Synthesis and Stereochemical Characterization of 1,2,7,11b-Tetrahydropyrrolo[1,2-*d*][1,4]benzodiazepine-3,6(5*H*)-diones, obtained *via* Raney Nickel Hydrogenation of Tetrahydroisoxazolo[2,3-*d*][1,4]benzodiazepinones

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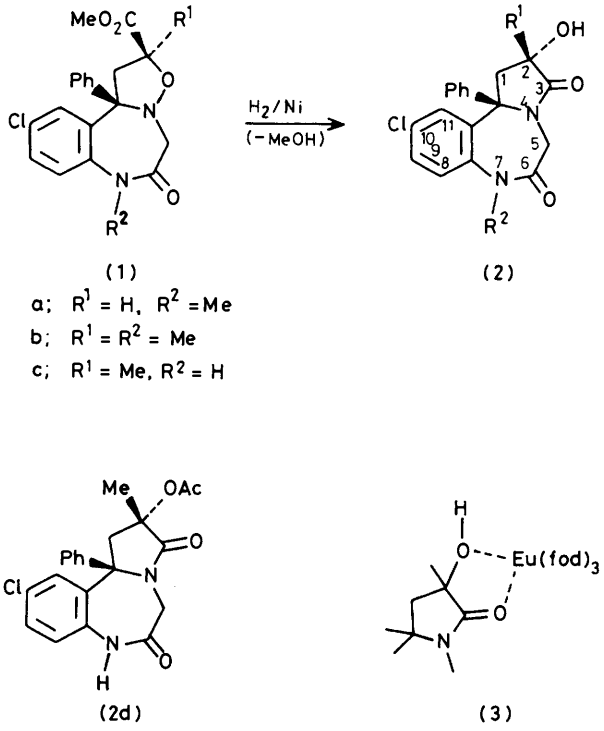
Catalytic hydrogenation (Raney nickel) of 2-alkoxycarbonyl-1,2,7,11b-tetrahydroisoxazolo[2,3-*d*][1,4]-benzodiazepin-6(5*H*)-ones (1) produces 1,2,7,11b-tetrahydro-2-hydroxypyrrolo[1,2-*d*][1,4]benzodiazepine-3,6(5*H*)-diones (2a—c). Their stereochemical characterization has been accomplished by ^{1}H n.m.r. spectroscopy, principally by computer simulation of the lanthanoid-induced shifts of the proton resonances. The results show that some 10-chloro-1,2,7,11b-tetrahydro-2-hydroxy-7-methyl-11b-phenylpyrrolo[1,2-*d*][1,4]benzodiazepine-3,6(5*H*)-diones exist predominantly in the *transoid* conformation in chloroform solution at room temperature; a related 7-unsubstituted product shows rapid conformational equilibration in comparison with the n.m.r. time scale, characterized by a slight conformational bias to the *cisoid* form.

The remarkable clinical success of the benzodiazepine anti-anxiety drugs is generally acknowledged. It is also well known that annelated 1,4-benzodiazepines often show higher sedative activities than the compounds from which they are derived, and are essentially non-toxic.[1]

In the course of structure elucidation of some 1,2,7,11b-tetrahydroisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-ones, synthesized by 1,3-dipolar cycloaddition of diazepam 4-oxide with acrylic esters,[2] we have hydrogenated the cycloadducts over Raney nickel: when the adducts are 2-methoxy-(or ethoxy)carbonyl-substituted, they give γ-lactams on hydrogenation in good yields, *via* reductive five-membered ring opening and MeOH (or EtOH) elimination. This reaction represents a new synthetic approach to the 1,2,7,11b-tetrahydro-5*H*-pyrrolo[1,2-*d*][1,4]benzodiazepine ring system. Few papers have thus far been published on the synthesis of analogous pyrrolo[1,2-*d*][1,4]benzodiazepines.[1c,d,3] However, several condensed tricyclic 1,4-benzodiazepines, in which variously hydrogenated pyrrole nuclei are fused to the *a*-,[1d,4] *c*-,[1d,5] or *j,k*-edges [1d] have been prepared, apart from the natural pyrrolo[2,1-*c*][1,4]benzodiazepines discovered in recent years, *e.g.* anthramycin, tomaimycin and oxotomaymycin, sibiromycin, neotramycins A and B,[1d] and tilivalline.[6]

In this paper we report the synthesis of 10-chloro-1,2,7,11b-tetrahydro-11b-phenylpyrrolo[1,2-*d*][1,4]benzodiazepine-3,6-(5*H*)-diones (2) and their stereochemical characterization, accomplished by computer simulation of lanthanoid-induced shifts (LIS) of ^{1}H n.m.r. signals.[7]



Results and Discussion

Structures were assigned from analytical data and mass, i.r., and ^{1}H n.m.r. spectra.†

Formation of pyrrolidones (2) from the appropriate tricyclic isoxazolidines occurs with retention of configuration.[8] Nevertheless, the stereochemistry of the title compounds is quite complex, mainly with respect to the possible equilibration between diastereoisomeric conformers (I) (*transoid*) and (II) (*cisoid*) (Figure),‡ as a result of the mobility of the seven-membered ring. We assume both nitrogen atoms to be trigonal in n.m.r. calculations (see later), in view of their fast pyramidal inversion as compared with the n.m.r. time scale.[2,9] Pseudorotational or ring-puckering processes of the pyrrolidone nucleus should influence the conformations of (2) only weakly, because of the much more appreciable steric modifications induced by seven-membered ring inversion.

Conformational preferences of the reaction products were attributed from ^{1}H n.m.r. lanthanoid probe analysis. The coupling constants (Table 1) were unchanged during addition of the lanthanoid shift reagent (LSR), showing that the conformational equilibrium is unaffected, so that the stereochemical deductions can be reasonably extended to the free molecules.[7,10] Moreover, considerable variations in substrate conformation are not expected to result from complexation of

† Structures given in this paper show one enantiomer only, where chirality exists.

‡ The terms *transoid* and *cisoid* refer to the relative positions of 2- and 7-methyl substituents in the two limit conformations of (2b).

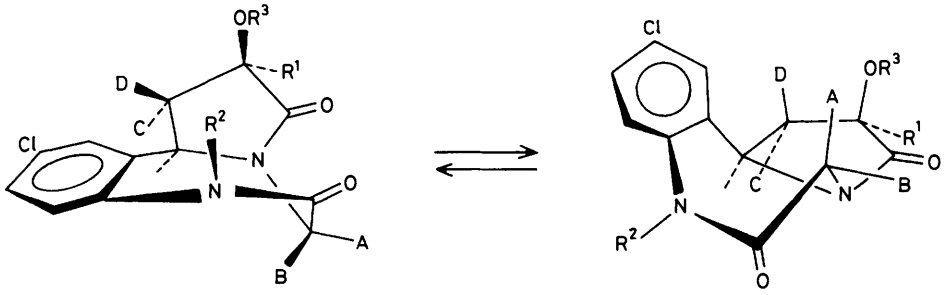


Figure. Conformational equilibrium for 10-chloro-1,2,7,11b-tetrahydro-11b-phenylpyrrolo[1,2-*d*][1,4]benzodiazepine-3,6(5*H*)-diones (2a; $R^1 = R^3 = H$, $R^2 = Me$), (2b; $R^1 = R^2 = Me$, $R^3 = H$), (2c; $R^1 = Me$, $R^2 = R^3 = H$), and (2d; $R^1 = Me$, $R^2 = H$, $R^3 = Ac$) (A—D label hydrogen atoms)

Table 1. ^1H N.m.r. spectral data of 10-chloro-1,2,7,11b-tetrahydro-11b-phenylpyrrolo[1,2-*d*][1,4]benzodiazepine-3,6(5*H*)-diones (2)

	(2a) δ (p.p.m.) [*J*/Hz]	(2b) δ (p.p.m.) [*J*/Hz]	(2d) δ (p.p.m.) [*J*/Hz]
Aromatics	7.8—6.7m	7.8—6.9m	7.5—7.0m
5-H_2	4.72d; 3.45d [a] [−13.5]	4.37d; 3.28d [a] [−13.9]	4.57d; 3.59d [−17.9]
2-H	4.60dd		
1-H_2	2.87dd; 2.34dd [b] [J_{gem} −13.0; J_{cis} 8.3; J_{trans} 5.0]	2.91d; 2.39d [b] [−13.2]	3.41d; 3.15d [−13.5]
NMe	2.36s	2.26s	
CMe		1.30s	1.42s
NH			9.06br s
Ac			2.07s

[a] The higher field resonance corresponds to the pseudoaxial proton, shielded by the fused benzene ring. [b] LIS computer simulation suggests that the higher field resonating proton is *cis* to 11b-Ph, as observed in compounds (1).[2]

Table 2. Experimental and calculated Eu LIS ratios of 10-chloro-1,2,7,11b-tetrahydro-11b-phenylpyrrolo[1,2-*d*][1,4]benzodiazepine-3,6(5*H*)-diones (2) [a] [H_A(5-H_2) as standard nucleus, ratio $R = 1$]

	(2a)		(2b)		(2d)	
Nucleus	Expt.	Calc.	Expt.	Calc.	Expt.	Calc.
H_B(5-H_2)	0.518	0.514	0.458	0.510	1.030	1.040
H_C(1-H_2)			0.362	0.359	0.191	0.177
H_D(1-H_2)			0.370	0.412	0.229	0.229
NMe	0.259	0.172	0.278	0.165		
CMe			0.500	0.529	0.125	0.134
Ac					0.106	0.081
TQRF [b]	0.150		0.150		0.029	

[a] For identification of methylene protons, see Figure. [b] The relative goodness-of-fit is evaluated in terms of the total quasi-*R*-factor, *i.e.* $[\sum_i(\text{Calc.}R_i - \text{Exp.}R_i)^2/\sum_i(\text{Exp.}R_i)^2]^{\frac{1}{2}}$, in which Calc.$R_i$ is the calculated LIS ratio and Exp.R_i the experimental value for nucleus *i*.

the lanthanoid ion to the substrate, particularly if the co-ordination sites are easily accessible from a steric viewpoint, as in the case under study.

LIS experiments were performed with Eu(fod)$_3$ in view of its ability to produce induced shifts to low field without appreciable line broadening. Its contact contribution to the measured shift may be disregarded for our purposes; therefore, a consistent average geometry for the substrates (2) can result from the application of the appropriate equation for the pseudocontact interaction, relating isotropic shifts to geometric parameters of the complexed and thus of the free molecule.

Molar ratios [L(ligand) : S(substrate)] in the range 0.05—0.40 were used. Limiting shifts were obtained by least squares fitting to experimental shift values obtained from ten solutions of different molar ratios, assuming an equilibrium for the 1 : 1 complex between substrate and LSR; this is confirmed by the linear behaviour of the measured shifts in relation to L/S.

In the pyrrolobenzodiazepines (2), which are potential polyfunctional substrates towards the LSR, the 3-carbonyl group appears to be the primary site of co-ordination for Eu^{3+}. In addition to the linear dependence of the LIS on L/S, the sequences of observed LIS values are consistent with complexation at C(3)O: for instance the C-5 pseudoequatorial proton (H_A, see Figure) exhibits a considerably greater shift than the 1-methylene protons, these last showing similar LIS values, larger than that experienced by N-Me protons (Table 2). An amide carbonyl might be considered *a priori* as a much better binder to Eu(fod)$_3$ than a 2-hydroxy group, because tertiary alcohols are very weak binders to an LSR.[11] However, the observed preferred complexation of europium by the pyrrolidone carbonyl (rather than by the amide 6-carbonyl group, which would be a site of comparable binding ability) may be explained in terms of an additional chelation of lanthanoid by the neighbouring hydroxyoxygen atom.[12] The effectiveness of Eu(fod)$_3$ in becoming involved in a sort of bidentate binding to C(3)O and 2-OH groups was verified by LIS computer simulation (see later).

The ^1H n.m.r. spectral analysis of compounds (2a and b) suggests that they exist as only one conformer, which does not show interconversion at room temperature on the n.m.r. time scale in chloroform solution (Table 1); the 5-methylene protons resonate as an AB system, with a chemical shift difference of *ca.* 1 p.p.m., similar to that observed for the 1,2,7,-11b-tetrahydroisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one system.[2] The algebraic decrease of the related geminal coupling constant observed on going from isoxazolidines (1a,b) [J_{gem}(5-H_2) — 9.8 Hz, mean value] to pyrrolidones (2a,b) [J_{gem}(5-H_2) — 13.7 Hz, mean value], is supported by considering the influence on J_{gem} of N-4, directly bonded to the 5-methylene group [=N–O– in (1a,b), =N–CO– in (2a,b)]. Two co-operative effects are expected:[13] first, there will be an inductive withdrawal of electrons through the σ bond joining C-5 and N-4, greater by the =N–O– than by the =N–CO– moiety, which will remove electrons from the symmetric

bonding orbital of the $C(5)H_2$ group, thus leading to a positive contribution to J_{gem} on going from (2a and b) to (1a and b). Secondly, some back-donation from the unshared pair on N-4 into the antisymmetric bonding orbitals of the $C(5)H_2$ groups also provides a positive contribution to J_{gem}. This second effect will be more noticeable in (1a and b) than in (2a and b) because the N-4 lone pair is delocalized towards C(3)O in pyrrolidones (2).

To solve the problem of the conformational preference of (2a and b) both possible limit conformers (Figure) were tested by least-squares analysis to match the experimental limiting shifts induced by the LSR to those calculated. Calculations were carried out by the LISCA program,[14] treating the molecule as a rigid unit, and optimizing lanthanoid–substrate bond length and the lanthanoid–O–C(3) bond angle. Geometrical factors of the systems under study were obtained from Dreiding models. The principal magnetic axis of the lanthanoid–substrate complex was assumed to be collinear with the Eu–O bond;[2,14,15] moreover our LISCA analyses were also performed with the magnetic axis alignment variable: all cases with a reasonable fit showed an optimized $\alpha < 5°$.

For the tricyclic pyrrolidones (2a and b), only the *transoid* conformer was consistent with the experimental LIS data: europium binding occurs almost exclusively on the C(3)O unshared pair orbital oriented towards the 2-hydroxy group (see bidentate chelate species 3) with an optimized Eu–O bond length of 3.44 Å.

The stereochemical characterization of (2c) could not be directly accomplished by ^{1}H n.m.r. lanthanoid probe analysis, because of its low solubility in suitable solvents. To overcome this difficulty, (2c) was converted into its acetate *i.e.* *r*-2-acetoxy-10-chloro-1,2,7,11b-tetrahydro-*t*-2-methyl-*t*-11b-phenylpyrrolo[1,2-*d*][1,4]benzodiazepine-3,6(5*H*)-dione (2d). The ^{1}H n.m.r. spectrum of (2d) (Table 1) shows $J_{gem}(5\text{-}H_2)$ − 17.9 Hz, unaltered upon addition of $Eu(fod)_3$: this marked algebraic decrease, on going from (2a and b) to (2d), may be indicative of an orientation in (2d) of the 5-methylene protons such that their internuclear axis is perpendicular to the nodal plane of C(6)O π orbitals.[13] These circumstances could reflect an ' average ' position of $C(5)H_2$ with respect to C(6)O, due to diastereoisomeric *transoid* and *cisoid* conformers of (2d) (Figure) which interconvert rapidly in comparison with the n.m.r. time scale. This hypothesis is further corroborated by the LIS of the 5-methylene protons, which are similar in magnitude in compound (2d), whereas in (2a and b) the shift experienced by the C-5 pseudoequatorial proton is twice as large as that suffered by the pseudoaxial one. The best LISCA solution for (2d) actually indicates the presence of 64% *cisoid* conformer (II) in equilibrium with the *transoid* conformation (I), at room temperature and in chloroform solution; the lanthanoid tries to bind almost symmetrically to the 3-carbonyl oxygen atom with an Eu–O bond length of 3.50 Å and a Eu–O–C(3) angle of 111°. In the LISCA analysis the molecule (2d) was treated as a set of three rigid units, connected to one another by a bond about which rotation could occur without restriction; the alternative unit facility was used,[14] which allowed for the treatment of two alternative portions of the substrate which differ geometrically in the conformation of the seven-membered ring.

Conclusion

Our results concerning the stereochemical characterization of pyrrolobenzodiazepinediones (2) closely agree with the suggestion that annelation of a five-membered nucleus to the *d*-edge of the 1,3-dihydro-5-phenyl-1,4-benzodiazepin-2(2*H*)-one system has little effect on the ring-inversion barrier of the seven-membered ring, when the position of the phenyl substituent is maintained.[2] Compounds (2a and b) exist in only one preferred conformation at room temperature, and in chloroform solution as their precursor diazepam [7-chloro-1,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepin-2(2*H*)-one]; under the same conditions (2d) shows a biased mobile equilibrium, as verified for *N*-demethyldiazepam, unsubstituted at N-1, like (2d).[9a,c,d,16]

The magnitude of J_{gem} ($5\text{-}H_2$) appears to be a sensitive probe for the conformational situation of the systems under study.

Experimental

M.p.s were determined with a Kofler hot-stage apparatus. Analyses were performed with a Perkin-Elmer 240 elemental analyser. I.r. spectra ($CHCl_3$ solutions, unless otherwise stated) were measured with a Perkin-Elmer 225 instrument. Electron impact mass spectra were run on a Varian MAT CH5 spectrometer operating with an electron beam energy of 70 eV. ^{1}H N.m.r. spectra were measured with a Varian EM 360 A instrument, for *ca.* 0.3M-solutions in deuteriochloroform (Me_4Si as internal standard and frequency lock) containing increasing amounts of $Eu(fod)_3$ up to an L/S value of 0.4 (molar ratio). $Eu(fod)_3$ was purchased from C. Erba. The LSR was added stepwise from a stock solution (*ca.* 300 mg ml^{-1}) using a 50 μl syringe. The LIS values were found to be directly proportional to the L/S ratio. The calculations were carried out using an IBM 4341 computer.

10-*Chloro*-1,2,7,11b-*tetrahydro*-r-2-*hydroxy*-7-*methyl*-t-11b-*phenylpyrrolo*[1,2-d][1,4]*benzodiazepine*-3,6(5H)-*dione* (2a).—10-Chloro-1,2,7,11b-tetrahydro-*r*-2-methoxycarbonyl-7-methyl-*c*-11b- phenylisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one (1a) (2 mmol)[2] in absolute ethanol (40 ml) was reduced at room temperature under hydrogen (slight overpressure) over W2 Raney nickel (1 g).[17] When the reaction appeared to be complete (t.l.c. after *ca.* 20 h on silica gel Merck GF_{254} plates; elution with diethyl ether–acetone, 95 : 5), the catalyst was filtered off, and the solution, after partial removal of the solvent *in vacuum*, was left to crystallize, giving the *product* (2a) (85%), m.p. 228—230 °C (Found: C, 64.35; H, 4.9; N, 8.05. $C_{19}H_{17}ClN_2O_3$ requires C, 63.95; H, 4.8; N, 7.85%); $\nu_{max.}$ 1 670br cm^{-1} (CO).*

10-*Chloro*-1,2,7,11b-*tetrahydro*-r-2-*hydroxy*-t-2,7-*dimethyl*-t-11b-*phenylpyrrolo*[1,2-d][1,4]*benzodiazepine*-3,6(5H)-*dione* (2b).—This *product* (2b) was prepared (83%) from 10-chloro-1,2,7,11b-tetrahydro-*r*-2-methoxycarbonyl-*t*-2,7-dimethyl-*c*-11b-phenylisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one (1b),[2] according to the procedure for (2a); m.p. 232—234 °C (Found: C, 64.8; H, 5.1; N, 7.6. $C_{20}H_{19}ClN_2O_3$ requires C, 64.75; H, 5.15; N, 7.55%); $\nu_{max.}$ 1 670br cm^{-1} (CO); *m/z* 336 [(*M*H − Cl)$^+$, 100%], 279 (37), 278 (93), 260 (35), 259 (100), 251 (80), 250 (90), 249 (100), 231 (80), 194 (50), 193 (30), 189 (41), 161 (45), 91 (30), 77 (35), and 43 (40).[1e]

10-*Chloro*-1,2,7,11b-*tetrahydro*-r-2-*methoxycarbonyl*-t-2-*methyl*-c-11b-*phenylisoxazolo*[2,3-d][1,4]*benzodiazepin*-6(5H)-*one* (1c).—This *compound* (1c) was prepared according to the procedure described in the literature for (1a and b);[2] yield 65%, m.p. 183—185 °C (Found: C, 62.25; H, 4.9; N, 7.45. $C_{20}H_{19}ClN_2O_4$ requires C, 62.1; H, 4.95; N, 7.25%); $\nu_{max.}$ 3 400 (NH), 1 728 (ester CO), and 1 682 cm^{-1} (amide CO); δ_H 8.56 (1 H, br s, NH), 7.7—6.8 (8 H, m, C_6H_3 and Ph), 3.66

* The OH stretching bands are not easily identifiable from spectra of chloroform solutions of (2); intramolecular association causes broad weak OH absorptions, frequently overlaid by other bands.

(3 H, s, OMe), 3.66 and 2.62 (2 H, AB, J_{gem} − 13.6 Hz, 1-H_2), 3.44 and 3.32 (2 H, AB, J_{gem} − 11.7 Hz, 5-H_2), and 1.48 (3 H, s, 2-Me); *m/z* 386 (M^+, 38%), 311 (30), 309 (100), 285 (34), 270 (43), 242 (35), and 241 (44).

10-*Chloro*-1,2,7,11b-*tetrahydro*-r-2-*hydroxy*-t-2-*methyl*-t-11b-*phenylpyrrolo*[1,2-d][1,4]*benzodiazepine*-3,6(5H)-*dione* (2c).—This *compound* (2c) was prepared (87%) from (1c), following the reductive procedure described for (2a), m.p. 228—230 °C (Found: C, 64.05; H, 4.75; N, 8.0. $C_{19}H_{17}ClN_2O_3$ requires C, 63.95; H, 4.8; N, 7.85%); $\nu_{max.}$ (Nujol) 3 400 (NH) and 1 675br cm^{-1} (CO); *m/z* 332 [(*M*H − Cl)$^+$, 30%], 264 (67), 245 (100), 236 (45), 235 (69), 217 (78), 175 (32), 147 (43), and 42 (63).

r-2-*Acetoxy*-10-*chloro*-1,2,7,11b-*tetrahydro*-t-2-*methyl*-t-11b-*phenylpyrrolo*[1,2-d][1,4]*benzodiazepine*-3,6(5H)-*dione* (2d).—Under standard conditions (pyridine–Ac_2O),[18] (2c) gave quantitatively the *monoacetyl derivative* (2d), m.p. 286—288 °C (from MeOH) (Found: C, 63.45; H, 4.75; N, 7.35. $C_{21}H_{19}ClN_2O_4$ requires C, 63.25; H, 4.8; N, 7.0%); $\nu_{max.}$ 3 380 (NH) and 1 713br cm^{-1} (CO); *m/z* 364 [(*M*H − Cl)$^+$ 74%], 304 (30), 287 (66), 265 (65), 264 (100), 237 (60), 236 (67), 235 (65), 229 (55), 228 (61), 227 (70), 220 (30), 209 (30), 208 (38), 207 (30), 194 (30), 180 (40), 171 (30), 103 (30), and 91 (40).

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