Reactions of Chlordiazepoxide and Diazepam N-Oxide with Dimethyl Acetylenedicarboxylate with Rearrangement to Quinoxaline Derivatives and X-Ray Analysis of a Resultant Tetracyclic Compound

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Three 1,4-benzodiazepine N-oxides, diazepam N-oxide (IIIa), nordiazepam N-oxide (IIIb) and chlordiazepoxide (IV) were submitted to 1,3-dipolar cycloaddition reaction with dimethyl acetylenedicarboxylate to give quinoxaline derivatives (Va from IIIa; Vb from IIIb; XI and XII from IV). It is likely that the cycloaddition reactions involve the rearrangement of Beckmann type in which initially formed adducts (i.e., VIa) rearrange to quinoxaline derivatives (i.e., VIIa). The structural determination of XII was made by X-ray crystallographic analysis.

Keywords——chlordiazepoxide; diazepam N-oxide; dimethyl acetylenedicarboxylate; Beckmann rearrangement; quinoxaline derivatives; 1,3-dipolar cycloaddition reaction; X-ray analysis

In view of their chemical reactions which include a variety of rearrangements,[2] 1,4-benzodiazepines are of both chemical and pharmacological importance. Previous papers[3] described how oxazolidine-fused benzodiazepines (I) underwent rearrangements to quinolones and isoindoles. The present investigation is concerned with the rearrangement reactions of benzodiazepine N-oxides such as diazepam N-oxide (IIIa), nordiazepam N-oxide (IIIb) and chlordiazepoxide (IV) leading to quinoxaline derivatives which we found in an attempt to obtain isoxazolidinobenzodiazepines (II).

Following the syntheses of benzodiazepinooxazolidine minor tranquilizers,[4] the aim of our investigation was to prepare isoxazolidine-fused benzodiazepine derivatives. In our first attempt to form an isoxazoline nucleus, diazepam N-oxide (IIIa) was submitted to a 1,3-dipolar cycloaddition reaction with dimethyl acetylenedicarboxylate. Heating of IIIa

I   II   IIIa : R=CH₃   IV
                                   IIIb : R=H

Ph=phenyl

Chart 1

1) Location: 1-2-58, Hiromachi, Shinagawa-ku, Tokyo.
2) For a review see R.I. Fryer, J. Heterocycl. Chem., 9, 747 (1972).
3) A. Terada, Y. Yabe, T. Miyadera, and R. Tachikawa, Chem. Pharm. Bull. (Tokyo), 21, 742 (1973); idem, ibid., 21, 807 (1973); idem, ibid., 21, 1404 (1973).
4) T. Miyadera, A. Terada, M. Fukunaga, Y. Kawano, C. Tamura, H. Takagi, and R. Tachikawa, J. Med. Chem., 14, 520 (1971).

III $H_3COOCC \equiv CCOOCH_3$ →

Va : R=CH₃ → Va : $R=CH_3$

Va : $R=CH_3$
Vb : $R=H$

VIa : $R=CH_3$

$PhC=C(COOCH_3)COCOOCH_3$

VIIa : $R=CH_3$
VIIb : $R=H$

Ph = phenyl

Chart 2

with the dimethyl ester in ethanol resulted in the formation of an aromatic compound (Va) assigned the Formula, $C_9H_7ClN_2O$ which is apparently missing one phenyl group. Treatment of nordiazepam N-oxide (IIIb) with the dimethyl ester for a long period of time at room temperature also afforded the corresponding product (Vb) with the molecular formula, $C_8H_5ClN_2O$. The structures of the two products were assigned on the basis of mechanistic consideration and spectroscopic data, and finally confirmed by comparison with an authentic sample of Vb. There is no doubt that the extensive degradation proceeded by multiple steps including an addition reaction and a subsequent rearrangement. With the view of obtaining a possible adduct and rearranged intermediate, diazepam N-oxide IIIa was treated with dimethyl acetylenedicarboxylate in ethanol or methylene chloride–ether under mild conditions. The 1,3-dipolar cycloaddition reaction gave rise to the adduct (VIa) assigned the Formula, $C_{22}H_{19}ClN_2O_6$ in good yield, along with the rearrangement product (VIIa) with the same empirical formula. The latter was formed by heating the adduct (VIa) in ethanol for a short period of time. The two intermediates could be converted to Va by prolonged heating in ethanol.

The structures of VIa and VIIa were determined on the basis of mass (MS), infrared (IR) and nuclear magnetic resonance (NMR) spectra. Although VIa seemed to be a single material on thin–layer chromatography, it was shown by spectroscopic data to exist possibly as a 4:3 mixture of two interconvertible isomers (A and B). As is summarized in Table I, the NMR spectrum exhibits a pair of peaks assignable to the protons indicated with subscripts a—e and to the remaining protons. The ^{13}C–NMR spectrum also showed peaks doubled in number: N-methyl peaks at 33.9 and 34.8 ppm, O-methyl peaks at 51.9, 52.0, 53.3 and 53.4 ppm, methylene peaks at 56.5 and 57.9 ppm. Based on the spectral data, the two components in the $CDCl_3$ solution were tentatively concluded to be conformational isomers which

TABLE I.   NMR Spectral Data (100 MHz) of VIa in $CDCl_3$ at Room Temperature

		Ha	Hb	Hc	Hd, He	OCH₃	NCH₃	C₆H₅
A	ppm	7.63	7.48	7.13	4.13, 3.64	3.91, 3.55	2.52	7.1—7.4
	Hz	$J_{ab}=2.5$	$J_{bc}=8.5$		$J_{de}=9$			
B	ppm	6.66	7.37	7.12	3.94, 3.68	3.84, 3.66	3.27	7.1—7.4
	Hz	$J_{ab}=2.5$	$J_{bc}=8.5$		$J_{de}=15$			

Ha, C-11 H; Hb, C-9 H; Hc, C-8 H; Hd, He, C-5 H₂.

are responsible for the seven-membered ring, as is the case with the adduct of diazepam N-oxide and ethyl propiolate.[5]   It is interesting to note that oxazolidine-fused benzodiazepines did not reveal this type of NMR spectra at room temperature, although some derivatives possessing two chiral centers exist as a mixture of two stereoisomers in a crystal form or in solution.[6]

In contrast, VIIa exhibited a simple NMR spectrum with four singlets at 4.18, 3.48, 3.40 and 3.75 ppm corresponding to the methylene, N-methyl and two O-methyl groups, respectively.

Fragments arising from the cycloaddition reaction could be isolated by column chromatography and were proved to be methyl and ethyl benzoylacetate.   The IR spectrum of the ethyl ester was superimposable on that of an authentic sample and the methyl ester showed similar absorption bands.   The keto group of the two esters was indicated by the NMR spectrum to be present as a tautomeric mixture of keto and enol forms in deuterochloroform. The presence of the enolizable ketone was also supported by trimethylsilylation of the methyl ester and the mass spectrum of the resulting product showed a molecular ion peak at m/e 250. The ethyl ester is thought to be formed as the result of an ester exchange of the methyl group in boiling ethanol.   The methyl ester is probably formed by way of a 1,3-diketo diester (IX) capable of undergoing a retrograde Claisen reaction, although the isolation of IX was unsuccessful.   The enamine N–C bond of VII may be cleaved in the presence of water to form a dihydroquinoxalone derivative (VIII) and IX.   The dihydro intermediate is thought to be a possible precursor of V, since dihydroquinoxalone is readily oxidized by air.[7]

Ph = phenyl
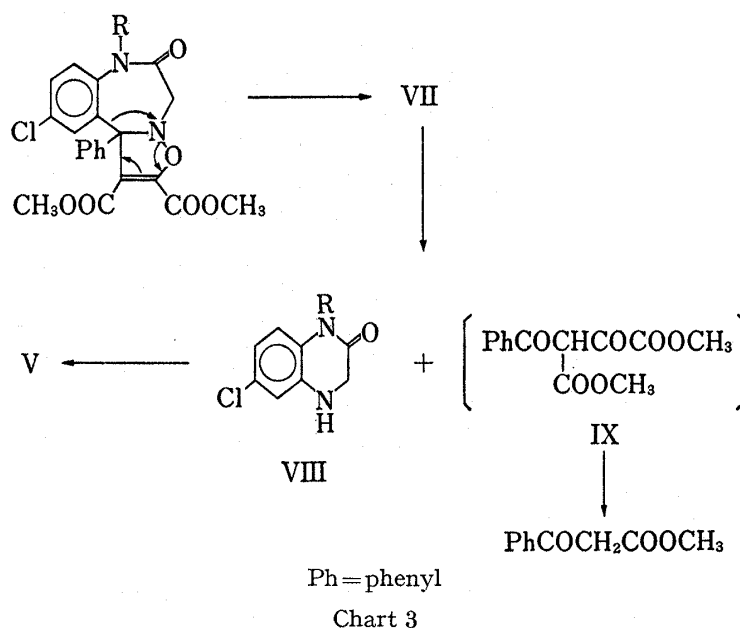
Chart 3

The structure of VIIa was not conclusively determined, but it seems certain that it is derived from the adduct VI through a Beckmann type of rearrangement as depicted in Chart 3. The driving force of the facile isomerization to the quinoxalone derivatives is the formation of the extended conjugated system.   This type of rearrangement has been reported to take

5) M. Raban, E.H. Carlson, J. Szmuszkovicz, G. Slomp, C.G. Chidester, and D.J. Duchamp, *Tetrahedron Lett.*, **1975**, 139.

6) T. Miyadera, A. Terada, C. Tamura, M. Yoshimoto, and R. Tachikawa, *Takamine Kenkyusho Nempo*, **28**, 1 (1976).

7) Y.T. Pratt, "Heterocyclic Compounds," Vol. 6, ed. by R.C. Elderfield, John Wiley and Sons, Inc., New York, 1956, p. 455.
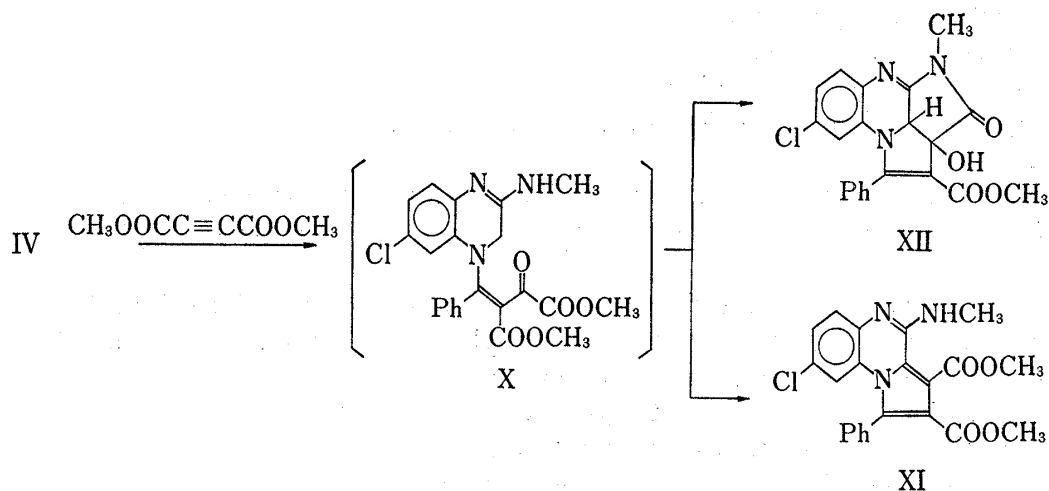
Ph=phenyl

Chart 4

place on treatment of IIIa with ethyl propiolate.[8] In this case, however, the cleavage of the 4-substituent of the rearrangement product has not been observed in the cycloaddition reaction. Rearrangement with the formation of a dihydroquinoxalone has been earlier found by Bell and Childress when IIIb was treated with *p*-toluenesulfonyl chloride.[9]

The reaction of IV with dimethyl acetylenedicarboxylate in boiling ethanol afforded two crystalline products (XI and XII) in yields of 15.6 and 35.2%, respectively. The lower melting substance (XI) exhibited a molecular ion peak at m/e 423 which agrees with the empirical formula, $C_{22}H_{18}ClN_4O_4$. The molecular formula corresponds to a condensation product with the loss of water from the 1,3-dipolar cycloaddition reaction intermediate (X). The NH group remains as is evident from the NMR and IR spectra showing a peak at 9.15 ppm (in $CDCl_3$) and an absorption band at 3330 cm^{-1}, respectively. The presence of the two ester methyl groups was indicated by the NMR spectrum which showed two methyl singlets at 3.70 and 3.91 ppm in addition to a methyl doublet ($J=5$ Hz) at 3.19 ppm due to the aminomethyl group. Although the spectroscopic data are not sufficient to determine the full structure, it can be assumed that XI was formed by dehydration of the intermediate (X). The higher melting product (XII) showed a molecular ion peak at m/e 409 in accord with the empirical formula, $C_{21}H_{16}ClN_3O_4$. Evidently one of the two ester methyls was expelled as methanol from X. The NMR spectrum of XII exhibited two methyl singlets at 3.35 and 3.58 ppm assignable to the aminomethyl and ester methyl group, respectively. The IR spectrum indicated the presence of a hydroxyl group at 3450 cm^{-1}, ester at 1690 cm^{-1} and amide carbonyl at 1760 cm^{-1}. The extremely high frequency of the amide carbonyl is reasonable, since the carbonyl group is a part of the moiety –N=C–N–CO–. Taking into account the mechanism of the cycloaddition reaction of IIIa with dimethyl acetylenedicarboxylate, the structure of XII was assumed to be a tetracyclic compound, although the stereochemistry remains unsettled. The full structure of XII including the stereochemistry was determined by X-ray crystallographic analysis.

The reaction of IV with dimethyl acetylenedicarboxylate may proceed through a 1,3-dipolar cycloaddition reaction with the formation of an adduct and subsequent Beckmann type of rearrangement to X. The pathway of the conversion of X to XI or XII may involve the cyclization of the ketone carbonyl carbon with the C-3 methylene carbon to form a

8) C.G. Chidester, D.J. Duchamp, and J. Szmuskovicz, American Crystallographic Association, Winter Meeting, University of New Mexico, Alburquerque, N.M., April 3–7, 1972, Abstract E9.

9) S.C. Bell and S.J. Childress, *J. Org. Chem.*, **29**, 506 (1964).

TABLE II. Final Positional ($\times 10^4$) and Anisotropic Thermal ($\times 10^4$) Parameters with Estimated Standard Deviations in Parentheses

Anisotropic Thermal Parameters are in the Form
$$\exp[-(h^2\beta_{11}+k^2\beta_{22}+l^2\beta_{33}+2hk\beta_{12}+2hl\beta_{13}+2kl\beta_{23})]$$

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
CL(1)	−108(1)	2303(2)	4478(1)	14(0)	414(4)	95(1)	19(1)	3(0)	−22(2)
N(2)	2552(2)	1632(4)	2412(2)	17(1)	147(6)	32(2)	−4(2)	0(1)	7(3)
C(3)	3048(2)	1082(5)	2982(3)	16(1)	103(6)	33(2)	−1(2)	2(1)	−6(3)
N(4)	3726(1)	1251(4)	2754(2)	15(1)	133(6)	35(2)	0(2)	4(1)	4(3)
C(5)	4146(2)	935(5)	3632(3)	16(1)	94(6)	42(2)	0(2)	3(1)	−1(3)
C(6)	3685(2)	670(5)	4590(3)	13(1)	102(6)	37(2)	1(2)	0(1)	8(3)
C(7)	2991(2)	273(5)	4067(3)	12(1)	94(6)	34(2)	0(2)	1(1)	1(3)
N(8)	2482(1)	1275(4)	4640(2)	12(1)	105(5)	33(2)	2(2)	0(1)	−1(2)
C(9)	1865(2)	1561(5)	4030(3)	14(1)	95(6)	39(2)	−1(2)	−2(1)	0(3)
C(10)	1247(2)	1746(6)	4516(3)	14(1)	155(8)	44(2)	0(2)	0(1)	−7(4)
C(11)	669(2)	1988(6)	3884(3)	13(1)	159(8)	67(3)	0(2)	0(1)	−4(4)
C(12)	695(2)	1976(6)	2801(3)	16(1)	161(8)	64(3)	−5(2)	−8(1)	16(4)
C(13)	1317(2)	1749(6)	2320(3)	19(1)	163(8)	42(2)	−9(2)	−6(1)	17(4)
C(14)	1917(2)	1583(5)	2923(3)	15(1)	108(6)	40(2)	−2(2)	−2(1)	10(3)
C(15)	3515(2)	2341(5)	5182(3)	14(1)	110(6)	33(2)	0(2)	−1(1)	0(3)
C(16)	2831(2)	2607(5)	5195(2)	16(1)	96(6)	27(2)	0(2)	0(1)	7(3)
C(17)	3987(2)	1798(7)	1735(3)	23(1)	214(10)	42(3)	0(3)	10(1)	19(4)
O(18)	4757(1)	876(4)	3616(2)	13(1)	169(6)	57(2)	0(2)	2(1)	−1(3)
O(19)	3917(1)	−718(4)	5228(2)	15(1)	132(5)	53(2)	7(1)	−1(1)	26(3)
C(20)	4052(2)	3318(5)	5731(3)	17(1)	122(7)	37(2)	−1(2)	−2(1)	3(3)
O(21)	4644(1)	2912(5)	5703(3)	16(1)	230(8)	100(3)	10(2)	−14(1)	−60(4)
O(22)	3824(1)	4687(4)	6265(2)	18(1)	139(6)	79(2)	−4(2)	−4(1)	−33(3)
C(23)	4319(2)	5826(6)	6756(4)	26(1)	127(8)	99(4)	−7(3)	−13(2)	−34(5)
C(24)	2434(2)	3979(5)	5724(3)	14(1)	117(6)	31(2)	0(2)	−2(1)	−6(3)
C(25)	2085(2)	3592(6)	6636(3)	24(1)	138(8)	46(3)	−2(2)	6(1)	1(4)
C(26)	1719(2)	4886(7)	7140(3)	29(1)	211(10)	51(3)	0(3)	14(2)	−23(5)
C(27)	1697(2)	6552(7)	6729(4)	27(1)	189(10)	62(3)	20(3)	1(2)	−39(5)
C(28)	2040(3)	6957(6)	5827(4)	39(2)	136(8)	59(3)	24(3)	2(2)	1(4)
C(29)	2410(2)	5656(6)	5327(3)	29(1)	147(8)	43(3)	14(3)	9(1)	11(4)

TABLE III. Final Hydrogen-atom Positional Parameters ($\times 10^3$) and Thermal Parameters

	x	y	z	$B(\text{Å}^2)$
H(7)	288(2)	−97(5)	402(3)	2.3(0.8)
H(10)	121(2)	162(5)	531(3)	2.7(0.8)
H(12)	27(2)	231(6)	242(3)	5.0(1.1)
H(13)	134(2)	177(6)	158(3)	4.0(1.0)
H(17A)	442(3)	144(7)	166(4)	7.6(1.5)
H(17B)	386(3)	293(7)	153(4)	7.1(1.4)
H(17C)	379(3)	96(7)	112(4)	7.3(1.5)
H(19)	426(2)	−52(6)	533(3)	3.8(1.0)
H(23A)	409(3)	690(7)	697(4)	7.2(1.4)
H(23B)	465(3)	595(7)	640(4)	6.4(1.3)
H(23C)	449(3)	547(7)	746(4)	6.5(1.3)
H(25)	210(2)	247(5)	688(3)	3.3(0.9)
H(26)	150(2)	460(6)	782(3)	4.5(1.0)
H(27)	146(2)	744(7)	708(4)	6.0(1.3)
H(28)	207(2)	833(7)	558(4)	5.9(1.2)
H(29)	264(2)	584(6)	474(3)	4.9(1.1)

The hydrogen atoms are numbered according to the atoms to which they are attached.

TABLE IV. Bond Lengths (Å)

CL(1)-C(11)	1.727(4)	C(10)-C(11)	1.386(5)	C(7)-H(7)	0.98(4)
N(2)-C(3)	1.270(5)	C(11)-C(12)	1.370(6)	C(10)-H(10)	1.01(4)
N(2)-C(14)	1.413(4)	C(12)-C(13)	1.383(5)	C(12)-H(12)	0.98(4)
C(3)-N(4)	1.371(4)	C(13)-C(14)	1.393(5)	C(13)-H(13)	0.94(4)
C(3)-C(7)	1.508(5)	C(15)-C(16)	1.356(5)	C(17)-H(17A)	0.89(5)
N(4)-C(5)	1.389(5)	C(15)-C(20)	1.454(5)	C(17)-H(17B)	0.93(6)
N(4)-C(17)	1.454(5)	C(16)-C(24)	1.470(5)	C(17)-H(17C)	1.08(5)
C(5)-C(6)	1.538(5)	C(20)-O(21)	1.201(4)	O(19)-H(19)	0.70(4)
C(5)-O(18)	1.197(4)	C(20)-O(22)	1.324(5)	C(23)-H(23A)	0.97(6)
C(6)-C(7)	1.531(5)	O(22)-C(23)	1.433(6)	C(23)-H(23B)	0.81(5)
C(6)-C(15)	1.517(5)	C(24)-C(25)	1.383(5)	C(23)-H(23C)	0.98(5)
C(6)-O(19)	1.401(4)	C(24)-C(29)	1.374(6)	C(25)-H(25)	0.91(4)
C(7)-N(8)	1.459(4)	C(25)-C(26)	1.381(6)	C(26)-H(26)	0.99(4)
N(8)-C(9)	1.436(4)	C(26)-C(27)	1.372(7)	C(27)-H(27)	0.94(5)
N(8)-C(16)	1.403(4)	C(27)-C(28)	1.369(7)	C(28)-H(28)	1.09(5)
C(9)-C(10)	1.375(5)	C(28)-C(29)	1.387(6)	C(29)-H(29)	0.88(4)
C(9)-C(14)	1.404(5)				

TABLE V. Bond Angles (Å)

C(9)-C(10)-C(11)	118.3(3)	C(3)-C(7)-N(8)	107.4(3)
C(10)-C(9)-C(14)	121.6(2)	C(3)-C(7)-C(6)	103.3(2)
N(8)-C(9)-C(14)	117.4(2)	C(3)-N(4)-C(17)	124.8(2)
C(12)-C(13)-C(14)	120.8(3)	C(6)-C(15)-C(20)	120.1(2)
C(11)-C(12)-C(13)	119.3(3)	C(6)-C(15)-C(16)	111.0(3)
C(10)-C(11)-C(12)	121.9(2)	C(3)-N(4)-C(5)	112.2(2)
N(8)-C(9)-C(10)	121.0(3)	N(4)-C(3)-C(7)	108.6(2)
C(9)-N(8)-C(16)	123.7(4)	N(2)-C(3)-C(7)	125.5(2)
C(7)-N(8)-C(16)	107.2(1)	N(2)-C(3)-N(4)	125.7(4)
C(7)-N(8)-C(9)	112.9(2)	C(3)-N(2)-C(14)	113.8(3)
C(15)-C(16)-C(24)	129.9(4)	CL(1)-C(11)-C(10)	119.1(3)
C(16)-C(15)-C(20)	128.6(5)	CL(1)-C(11)-C(12)	119.0(2)
C(15)-C(6)-O(19)	115.0(2)	N(2)-C(14)-C(9)	122.4(2)
C(6)-C(7)-N(8)	107.0(2)	N(2)-C(14)-C(13)	119.2(3)
C(7)-C(6)-O(19)	112.0(3)	C(20)-O(22)-C(23)	117.8(1)
C(7)-C(6)-C(15)	100.2(2)	O(21)-C(20)-O(22)	123.5(5)
C(5)-C(6)-O(19)	111.2(2)	C(15)-C(20)-O(22)	113.5(2)
C(5)-C(6)-C(15)	114.6(3)	C(15)-C(20)-O(21)	123.0(5)
C(9)-C(14)-C(13)	118.0(2)	C(16)-C(24)-C(29)	120.7(2)
C(5)-C(6)-C(7)	102.5(2)	C(16)-C(24)-C(25)	120.1(5)
C(6)-C(5)-O(18)	127.6(4)	C(25)-C(24)-C(29)	119.2(4)
N(4)-C(5)-O(18)	124.7(4)	C(24)-C(25)-C(26)	120.1(6)
N(8)-C(16)-C(24)	119.0(2)	C(27)-C(28)-C(29)	119.2(6)
N(8)-C(16)-C(15)	111.0(3)	C(26)-C(27)-C(28)	120.7(5)
N(4)-C(5)-C(6)	107.6(1)	C(25)-C(26)-C(27)	120.0(4)
C(5)-N(4)-C(17)	122.9(2)	C(24)-C(29)-C(28)	120.9(3)

hydroxyl compound. The dehydration of the hydroxyl intermediate (possibly *trans* isomer) may give rise to XI. Once the dehydration occurrs, further cyclization to a tetracyclic compound seems impossible, because of the appearance of a large strain. Further cyclization to XII with the loss of methanol is possible with *cis* isomer of the hydroxyl intermediate.

Structure Determination of XII by X-Ray Analysis

The crystals of XII for X-ray analysis were grown from acetone as colorless prisms. The crystal data of this compound are: $a=19.59$, $b=7.62$, $c=12.63\text{Å}$, $\beta=91.1°$, space group $P2_1/n$, $D_{obs.}=1.43$, $D_{calc.}=1.44$ g/cm³. Intensities of 3250 independent reflections were collected on a Rigaku four-circle difractometer with Mo-Kα radiation, 2θ up to 55°. The structure

was solved by the symbolic addition procedure. All non-hydrogen atoms were found in the first E-map. Block-diagonal least-squares refinement reduced R-value to 11.3%. A three-dimentional difference Fourier map showed the positions of all H atoms. At the next stage of least-squares refinement, the contributions of the H atoms were included and the final R-value reached was 5.9%. The final atomic parameters with their estimated standard deviations are listed in Tables II and III. The molecular stereographic view is shown in Fig. 1. The bond lengths and angles are given in Tables IV and V, respectively.
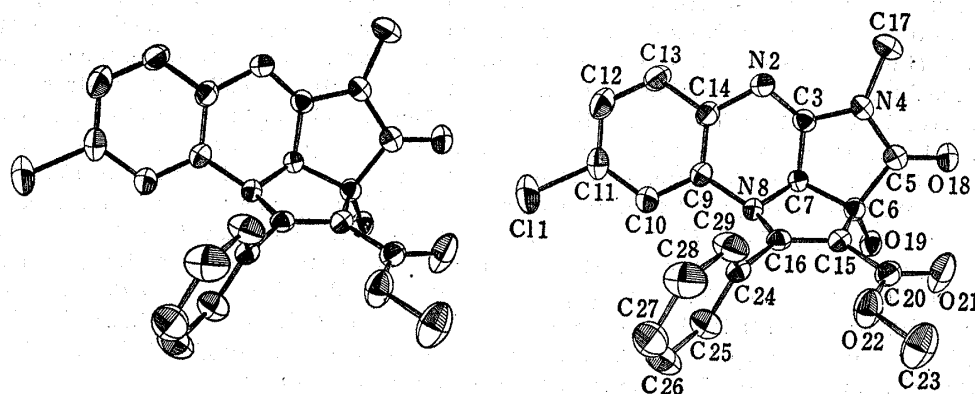
Fig. 1. Stereoscopic View of the Conformation of XII

Thermal ellipsoids representing 50% probability are shown.

TABLE VI. Deviations (Å) of Atoms from the Least-squares Plane

Ring A		Ring B		Ring C		Ring D		Ring E	
C (9)*	0.001	C (3)*	0.001	C (3)*	0.000	C (6)*	−0.003	C (24)*	0.000
C (10)*	0.014	N (8)*	−0.002	N (4)*	0.000	N (8)*	0.003	C (25)*	0.003
C (11)*	−0.015	C (9)*	0.003	C (5)*	0.000	C (15)*	0.005	C (26)*	−0.004
C (12)*	−0.001	C (14)*	−0.002	C (6)	−0.135	C (16)*	−0.006	C (27)*	0.002
C (13)*	0.018	N (2)	−0.234	C (7)	0.262	C (7)	0.293	C (28)*	0.000
C (14)*	−0.017	C (7)	0.599					C (29)*	−0.001
Cl(1)	−0.061							C (16)	−0.010
N (2)	−0.210								
N (8)	0.053								

Atoms included in the calculation are marked with an asterisk.

As shown in Table VI, the ring B is assumed to be in a twisted boat conformation; the atoms C(3), N(8), C(9) and C(14) are almost in the same plane with a maximum deviation of 0.003Å. N(2) and C(7) are displaced by −0.23 and 0.60Å from this plane, respectively. The five-membered ring system, C, is in a half chair conformation and the atoms C(6) and C(7) are displaced by −0.14 and 0.26Å, respectively, from the plane of the other three atoms in this ring. Another five-membered ring system, D, is in an envelope conformation where the atom C(7) lies 0.29Å out of the plane through the other ring atoms.

The N(8) atom is displaced by 0.34Å from the plane consisting of three attached carbon atoms and the mean bond angle about N(8) is 114.6°. These values indicate that the atomic configuration of this atom is sp^3. The lone pair of N(8), the hydrogen atom adjacent to C(7) and the O(19)H group are all directed to the same side with respect to the plane of the three atoms N(8), C(7) and C(6). The O(19)—H(7) interatomic distance is 2.53Å which is somewhat shorter than the sum of Van der Waals radii.

Experimental

Melting points were uncorrected. NMR spectra were recorded on a Varian Model A-60 or HA-100; chemical shifts were recorded in parts per million downfield from Me_4Si. IR spectra were taken using a

Perkin-Elmer Model 225. Mass spectra were recorded using a JEOL JMS-01SG. GCMS spectra were recorded using a Shimazu LKB-9000. The silica gel used for column chromatography was obtained from Kanto Chemical Co., Inc., Tokyo, Japan.

Reaction of Diazepam N-Oxide (IIIa) with Dimethyl Acetylenedicarboxylate——(A) A solution of diazepam N-oxide (IIIa, 3.0 g) and dimethyl acetylenedicarboxylate (1.42 g) in EtOH (150 ml) was heated under reflux for 12 hr. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel eluting with benzene–ethyl acetate (19: 1) to give 6-chloro-1-methyl-2-quinoxalone (Va), mp 125—128° (from EtOH). Yield, 1.7 g. *Anal.* Calcd. for $C_9H_7ClN_2O$: C, 55.54; H, 3.62; N, 14.39; Cl, 18.21. Found: C, 55.60; H, 3.71; N, 14.33; Cl, 18.33. IR ν_{max}^{Nujol} cm^{-1}: 1660 (amide CO). NMR (CDCl$_3$) δ: 3.70 (3H, singlet, N-methyl), 8.30 (1H, singlet, C-3 H), 7.2—7.9 (3H, aromatic protons). MS *m/e*: 194 (M$^+$).

(B) A solution of diazepam N-oxide (IIIa, 21 g) and dimethyl acetylenedicarboxylate (9.94 g) in ether (1 l) and CH$_2$Cl$_2$ (140 ml) was stirred for 3 days at room temperature. After collecting the precipitate (2.8 g) by filtration, the filtrate was concentrated to *ca.* 500 ml and the crystals were collected by filtration and washed with EtOH to give dimethyl 10-chloro-5,6,7,11b-tetrahydro-7-methyl-6-oxo-11b-phenyl-isooxazolo[2,3-d][1,4]-benzodiazepine-1,2-dicarboxylate (VIa, 22.5 g). The filtrate was evaporated to dryness and the residue was chromatographed and eluted with benzene-ethyl acetate (20: 1) to give VIa (270 mg), mp 153° (from EtOH), methyl 4-[4-(1-methyl-6-chloro-1,2,3,4-tetrahydro-2-oxoquinoxalinyl)]-3-methoxycarbonyl-2-oxo-4-phenyl-3-butenoate (VIIa, 1.1 g), mp 174—175° (from EtOH) and the starting material (IIIa, 1.58 g). *Anal.* Calcd. for $C_{22}H_{19}ClN_2O_6$ (VIa): C, 59.66; H, 4.29; N, 6.33; Cl, 8.02. Found: C, 59.93; H, 4.39; N, 6.24; Cl, 7.99. IR ν_{max}^{Nujol} cm^{-1}: 1680, 1720, 1750. NMR (CDCl$_3$) (100 MHz) δ: listed in Table I. *Anal.* Calcd. for $C_{22}H_{19}Cl-N_2O_6$ (VIIa): C, 59.66; H, 4.29; N, 6.33; Cl, 8.02. Found: C, 59.88; H, 4.32; N, 6.22; Cl, 8.21. IR ν_{max}^{Nujol} cm^{-1}: 1690, 1740. NMR (CDCl$_3$) δ: 3.40 (3H, singlet, COOCH$_3$), 3.48 (3H, singlet, NCH$_3$), 3.75 (3H, singlet, COOCH$_3$), 4.18 (2H, singlet, CH$_2$), 7.1—7.5 (8H, multiplet, aromatic protons).

Rearrangement of the Adduct (VIa) to Va——A solution of VIa (3.0 g) in EtOH (100 ml) was refluxed for *ca.* 30 hr. The solvent was evaporated off *in vacuo* and the residual products were separated by repeated preparative TLC with benzene–ethyl acetate (1: 1) and benzene–ethyl acetate (7: 1) to give Va (724 mg) as crystals, mp 125—128° (from EtOH) and two esters of benzoylacetic acid: ethyl benzoylacetate (261 mg) and methyl benzoylacetate (461 mg). Methyl ester: NMR (CDCl$_3$) δ: a tautomeric mixture (*ca.* 10: 1) of the keto and enol forms. 3.70 (singlet, COOCH$_3$ of keto form), 3.77 (singlet, COOCH$_3$ of enol form), 3.98 (singlet, CH$_2$), 5.69 (singlet, -C(OH)=CH-), 7.3—8.1 (multiplet, aromatic protons), 12.65 (singlet, enol OH). MS *m/e*: 178 (M$^+$).

The NMR and IR spectra of the ethyl ester were identical with those of an authentic sample.

Conversion of VIIa to Va——A solution of VIIa (50 mg) in EtOH (2.5 ml) was refluxed for 13 hr. The solvent was evaporated off *in vacuo* and the residue was purified by preparative TLC to give a quantitative yield of Va.

Reaction of Nordiazepam N-Oxide with Dimethyl Acetylenedicarboxylate——A solution of nordiazepam N-oxide (IIIb, 0.75 g) and dimethyl acetylenedicarboxylate (0.37 g) in EtOH (40 ml) and CH$_2$Cl$_2$ (10 ml) was stirred for 13 days at room temperature. The solvent was evaporated and the residue was recrystallized from EtOH to give 6-chloro-1,2-dihydro-2-quinoxalone (Vb, 280 mg), mp 306—308°, which was identified by comparison with an authentic sample. *Anal.* Calcd. for $C_8H_5ClN_3O$: C, 53.21; H, 2.79; N, 15.51; Cl, 19.63. Found: C, 53.15; H, 2.98; N, 15.27; Cl, 19.08.

Reaction of Chlordiazepoxide (IV) with Dimethyl Acetylenedicarboxylate——A solution of chlordiazepoxide (IV, 1.5 g) and dimethyl acetylenedicarboxylate (0.71 g) in EtOH (10 ml) was refluxed for 10 hr. The precipitate was collected by filtration and recrystallized from acetone to give two kinds of crystals. After separating the minor crystals with tweezers, the remaining crystals were recrystallized from acetone to give 8-chloro-2,3-dimethoxycarbonyl-4-methylaminopyrrolo[1,2-d]quinoxaline (XI, 600 mg), mp 244°. *Anal.* Calcd. for $C_{22}H_{18}ClN_3O_4$: C, 62.34; H, 4.25; N, 9.92; Cl, 8.38. Found: C, 62.63; H, 4.28; N, 10.08; Cl, 8.57. MS *m/e*: 423 (M$^+$). IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH), 1698, 1720 (esters). NMR (CDCl$_3$) δ: 3.19 (3H, doublet, $J=5$ Hz, NCH$_3$), 3.70 (3H, singlet, COOCH$_3$), 3.91 (3H, singlet, COOCH$_3$), 6.8—7.7 (8H, multiplet, aromatic protons), 9.15 (1H, NH). The separated minor crystals and the residue obtained from the filtrates were combined and the mixture was chromatographed on silica gel eluting with benzene–ethyl acetate (9: 1) to afford XI (100 mg). Successive elution with benzene-MeOH (6: 1) gave methyl 8-chloro-3-hydroxy-5-phenyl-1-methyl-2-oxo-2,3,3a,6-tetrahydropyrrolo[1,2,3-cd]pyrrolo[2,3-b]-1H-quinoxaline-4-carboxylate (XII, 280 mg), mp 264—266° (from acetone). *Anal.* Calcd. for $C_{21}H_{16}ClN_3O_4$: C, 61.54; H, 3.91; N, 10.26; Cl, 8.67. Found: C, 61.51; H, 4.02; N, 10.44; Cl, 8.57. MS *m/e*: 409 (M$^+$). IR ν_{max}^{Nujol} cm^{-1}: 3450 (OH), 1760 (amide), 1690 (esters). NMR (CDCl$_3$) δ: 3.35 (3H, singlet, NCH$_3$), 3.58 (3H, singlet, COOCH$_3$), 4.13 (1H, singlet, methine proton), 4.45 (1H, singlet, OH), 6.6—7.5 (8H, multiplet, aromatic protons).