (I) brings about successive lowering of the ketone Cotton effect (entries 1—6).^{*} A steady state is reached with one mol. equiv. of HCl;

^{*} The corresponding disappearance of the weak $n-\pi^*$ shoulder can be observed in the u.v. spectrum.

(I)⁵ (entries 15 and 16) does not result in complete disappearance of the $n-\pi^*$ Cotton effect. It retains about half its magnitude, measured in non-acidified acetonitrile (entry 14), suggesting the presence of the N(16) protonated, but not quaternized, species (IIa or b) in the equilibrium. Furthermore, the 'hemiacetal form' (X), when dissolved in acetonitrile gives a c.d. spectrum (entry 18) almost identical with that of the mono-



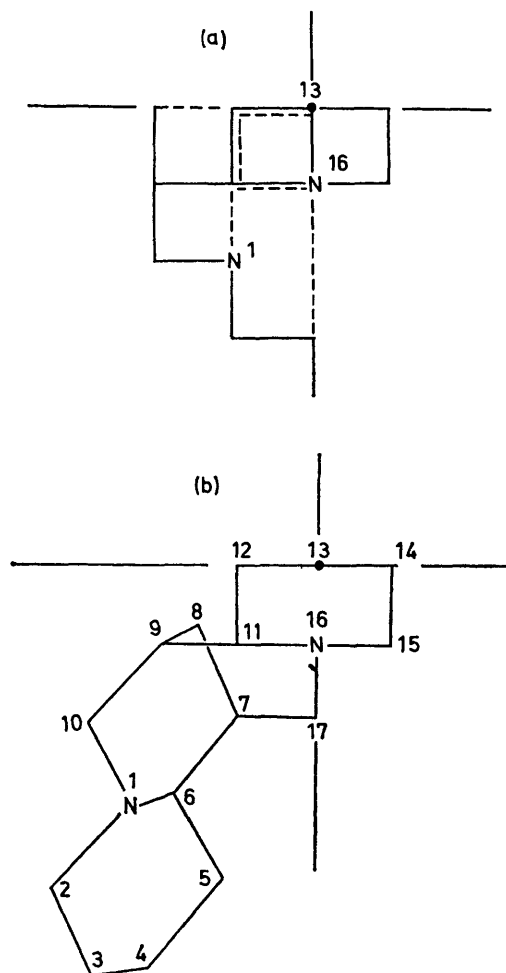
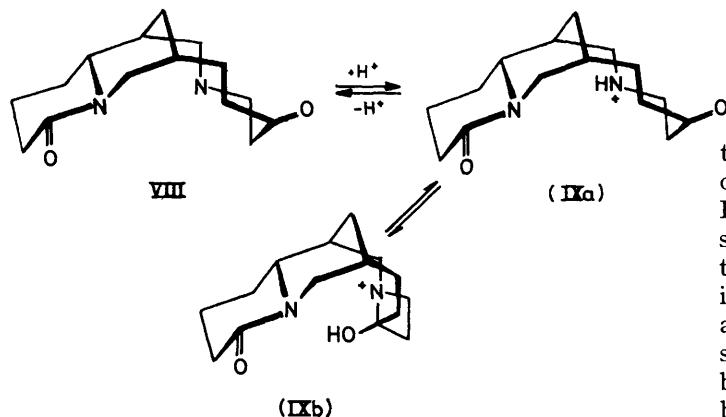


FIGURE 1 Octant projection of 13-oxo-11 α -sparteine (V) in the all-chair conformation (polar solvents); (b) in the c-boat form (non-polar solvents)

perchlorate (entry 15), indicating formation of the parent ketone (I). This 'hemiacetal form' is retained however in methanol (entry 12) and is also formed by acidification of the methanol solution (entry 11). Alternatively, the disappearance of the ketone $n-\pi^*$ Cotton effect in acidified methanol can be accounted for by the formation of bridged quaternary salts (II).



2,13-Dioxo-11 β -sparteine (VIII), despite a different configuration at C-11, displays very similar c.d. behaviour upon acidification of water solutions. The positive $n-\pi^*$ transition Cotton effect (in agreement with the octant projection, Figure 2) is lowered upon successive addition of HCl (Table 2). Again, no further change in the c.d. spectra is observed below pH 3.4 (1.5 mol. equiv. of HCl added). This furnishes good evidence for transannular amine-carbonyl interaction in the rigid, all-chair ketone (VIII) resulting in formation of the bridged quaternary ammonium salt (IXb).

TABLE 3

C.d. spectra of 13-oxo-11 α -sparteine (V)

No.	Solvent	pH	Ketone $n-\pi^*$	σ -coupled $n-\pi^*$
1	H ₂ O + 1 equiv. NaOH	11.7	-1.29 (285)	+0.57 (237)
2	H ₂ O	10.0	-0.75 (282)	+0.98 (233.5)
3	H ₂ O + 0.25 equiv. HCl	9.0	-0.76 (282)	+0.98 (233.5)
4	H ₂ O + 0.50 equiv. HCl	7.2	-0.765 (282)	+0.98 (233.5)
5	H ₂ O + 0.75 equiv. HCl	6.7	-0.775 (282)	+0.98 (233.5)
6	H ₂ O + 1 equiv. HCl	5.8	-0.775 (282)	+0.98 (233.5)
7	H ₂ O + 1.5 equiv. HCl	3.4	-0.735 (282)	+0.95 (233.5)
8	H ₂ O + 2.5 equiv. HCl	2.9	-0.675 (282)	+0.88 (233.5)
9	H ₂ O + 25 equiv. HCl	1.7	-0.25 (283)	+0.26 (233)
10	MeCN		-1.93 (294)	+0.55 (255.5) ^a
11	MeCN, HClO ₄		-0.865 (292)	^b
12	MeCN, 2HClO ₄		-0.86 (293)	^c

11 α -Sparteine (in H₂O): $\Delta\epsilon$ -0.26 (215).
^a +0.45 (230). ^b +1.0 (230). ^c +0.46 (227).

In contrast to the behaviour of the 2-oxo-derivatives, 13-oxo-11 α -sparteine (V) seems to be less susceptible toward formation of the D-ring bridged species upon acidification.

Inspection of Table 3 leads to the conclusion that there is very little change in the ketone $n-\pi^*$ Cotton effect in

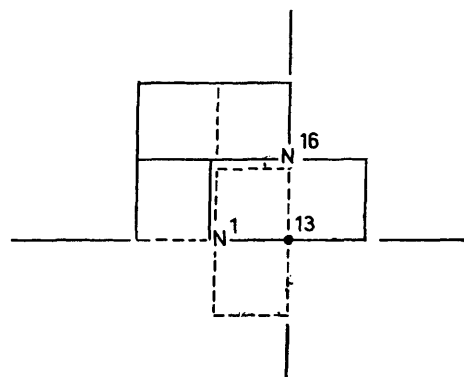


FIGURE 2 Octant projection of 13-oxo-11 β -sparteine (all-chair conformation)

the pH range 10.0—3.4, *i.e.* between an aqueous solution of (V) and a solution with 1.5 mol. equiv. of HCl added. Larger changes in $\Delta\epsilon$ occur only in strongly acidified solution (pH 1.74, 25 equiv. of HCl added), but even then the ketone Cotton effect is preserved to *ca.* 30% of its magnitude, measured in water. This effect can be accounted for by formation of the all-chair species (VIa), stabilized in acidic solution by intramolecular hydrogen bonding between N(1) and N(16). Formation of the bridged species (VIc or d) would require protonation of

(V) with two mol. equiv. of acid. The smaller $n-\pi^*$ ketone Cotton effect of (V) compared with (I) gives additional support for a relatively higher proportion of the all-chair conformation (Va), in equilibrium with (Vb). The trend in the ketone $n-\pi^*$ Cotton effect of (V) and its salts (entries 10–12) in acetonitrile is similar to that of (I), *i.e.* the Cotton effect retains *ca.* 50% of its magnitude in either mono- or di-perchlorate, compared with the free-base Cotton effect.

Finally, it should be noted that the ketone $n-\pi^*$ Cotton effects of (I), (V), and (VIII) appear with a very weak hump ($\Delta\epsilon \leq 0.02$) of opposite sign at longer wavelengths (330 ± 5 nm).

The c.d. band at *ca.* 250 nm was clearly observed in the spectrum of (I) in alkaline solution (Table 1, entry 1). In water solution (entry 2) as well as in partially acidified solutions (entries 3 and 4) this band is merely seen as a shoulder. In solutions of lower pH (entries 5–9) this band completely disappears, indicating its relationship to the electron density (the presence of a lone pair) at N(16) and the presence of the carbonyl chromophore. The N(16) lone pair is in a suitable position for the σ -bond-transmitted interaction with the excited state of the ketone chromophore. Thus this band is attributed to the σ -bonded interaction between n (amine) and π (ketone) orbitals^{6a} of the piperidone ring D. This is the first observation of such a transition in the c.d. spectra of 4-piperidones.* Recently, this transition has been detected in the u.v. spectra of 4-heteracyclohexanones^{6b} and in the c.d. spectra of 3-heteracyclohexanones.^{6c}

The weak c.d. band not only disappears on protonation of the amine nitrogen, but is also easily obscured by the neighbouring c.d. $n-\pi^*$ amide band in (I). In fact, it could only be observed in water solutions, due to the remarkable hypsochromic shift of the $n-\pi^*$ amide band. In other non-acidic solvents (entries 10, 11, 14, 19) this band merges with $n-\pi^*$ amide c.d. band, thus forming a new broad band at *ca.* 240 nm. No such obscuring of the new band by the amide c.d. bands is possible in ketone (V) which lacks an oxygen function at C(2). In fact, this band is seen distinctly both in water (λ_{max} 233.5 nm) and in acetonitrile solutions (λ_{max} 255.5 nm), being of the same order of magnitude as the ketone $n-\pi^*$ Cotton effect but of opposite sign (Table 3).

As this band disappears on acidification of the acetonitrile solution of (V) but, as with the ketone $n-\pi^*$ Cotton effect, is retained in acidified water solutions, one can conclude that in acetonitrile protonation occurs predominantly at N(16) while in water solutions the hydrogen-bonded form (VIa) is preferred.

On the other hand, in the absence of the 13-oxo-group no such charge-transfer band is found, for example in the structurally related 2-oxo-11 α -sparteine (III) (see Table 4) or in 11 α -sparteine (VII).

* The band around 246 nm was also observed in the c.d. spectra of the related 10,13-dioxo-11 α -sparteine, a derivative of lindenianine. However, it was interpreted in terms of spatial interaction between the lone pair orbital of N(16) and the lactam chromophore.⁷

TABLE 4

C.d. spectra of 2-oxo-11 α -sparteine (III)

Solvent	Lactam	
	$n-\pi^*$	$\pi-\pi^*$
H ₂ O	+5.8 (219.5)	-2.0 (201)
H ₂ O + 1 equiv. HCl	+8.9 (222)	+5.0 (186)
H ₂ O + 1 equiv. NaOH	+7.2 (219.5)	-11.2 (201)
		-1.71 (204)

In 2,13-dioxo-11 β -sparteine (VIII) the weak c.d. band at *ca.* 250 nm could be seen only in alkaline water solution (Table 2), and is again of opposite sign to that of the ketone $n-\pi^*$ c.d. band. This can be expected on the basis of opposite pseudo-symmetries of the lone-pair combinations in the two transitions.^{6d}

The lactam bands of (I) and (VIII) form a distinct pair of Cotton effects which are consistently positive (longer wavelength $n-\pi^*$) and negative (shorter wavelength $\pi-\pi^*$) but differ much in their amplitudes (Tables 1 and 2). The longer wavelength Cotton effect is remarkably blue-shifted in polar solvents, as expected for the $n-\pi^*$ type transition.

Examining the effect of protonation at N(16) in water solutions one finds remarkable changes in the magnitude of the lactam c.d. bands (Tables 1 and 2). The decrease of the ketone $n-\pi^*$ Cotton effect is accompanied by an increase in the amide Cotton effects, thus relating the rotatory strength of the lactam transitions to the positive charge at N(16). The presence of an equilibrium between protonated [(II), (IX)] and non-protonated [(I), (VIII)] forms is supported by the presence of isobestic points at 214, 250, and 260 [(I)] or 258, 218, and 192 nm [(VIII)] in the c.d. curves plotted against acid concentration.

Parallel changes are observed in acetonitrile solution in which the monoperchlorate (Table 1, entry 15) shows very strong amide bands, compared with the free base (entry 14). The diperchlorate salt in acetonitrile (entries 16 and 17), unlike the water solutions, is characterized by reduced rotatory strength of the amide bands, which reflects the partial vanishing of the amide chromophore due to its protonation by the excess of acid.

Finally, a strong increase of the rotatory strength of the amide transition is also observed in (IV), which is a protonated form of 2-oxo-11 α -sparteine (III) (Table 4; *cf.* similar changes in methanol solution upon protonation³).

EXPERIMENTAL

2,13-Dioxo-11 α -sparteine (I).—This was obtained by oxidation of natural 2-oxo-13-hydroxy-11 α -sparteine according to the methods described previously;⁸ m.p. 107 °C; $[\alpha]_D^{20} +22.5$ °C; ν_{max} 1 640 (ν_{CO} lactam) and 1 720 cm^{-1} (ν_{CO} ketone); (I)·HCl·2H₂O had m.p. 165 °C; (I)·CH₃OH·HClO₄ had m.p. 174–175 °C. Elemental analysis was in agreement with the molecular formula, C₁₅H₂₂N₂O₂.

2,13-Dioxo-11 β -sparteine (VIII).—This was obtained according to the method described previously;⁸ m.p. 115 °C; $[\alpha]_D^{19} +39$ °C; ν_{max} 2 800–2 700 (ν_{CH} of *trans*-quinolizidine, 1 600 (ν_{CO} lactam), and 1 700 cm^{-1} (ν_{CO}

ketone). Elemental analysis was in agreement with the molecular formula, $C_{15}H_{22}N_2O_2$.

13-Oxo-11 α -sparteine (III).—This was obtained by oxidation of 13-hydroxy-11 α -sparteine (obtained by reduction of natural 2-oxo-13-hydroxy-11 α -sparteine with $LiAlH_4$) with CrO_3 in 90% acetic acid containing 5% of perchloric acid. The resulting mixture was worked up by the method used previously;⁸ i.r. of free base, 1 720 (ν_{CO}), 2 800, and 2 760 cm^{-1} (*trans*-bands of high intensity); m.p. 154 °C. Elemental analysis was in agreement with the molecular formula, $C_{15}H_{24}N_2O_2$.

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