Tetrahydroisoxazolo[2,3-*d*][1,4]benzodiazepinone Ring System: Synthesis, Stereochemistry, and Conformation †

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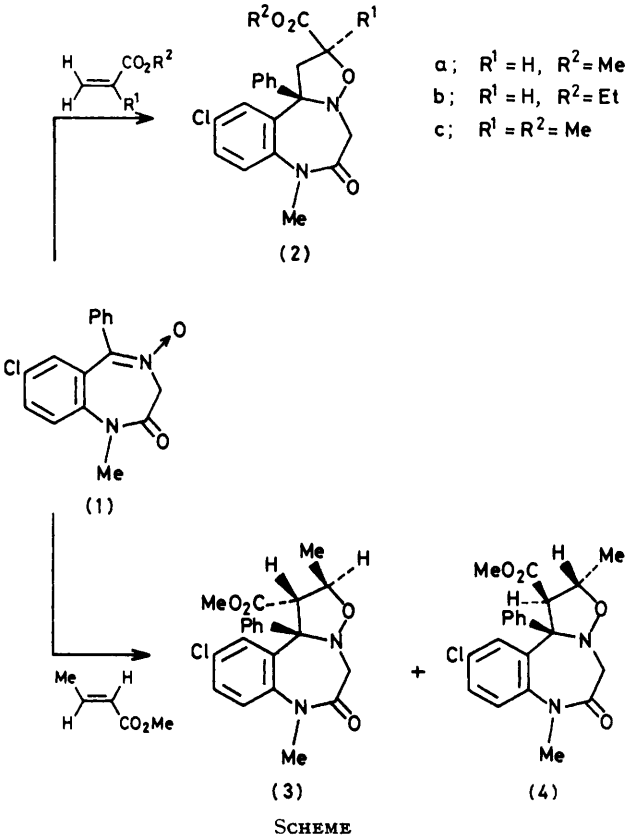
Reaction of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (diazepam 4-oxide) with acrylic esters produces annelated substituted isoxazolidines: 1,3-dipolar cycloaddition is regiospecific, the adducts with methyl crotonate showing a ' reverse ' direction of addition, in comparison with the ' normal ' products of the reaction between diazepam 4-oxide and acrylic or methacrylic esters. Structures and conformations of cycloadducts have been assigned by means of ^{1}H n.m.r. spectroscopy, largely by the computer simulation of the lanthanide-induced shifts and broadenings of the n.m.r. spectral lines: a small increase in the conformational rigidity of the seven-membered ring is observed, on going from diazepam to the previously unknown isoxazolobenzodiazepinones. Their structural assignments are supported by the results of catalytic hydrogenation (Raney nickel).

1,4-BENZODIAZEPINES have been known as therapeutically important compounds for many years.[1] More recently, derivatives with heterocyclic groups annelated to the *a*-edge of the molecule have become of interest for their physical, chemical, and biological properties.[2,3] Several derivatives with the heterocycle fused to the *c*- or *d*-edges are also known.[3,4] We report here an investigation of a hitherto unknown series of compounds related to diazepam [7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one] in which an isoxazolidine nucleus is fused to the *d*-edge. The nature and substitution of the additional heterocycle nuclei are related to the conformational properties of the new tricyclic system.

Synthesis.—In an attempt to fuse an isoxazolidine nucleus onto the *d*-edge of the dihydrobenzodiazepinone ring system, diazepam 4-oxide (1) [5] (see Scheme) was subjected to a 1,3-dipolar cycloaddition reaction with various substituted acrylates, in the absence of a solvent, at the boiling point of the dipolarophile.

From elemental analyses the respective molecular formulae (see Experimental section) were assigned to compounds (2)—(4). These suggested the occurrence of 1,3-dipolar cycloaddition between the diazepam (i) and the acrylates under investigation. Structures (2)—(4) ‡ were assigned to the cycloadducts on the basis of (1) ^{1}H n.m.r. spectroscopic evidence, and (ii) Raney-nickel hydrogenolysis. As indicated in the Scheme, the cycloaddition is found to be regiospecific, the adducts with methyl *trans*-crotonate [(3) and (4)] showing a ' reverse ' direction of addition, compared with the ' normal ' products (2a—c) of the reaction between compound (1) and acrylic or methacrylic esters.[6]

The ^{1}H n.m.r. spectra of the adducts were compared to that of diazepam 4-oxide (Table 1). The protons of compound (1) were all present in the products (2)—(4). In addition, the spectra of the adducts contained the absorptions from the dipolarophile. The AB patterns attributed to the methylene in the seven-membered ring of compounds (2)—(4) were significantly changed from that of (1), with the A and B hydrogens shifted farther apart. Moreover, although both (2a) and (2b) appeared



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to be single materials on the basis of t.l.c., the spectroscopic data suggested they were a 1 : 1 mixture of two interconvertible isomers (E) and (F) (Figure): as summarized in Table 1, all the resonance signals in (2a) and

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‡ Structures given in this paper show the enantiomeric forms where chirality is possible.

(2b) were doubled in number. The spectral data and preliminary variable temperature results suggest that the two components in the $CDCl_3$ solution are diastereoisomeric conformational isomers [(E) extended and (F) folded in the Figure] which are distinguishable on the

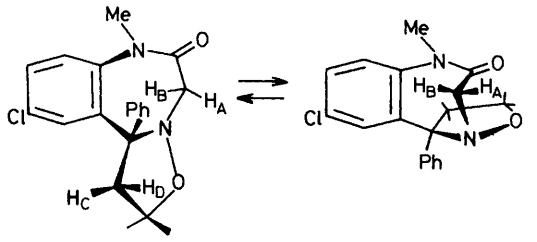

FIGURE Conformational isomers for the 10-chloro-1,2,7,11b-tetrahydro-7-methyl-11b-phenylisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one system

n.m.r. time scale. These are the result of the seven-membered ring mobility. Diazepam 4-oxide (1) exists in only one boat (cycloheptatriene-like) conformation at ambient temperature;[4j] when it is subjected to the cycloaddition reaction with acrylic esters, at least two additional units of asymmetry (C-2 and -11b) are present in the adducts obtained. The determination of the relative structures of these adducts is quite complex: two stereoisomers (per regioisomer), both in two different conformations, extended and folded, are theoretically possible. The following situation is considered as far as the nitrogen atoms are concerned: the methyl substituted 7-N atom undergoes a fast pyramidal inversion compared to the n.m.r. time scale,[4j,7,8] so we assumed it to be trigonal in n.m.r. calculations (*vide infra*), and the 4-N atom, part of the isoxazolidine nucleus, is blocked in a preferred conformation by a high-energy barrier;[6] thus enantiomeric pairs exist for both extended and folded conformations. Ring inversion of the isoxazolidine nucleus, which shows an 'envelope' conformation,[9] should weakly influence the conformations of the adducts because of the much more appreciable steric modifications induced by seven-membered ring inversion.

The dipolarophiles were assigned the orientations shown in the Scheme on the basis of the considerations summarized below. As reported in the Experimental section, 2-alkoxycarbonyl derivatives (2) give γ-lactams on hydrogenation *via* reductive five-membered ring opening and MeOH (or EtOH) elimination; this occurs immediately with retention of configuration. On the other hand, with 1-methoxycarbonyl derivatives (3) and (4), lactam formation is not favourable, and only the 3-amino-alcohols are obtained.[10] The 2-CH n.m.r. absorption in compounds (3) and (4), which is easily recognizable because of its multiplicity due to spin–spin coupling of 1-CH with C-Me, resonates at lower field than 1-CH owing to its proximity to the 3-oxygen atom.[10a]

The assignment of the stereochemistry and preferred conformations of the reaction products was based on ^1H n.m.r. lanthanide probe analysis, which also supports the results concerning the regiospecificity of the cycloaddition reactions under investigation (see Scheme). The vicinal coupling constants (Table 1), which were unaltered during the lanthanide shift reagent (LSR) addition, indicate that the conformational equilibrium is unaffected by this addition so that the stereochemical

TABLE 1

^1H N.m.r. spectral data[a] of diazepam 4-oxide (1) and 10-chloro-1,2,7,11b-tetrahydro-7-methyl-11b-phenylisoxazolo-[2,3-*d*][1,4]benzodiazepin-6(5*H*)-ones (2)—(4)

	Compound							
Assignment	(1) δ (p.p.m.) [*J* (Hz)]	(2a) (E)-form δ (p.p.m.) [*J* (Hz)]	(2a) (F)-form δ (p.p.m.) [*J* (Hz)]	(2b) (E)-form δ (p.p.m.) [*J* (Hz)]	(2b) (F)-form δ (p.p.m.) [*J* (Hz)]	(2c) δ (p.p.m.) [*J* (Hz)]	(3) δ (p.p.m.) [*J* (Hz)]	(4) δ (p.p.m.) [*J* (Hz)]
NMe	3.48s	2.37s	2.39s	2.37s	2.44s	2.36s	2.25s	2.25s
5-CH_2[b]	4.71d	4.07d	4.22d	3.77d	3.83d	3.87d	3.81d	3.81d
	[−12.7]	[−9.8]	[−9.9]	[−9.8]	[−9.9]	[−9.7]	[−10.0]	[−9.8]
	4.60d	3.44d	3.69d	3.19d	3.24d	3.26d	3.24d	3.24d
1-CH_2[c]		3.70dd	3.68dd	3.72dd	3.70dd	3.75d		
		[J_{gem} −12.2]	[J_{gem} −13.0]	[J_{gem} −12.5]	[J_{gem} −12.7]	−14.2		
		2.41dd	2.39dd	2.40dd	2.40dd	2.46d		
		[J_{cis} 8.5] [J_{trans} 4.3]	[J_{cis} 8.3] [J_{trans} 4.4]	[J_{cis} 8.6] [J_{trans} 4.0]	[J_{cis} 8.5] [J_{trans} 4.1]			
2-CH		4.80dd	4.82dd	4.78dd	4.80dd		4.77m	4.63m
							[J_{trans} 8.7] [$J_{H,Me}$ 6.0]	[J_{trans} 9.0] [$J_{H,Me}$ 6.0]
OMe		3.76s	3.09s			3.78s	3.10s	3.60s
OCH_2				4.05q [7.0]	4.10q [7.0]			
CMe				1.30t	1.25t	1.63s	1.34d	1.44d
1-CH							3.79d	3.82d

[a] s = Singlet; d = doublet; dd = doublet of doublets; t = triplet; q = quadruplet; m = multiplet. [b] The higher field resonance corresponds to the pseudoaxial proton, shielded by the fused benzene ring. [c] LIS and LIR computer simulation suggests that the higher field resonating proton is *cis* to 11b-Ph; presumably the C-1 *trans*-hydrogen atom is deshielded by the condensed benzene nucleus.

information concerning the complexed molecules can be reasonably extended to the uncomplexed ones.[11] On the other hand, gross changes in substrate conformation are not expected to be induced by the weak co-ordination of the lanthanide ion to the substrate molecule, especially when the co-ordination sites are easily accessible to it on steric grounds, as in the case under investigation.

^{1}H *N.m.r. Lanthanide Probe Analysis.*—Experiments using the lanthanide-induced shift (LIS) technique[12] have been carried out with Eu(fod)$_3$ as the lanthanide shift reagent. The choice of the LIS reagent was based on consideration of two factors; the shift toward low fields, and the small broadening of resonance signals. Its contact contribution to the observed shift may be regarded as negligible for our purposes; therefore, a consistent average geometry for the substrates (2)—(4) can result from the application of the appropriate equation for the pseudocontact interaction, relating isotropic shifts with geometrical parameters of the complex and thus of the substrate.

In the isoxazolobenzodiazepines (2)—(4), the 6-carbonyl group is the preferred site of complexation for Eu^{3+}: this deduction was based on the fact that, in addition to the linear dependence of the LIS on the ligand : substrate ratio, we observed a comparable, high LIS for the NMe and 5-CH$_2$ groups, while all the other absorptions were weakly shifted by addition of the LSR. The effectiveness of Eu(fod)$_3$ co-ordination at the 6-CO group was verified by LIS computer simulation (*vide infra*).

The analysis of the spectra was found to be complicated by the extensive overlapping of several signals. A good separation was achieved on simplification of the spectra induced by the LIS reagent, using a molar ratio of ligand : substrate in the range 0.05—0.35. Limiting shifts were derived by mean-square fitting on experimental shift values obtained from ten solutions of different molar ratios, assuming an equilibrium for the 1 : 1 complex from the substrate and the paramagnetic reagent; this is also confirmed by the linear behaviour of the measured shifts against the ratio ligand : substrate. All eight possible isomers for every adduct (see above) were tested by least-squares analysis to fit the experimental limiting shifts; at the same time the two interchangeable assignments of the 1-CH$_2$ signals were verified (see note *c* in Table 1). This procedure allows us to be confident of the proper assignment of each n.m.r. transition. The geometrical interpretation of spectral parameters and the correct assignment of signals have been carried out according to the LISCA program.[13] Every molecule under examination was treated as a set of three rigid units, connected to one another by a bond about which rotation could occur without restriction. Calculations have been carried out for the different models fixing the lanthanide–substrate bond length at 3 Å, and optimizing the rotatable bonds and lanthanide–O–C(6) bond angle. Geometrical parameters of the systems under investigation were taken from suitable Dreiding models. Lanthanide binding to each of the lone pairs of the 6-carbonyl oxygen atom have been considered: our results show that steric hindrance by the 7-Me group considerably reduces the fraction binding on that side. In the reported LISCA analyses, the magnetic axis of the complex is always aligned along the lanthanide–oxygen bond: in fact all the analyses were also carried out with the magnetic axis alignment variable. In all cases with a reasonable fit (TQRF = total quasi-R factor <0.15), α optimized to $<5°$. This may be interpreted as evidence for the suggestion that the binding site is indeed the 6-carbonyl oxygen atom (see above).

For adducts (2a), (3), and (4), only one of the possible isomers was consistent with the experimental LIS data; for (2c), more than one acceptable solution for the structure was obtained from the LISCA analyses. It was therefore essential to examine other experimental data such as line broadenings induced by gadolinium; these are dependent upon the inverse sixth-power of the distance separating the gadolinium and the observed nucleus.[14] Consideration of both shifts and broadening induced by lanthanides, together with chemical data (Raney-nickel hydrogenolysis), were sufficient to define a unique solution to the structure of compound (2c): in particular, we observed the broadening of the CMe and OMe signals resulting from the addition of Gd(fod)$_3$ to a solution of (2c). Again, we examined this substrate in the presence of Eu(fod)$_3$ (ligand : substrate 0.26) so that all the signals were well separated. The experimental CMe to OMe broadening ratio is 3.2(±1.0) : 1. Apart

TABLE 2

Eu LIS ratios (OMe protons as standard nuclei) of 10-chloro-1,2,7,11b-tetrahydro-7-methyl-11b-phenylisoxazolo-[2,3-*d*][1,4]benzodiazepin-6(5*H*)-ones (2)—(4) [a]

	Compound									
	(2a) (E)-conformer		(2a) (F)-conformer		(2c)		(3)		(4)	
Nucleus	Exptl.	Calcd.	Exptl.	Calcd.	Exptl.	Calcd.	Exptl.	Calcd.	Exptl.	Calcd.
H_A(5-CH$_2$)	10.255	10.475	7.937	7.936	13.213	13.864	9.138	9.162	9.373	9.638
H_B(5-CH$_2$)	6.801	7.106	5.579	5.579	8.554	9.310	5.374	6.102	5.512	6.476
NMe	7.201	5.977	3.722	3.724	11.133	9.587	7.350	6.574	7.539	6.724
CMe					1.306	2.052	0.806	0.724	0.840	1.410
H_C(1-CH$_2$)					3.253	2.810				
H_D(1-CH$_2$)					3.158	2.648				
TQRF	0.0898		0.0002		0.1057		0.0826		0.1064	

[a] For identification of methylene protons, see the Figure.

from the satisfactory solutions to the LIS ratios, which suggest that CO_2Me is attached to C-1 (discarded on the basis of Raney-nickel hydrogenolysis results), the extended conformation of the adduct with methacrylate (where CO_2Me is bonded to 2-C and *trans*-situated to 11b-Ph) gives a calculated CMe : OMe broadening ratio of 6.7 : 1 (TQRF = 0.1480). For the extended conformer with the 2-CO_2Me group *cis* to 11b-Ph, the calculated ratio is 2.7 : 1 (TQRF = 0.1057). We consider the above results are good evidence for the postulate that the adduct of methyl methacrylate and diazepam 4-oxide has this last structure (2c) (Scheme) and that it prefers the extended conformation at ambient temperature and in $CDCl_3$ solution.

In conclusion, the stereochemistry, is assigned to the adducts (2)—(4) as shown in the Scheme: (2a) and (2b) exist in $CDCl_3$ solution as both conformations in equal proportions [extended and folded (Figure)] while (2c), (3), and (4) prefer the less hindered extended conformation (E). In Table 2, experimental isotropic LIS ratios and the relative calculated LIS ratios for the selected structures with the lowest TQRF are reported. The OMe protons have been taken as standard nuclei.

DISCUSSION

As shown in the Scheme, the investigated cycloaddition was found to always be regiospecific and, moreover, only stereoselective in the reaction between diazepam 4-oxide (1) and acrylic esters. Both steric and electronic environments of the olefin are important in orienting the dipolarophile: the cycloadducts (2a—c) with acrylic and methacrylic esters have the alkoxycarbonyl group on C-2, adjacent to the oxygen atom, while the cycloadducts (3) and (4) from *trans*-crotonate esters have 'reverse' orientation. These results are easily explicable by taking into account the fact that, when the dipolarophile shows comparable steric hindrance at both of its unsaturated centres, then the electronic effects of the substituents determine the orientation of the dipolarophile.[10a]

Compounds (2c), (3), and (4) prefer the less hindered, extended conformation, while (2a) and (2b) almost equally populate both the extended and folded conformations; these do not interconvert at ambient temperature in chloroform solution. This situation may be related to the increased substitution of the olefin system in methacrylate and crotonate esters: for instance, the presence of methyl and methoxycarbonyl groups on 2-C in the adduct with methacrylate should render the folded conformation so sterically hindered that it is not observed at room temperature. The reduced stereoselectivity of the cycloaddition with *trans*-crotonate ester may be ascribed to the enhanced symmetry of the olefin system.

The slow heptatomic ring reversal, compared to the n.m.r. time scale, which we observed in adducts (2)—(4) at room temperature, is consistent with some of the results from the derivatives of diazepam, which show a pentatomic nucleus annelated to the *d*-edge of the molecule with the position of the phenyl substituent maintained. Only one preferred conformation is reported for some hexahydro-oxazolo[3,2-*d*][1,4]benzodiazepin-6-ones.[4h] Two conformers which slowly interconvert (compared to the n.m.r. time scale) have been observed for 1-ethoxycarbonyl-[4j] and 1,2-dimethoxycarbonyl-10-chloro-7,11b-dihydro-7-methyl-11b-phenylisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-ones.[4p]

Preliminary results with adducts (2)—(4) (employing temperature dependent n.m.r. analysis of the non-equivalent 5-methylene protons) indicate that annelation of an isoxazolidine ring to the *d*-edge of diazepam has little effect on the ring-inversion barrier of the seven-membered ring [ΔF^* = 19.2 for (2c) *vs.* 17.7 kcal mol^{-1} * for diazepam [7]]. In contrast, it was found[4m] that replacement of the phenyl group in diazepam with a fused triazole or triazolone ring results in a significant increase in the conformational mobility of the seven-membered ring, indicating that the 11b-phenyl group in compounds (2)—(4) is primarily responsible for the lack of inversion of the seven-membered ring at room temperature.

CONCLUSIONS

The assignment of stereochemistry and preferred conformation to the cycloadducts (2)—(4) represents a cogent example of the usefulness of lanthanide(gadolinium)-induced relaxation (LIR) enhancements in determining the molecular topology, especially when, as far as the LIS data alone are concerned, more than one acceptable solution to the structure is obtained, and other experimental evidence is not available.

The slow reversal of the heptatomic ring in all synthesized products (characterized by a slightly enhanced energy barrier in comparison with diazepam) seems promising in relation to their potential biological activity.[15]

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Analyses were performed on a Perkin-Elmer 240 elemental analyzer. I.r. spectra ($CHCl_3$ solutions) were measured on a Perkin-Elmer 225 and ^1H n.m.r. spectra on a Varian EM 360A instrument. $Eu(fod)_3$ was purchased from C. Erba and $Gd(fod)_3$ was prepared by the standard method.[16] For the n.m.r. measurements the solvent used was deuteriochloroform, with *ca.* 0.5% Me_4Si added as internal standard and frequency lock. Series of spectra were obtained at constant substrate concentration (*ca.* 0.4M) by the incremental dilution method.[17] Molar ratios of shift reagent to substrate in the range 0—0.35 were used. $Eu(fod)_3$ was used to separate the signals for observation of the broadening due to $Gd(fod)_3$. The calculations were carried out using an IBM 4331 computer.

Cycloaddition Reactions of Diazepam 4-Oxide (7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one 4-Oxide) (1) *with Acrylic Esters.*—The general procedure for the preparation of 10-*chloro*-1,2,7,11b-*tetrahydro*-r-2-*methoxycarbonyl*-7-*methyl*-c-11b-*phenylisoxazolo*[2,3-d][1,4]*benzodiazepin*-6(5H)-*one* (2a) is as follows. Diazepam 4-oxide (1) and an excess (30 : 1) of methyl acrylate were refluxed for

* 1 Cal = 4.184 J.

ca. 2 h under nitrogen; the reaction was monitored by t.l.c. When no further increase in the amount of reaction product could be observed, the excess of methyl acrylate was distilled off under reduced pressure and the residue worked up with diethyl ether to allow the crystallisation of unchanged compound (1). The residual ethereal solution was then concentrated and the cycloadduct (2a) purified by p.l.c. [silica-gel plates; elution with ethyl acetate–light petroleum, (b.p. 30—50 °C) 1 : 1] to afford white crystals, m.p. 157—159 °C (yield 64%), $\nu_{max.}$ 1 727 (ester CO) and 1 670 cm^{-1} (amide CO) (Found: C, 62.2; H, 4.9; N, 7.0. $C_{20}H_{19}ClN_2O_4$ requires C, 62.1; H, 5.0; N, 7.2%).

10-*Chloro*-r-2-*ethoxycarbonyl*-1,2,7,11b-*tetrahydro*-7-*methyl*-11b-*phenylisoxazolo*[2,3-d][1,4]*benzodiazepin*-6(5H)-*one* (2b).—The cycloaddition between compound (1) and ethyl acrylate afforded the *ethoxycarbonyl compound* (2b), m.p. 180—182 °C (yield 60%), $\nu_{max.}$ 1 735 (ester CO) and 1 672 cm^{-1} (amide CO) (Found: C, 62.8; H, 5.3; N, 7.1. $C_{21}H_{21}ClN_2O_4$ requires C, 62.9; H, 5.3; N, 7.0%).

10-*Chloro*-1,2,7,11b-*tetrahydro*-r-2-*methoxycarbonyl*-t-2,7-*dimethyl*-c-11b-*phenylisoxazolo*[2,3-d][1,4]*benzodiazepin*-6-(5H)-*one* (2c).—The cycloaddition between compound (1) and methyl methacrylate affords the product (2c), m.p. 173—175 °C (yield 70%), $\nu_{max.}$ 1 734 (ester CO) and 1 670 cm^{-1} (amide CO) (Found: C, 63.0; H, 5.3; N, 7.0%).

10-*Chloro*-1,2,7,11b-*tetrahydro*-r-1-*methoxycarbonyl*-t-2,7-*dimethyl*-t-11b- *and* -c-11b-*phenylisoxazolo*[2,3-d][1,4]*benzodiazepin*-6(5H)-*one* (3) *and* (4).—The cycloaddition between compound (1) and methyl *trans*-crotonate gave, after separation of the unchanged diazepam 4-oxide and t.l.c. purification (see above), a diastereoisomeric mixture (yield 74%) of cycloadducts, which was separated by t.l.c. [elution with ethyl acetate–light petroleum, (b.p. 30—50 °C), 1.5 : 1] affording *ca.* equimolar amounts of isomers (3) and (4). Adduct (3), m.p. 161—163 °C, $\nu_{max.}$ 1 730 (ester CO) and 1 670 cm^{-1} (amide CO) (Found: C, 62.8; H, 5.2; N, 6.9%). Adduct (4), m.p. 169—171 °C, $\nu_{max.}$ 1 732 (ester CO) and 1 672 cm^{-1} (amide CO) (Found: C, 62.9; H, 5.2; N, 6.9%).

Raney-nickel Hydrogenolysis of Cycloadducts (2)—(4).—In the general procedure, the cycloadduct (2 mmol) in absolute ethanol (40 ml) was hydrogenated at room temperature under hydrogen (slightly raised pressure) over W2 Raney nickel (1 g). When the reaction appeared to be complete by t.l.c. (after *ca.* 20 h), the catalyst was filtered off, and the solvent evaporated off under reduced pressure. Both adducts (2a) and (2b) afforded 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*, and (2c) gave 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*. These hydrogenolysis products lack the typical alkoxy ^1H n.m.r. absorptions and show broad i.r. absorption at 1 670 cm^{-1}, due to 3-CO and 6-CO stretching vibrations. On the other hand, the diastereoisomeric mixture of cycloaddition products from the diazepam (1) and methyl *trans*-crotonate yielded 7-*chloro*-1,3,4,5-*tetrahydro*-5-(1-*methoxycarbonyl*-2-*hydroxypropyl*)-1-*methyl*-5-*phenyl*-1,4-*benzodiazepin*-2-*one* (diastereoisomeric mixture) which still shows an OMe signal in its ^1H n.m.r. spectrum near δ 3.8 and i.r absorptions at 1 733 (ester CO) and 1672 cm^{-1} (amide CO).

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