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Molecular Structures of 8-Chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine, 2-Acetoxyamino-4-acetyl-8-chloro-3,4-dihydro-6-phenyl-1,4,5-benzotriazocine and 8-Chloro-4,11-diacetyl-4,11-dihydro-2-methyl-6-phenyloxazolo[4,5-*b*]-[1,4,5]benzotriazocine. Formation of an Eight-Membered Ring from a Quinazoline Derivative on Treatment with Hydrazine evidenced by X-Ray Analysis[1]

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7-Chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine was synthesized by the reaction of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine with hydrazine.[3] The compound was, however, obviously different from the one to which the same structure was assigned by Derieg, *et al.*[4] In order to distinguish between them, an X-ray analysis was carried out on some crystalline derivatives of these compounds and the structure of Derieg's compound was revised to 2-amino-8-chloro-3,4-dihydro-6-phenyl-1,4,5-benzotriazocine.

The conformation of the 1,4-benzodiazepine clarified in the present analysis resembled to the 1,4-benzodiazepine derivatives previously reported.[5-7] But the conformations of the 1,4,5-benzotriazocines, especially the arrangement of the two aromatic rings and the positioning of electron-donating groups in each molecule, were not identical to those of 1,4-benzodiazepines. Such conformational difference may account for the differences in pharmacological activities of these compounds.

During the course of synthetic work on 1,4-benzodiazepine derivatives in this laboratories, it was found that treatment of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (I) with hydrazine gave 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (II) (mp 170° (browning), 202—204° (decomp.)), and that cyclization of II with ethyl orthoformate afforded 8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (III).[3] These structures, II and III, were assigned on the basis of spectroscopic and chemical evidences (Chart 1).

On the other hand, Derieg, *et al.*[4] reported that treatment of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (IV) with hydrazine gave a compound A (mp 235—238° (decomp.)). Catalytic reduction of A over Raney nickel readily afforded a compound B (mp 175—179° (decomp.)). Structures of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide and 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine were assigned to the compounds A and B, respectively, on the basis of their Mass, nuclear magnetic resonance (NMR), ultraviolet (UV) and infrared (IR) data.[4] Although the same structure was given to the compounds II and B, it was thought that they could not be identical because the physico-chemical properties of II were obviously different from those reported for B.[4] Con-

1) A part of this work was presented at the 24 th Annual Meeting of the Chemical Society of Japan, Osaka, April, 1971.
2) Location: *Juso-Nishinocho, Higashiyodogawa-ku, Osaka.*
3) K. Meguro and Y. Kuwada, *Tetrahedron Letters*, **1970**, 4039; K. Meguro and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), submitted.
4) M.E. Derieg, R.I. Fryer and L.H. Sternbach, *J. Chem. Soc.* (*C*), **1968**, 1103.
5) J. Karle and I.L. Karle, *J. Am. Chem. Soc.*, **89**, 804 (1967).
6) S. Sato, N. Sakurai, T. Miyadera, C. Tamura and R. Tachikawa, *Chem. Pharm. Bull.* (Tokyo), **19**, 2501 (1971).
7) A. Camerman and N. Camerman, *Science*, **168**, 1457 (1970); A. Camerman and N. Camerman, *J. Am. Chem. Soc.*, **94**, 268 (1972).

sequently experiments of Derieg, *et al.* were repeated under the same conditions and products A, B, C, D and E, which have the same physical properties as reported, were obtained (Chart 2). A direct comparison of II with B revealed that these compounds are not identical. In order to clarify the structural difference between II and B, the authors carried out the X-ray analysis of III, C and E, which appeared to be promising for crystallographic study.

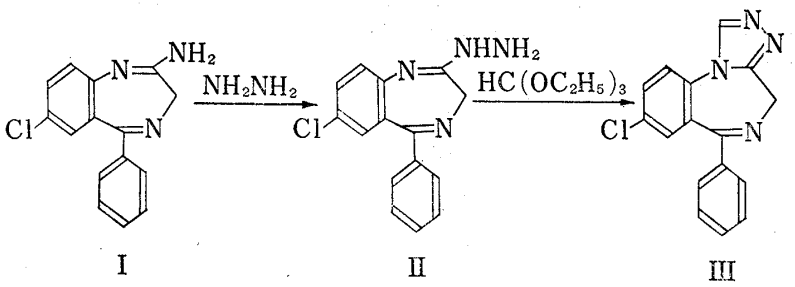


Chart 1

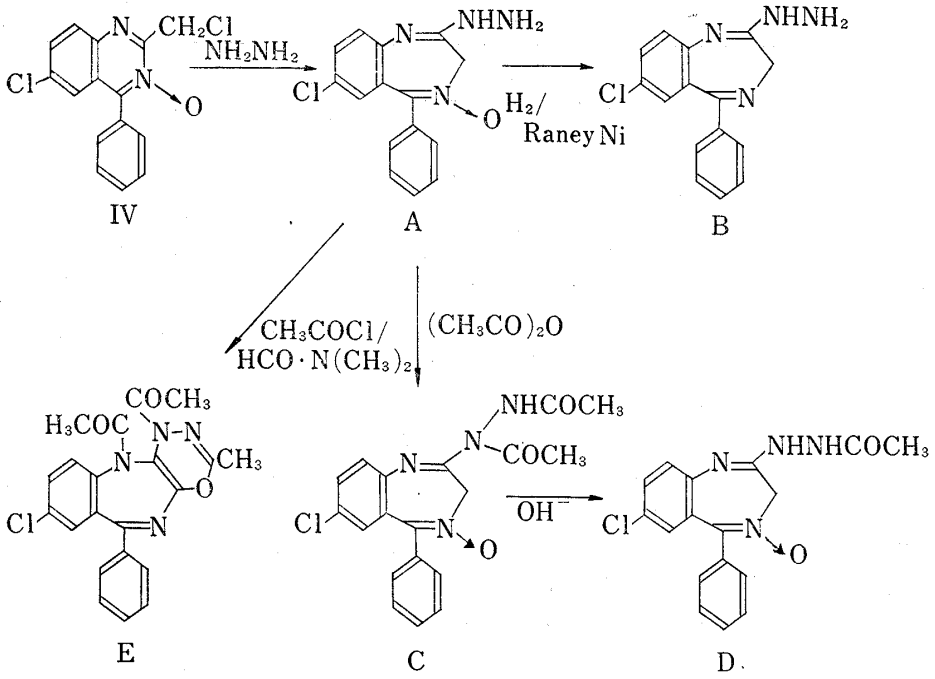


Chart 2

Experimental

Crystals of III——Recrystallization from ethyl acetate gave colourless plates or pillars, mp 226—227°. *Anal.* Calcd. for $C_{16}H_{11}N_4Cl$: C, 65.20; H, 3.76; N, 19.01. Found: C, 65.30; H, 3.48; N, 19.03.

Crystals of C——Recrystallization from methanol afforded colourless plates, mp 230—231°. *Anal.* Calcd. for $C_{19}H_{17}O_3N_4Cl$: C, 59.30; H, 4.45; N, 14.56. Found: C, 59.47; H, 4.30; N, 14.63.

Crystals of E——Recrystallization from a mixture of ethanol and petroleum ether gave pale yellow plates, mp 172—174°. *Anal.* Calcd. for $C_{21}H_{17}O_3N_4Cl$: C, 61.69; H, 4.19; N, 13.71. Found: C, 61.58; H, 4.11; N, 13.71.

Crystallographic Measurements——The cell dimensions and space groups were determined from oscillation and Weissenberg photographs taken with Cu-Kα radiation (λ=1.5418 Å). They are listed in Table I together with other crystal data. Measurements of intensities were carried out with a Hilger and Watts linear diffractometer using Mo-Kα radiation. Crystals were cut into columns measuring about $1.0\times0.3\times0.3$ mm. Intensities of 2199, 2490 and 2770 unique reflexions were obtained for III, C and E, respectively. These data were corrected for Lorentz and polarization factors in the usual manner and placed on an absolute scale by Wilson's method. No absorption corrections were made, since the absorption effects were small. Computations were performed on a NEAC 2206 digital computer using programs written by the authors.

The atomic scattering factors used in calculations of structure factors were taken from the International Tables for X-ray Crystallography.[8]

Table I. Crystal Data

	III	C	E
Crystal system	orthorhombic	monoclinic	monoclinic
Space group	*Pbca*	$P2_1/a$	$P2_1/a$
Cell dimensions (Å)			
a	7.95	22.21	16.28
b	34.80	7.81	14.10
c	10.48	12.80	10.78
β (°)	—	118.2	129.0
Volume (Å^3)	2899.4	1957.4	1923.1
Z	8	4	4
Formula	$C_{16}H_{11}N_4Cl$	$C_{19}H_{17}O_3N_4Cl$	$C_{21}H_{17}O_3N_4Cl$
F.W.	294.8	384.8	408.9
D_x	1.35	1.31	1.41
μ(Mo Kα) (cm^{-1})	2.7	2.3	2.4

Determination of the Structure

Starting with the coordinates of the chlorine atoms deduced from Patterson syntheses, the structures of III and C were easily determined by our usual procedures.[9] While in the case of E, the most probable coordinates of the chlorine atom presumed from the Patterson map was afterwords found to be spurious and a number of attempts to determine positions of remaining atoms based on this presumption had resulted in confusing sets of peaks. Other possibilities for coordinates of the chlorine atom were, therefore, investigated and several vector sets were selected from the Patterson map. To each set, minimum functions were successively applied, and from the set of the 8th trial, the molecular shape was visualized in the resulting map. Parallel to these trials, the symbolic addition procedure was also applied, which led to the same conclusion.

The atomic coordinates and temperature factors were refined by the block-diagonal least-squares treatments. The unweighted residual factors calculated for each structure are 0.15 (III), 0.17 (C) and 0.14 (E). The atomic parameters of III, C and E are given in Tables

Table II. Atomic Coordinates and Temperature Factors of III

Atom	*x/a*	*y/b*	*z/c*	*B*	Atom	*x/a*	*y/b*	*z/c*	*B*
Cl	0.7506	0.1473	0.3059	4.82	C (7)	0.3095	0.1318	0.6657	2.50
N (1)	0.2870	0.0487	0.6059	2.89	C (8)	0.3512	0.0806	0.8169	3.14
N (2)	0.2772	0.1183	0.7807	3.21	C (9)	0.2666	0.0499	0.7327	3.03
N (3)	0.1231	0.0009	0.6657	4.08	C (10)	0.1936	0.0170	0.5621	3.25
N (4)	0.1739	0.0213	0.7757	3.41	C (11)	0.2338	0.1710	0.6350	2.69
C (1)	0.5900	0.0801	0.3559	3.34	C (12)	0.1419	0.1763	0.5209	3.81
C (2)	0.6096	0.1183	0.3906	3.06	C (13)	0.0721	0.2136	0.4964	4.97
C (3)	0.5032	0.1358	0.4875	1.62	C (14)	0.1045	0.2431	0.5826	5.54
C (4)	0.4058	0.1122	0.5610	2.31	C (15)	0.1976	0.2383	0.6936	5.70
C (5)	0.3919	0.0728	0.5300	2.45	C (16)	0.2660	0.2010	0.7217	3.89
C (6)	0.4806	0.0571	0.4250	2.98					

8) "International Tables for X-Ray Crystallography," The Kynoch Press, Birmingham, England, 1962.
9) M. Nishikawa, K. Kamiya, M. Tomita, Y. Okamoto, T. Kikuchi, K. Osaki, Y. Tomiie, I. Nitta and K. Goto, *J. Chem. Soc.* (*B*), **1968**, 652.

Table III. Atomic Coordinates and Temperature Factors of VII

Atom	x/a	y/b	z/c	B	Atom	x/a	y/b	z/c	B
Cl	0.6864	0.2075	0.4583	4.96	C (7)	0.5632	0.0742	0.6917	2.83
O (1)	0.6519	0.2754	0.0555	4.55	C (8)	0.6863	0.9444	0.8962	3.63
O (2)	0.6861	0.1767	0.2280	10.47	C (9)	0.6702	0.1163	0.9370	3.71
O (3)	0.6606	0.6163	0.9209	4.60	C (10)	0.6653	0.2943	0.1636	6.15
N (1)	0.6652	0.2617	0.8779	3.05	C (11)	0.6449	0.4690	0.1853	6.96
N (2)	0.5605	0.9406	0.7463	3.26	C (12)	0.6106	0.6901	0.8495	3.95
N (3)	0.6203	0.8569	0.8201	3.37	C (13)	0.5409	0.6105	0.7858	5.08
N (4)	0.6674	0.1031	0.0299	3.96	C (14)	0.4980	0.1631	0.6319	3.17
C (1)	0.7233	0.3390	0.6638	3.63	C (15)	0.4828	0.2641	0.5348	4.26
C (2)	0.6797	0.2281	0.5815	3.20	C (16)	0.4195	0.3456	0.4767	5.06
C (3)	0.6290	0.1305	0.5904	3.52	C (17)	0.3685	0.3207	0.5118	5.77
C (4)	0.6229	0.1525	0.6911	2.81	C (18)	0.3848	0.2237	0.6092	4.98
C (5)	0.6682	0.2552	0.7742	2.83	C (19)	0.4486	0.1466	0.6681	3.90
C (6)	0.7176	0.3535	0.7657	3.41					

Table IV. Atomic Coordinates and Temperature Factors of IX

Atom	x/a	y/b	z/c	B	Atom	x/a	y/b	z/c	B
Cl	0.3616	0.8644	0.8949	4.96	C (8)	0.2716	0.2494	0.7149	3.09
O (1)	0.1632	0.1185	0.1265	3.52	C (9)	0.1927	0.3122	0.6755	3.90
O (2)	0.0488	0.0583	0.3797	5.08	C (10)	0.2138	0.3685	0.8008	4.37
O (3)	0.5062	0.2389	0.7411	4.10	C (11)	0.3074	0.3624	0.9552	4.36
N (1)	0.3334	0.1394	0.2499	3.36	C (12)	0.3859	0.3021	0.9896	4.25
N (2)	0.1768	0.2029	0.4443	3.20	C (13)	0.3713	0.2442	0.8687	3.49
N (3)	0.1557	0.1233	0.3399	2.85	C (14)	0.2140	0.1261	0.2870	2.98
N (4)	0.3947	0.1475	0.5236	2.88	C (15)	0.3158	0.1406	0.3623	3.04
C (1)	0.3710	0.9474	0.7840	3.12	C (16)	0.2418	0.1265	0.1144	2.80
C (2)	0.3097	0.0272	0.7339	3.15	C (17)	0.2109	0.1167	0.9536	3.59
C (3)	0.3173	0.0958	0.6472	3.04	C (18)	0.0931	0.0508	0.3218	3.20
C (4)	0.3871	0.0775	0.6147	2.69	C (19)	0.0815	0.9656	0.2271	4.35
C (5)	0.4485	0.9982	0.6696	3.11	C (20)	0.4508	0.2313	0.5954	3.30
C (6)	0.4409	0.9286	0.7542	3.72	C (21)	0.4387	0.3100	0.4915	4.02
C (7)	0.2519	0.1828	0.5911	2.62					

Table V. Bond Distances and Angles of III

Bond distances (angstrom)

Cl—C (2)	1.75	N (3)–N (4)	1.42	C (3)–C (4)	1.37	C (11)–C (12)	1.41
N (1)–C (5)	1.43	N (3)–C (10)	1.34	C (4)–C (5)	1.41	C (11)–C (16)	1.41
N (1)–C (9)	1.34	N (4)–C (9)	1.32	C (4)–C (7)	1.50	C (12)–C (13)	1.44
N (1)–C (10)	1.41	C (1)–C (2)	1.39	C (5)–C (6)	1.42	C (13)–C (14)	1.39
N (2)–C (7)	1.32	C (1)–C (6)	1.39	C (7)–C (11)	1.53	C (14)–C (15)	1.39
N (2)–C (8)	1.49	C (2)–C (3)	1.46	C (8)–C (9)	1.54	C (15)–C (16)	1.44

Bond angles (degree)

C (5)–N (1)–C (9)	127	C (1)–C (2)–C (3)	121	N (2)–C (7)–C (4)	127	C (7)–C (11)–C (16)	117
C (5)–N (1)–C (10)	126	C (2)–C (3)–C (4)	118	N (2)–C (7)–C (11)	116	C (12)–C (11)–C (16)	123
C (9)–N (1)–C (10)	107	C (3)–C (4)–C (5)	120	C (4)–C (7)–C (11)	117	C (11)–C (12)–C (13)	118
C (7)–N (2)–C (8)	118	C (3)–C (4)–C (7)	115	N (2)–C (8)–C (9)	108	C (12)–C (13)–C (14)	119
N (4)–N (3)–C (10)	109	C (5)–C (4)–C (7)	125	N (1)–C (9)–N (4)	113	C (13)–C (14)–C (15)	124
N (3)–N (4)–C (9)	105	N (1)–C (5)–C (4)	119	N (1)–C (9)–C (8)	122	C (14)–C (15)–C (16)	119
C (2)–C (1)–C (6)	119	N (1)–C (5)–C (6)	120	N (4)–C (9)–C (8)	125	C (11)–C (16)–C (15)	118
Cl—C (2)–C (1)	119	C (4)–C (5)–C (6)	121	N (1)–C (10)–N (3)	106		
Cl—C (2)–C (3)	119	C (1)–C (6)–C (5)	120	C (7)–C (11)–C (12)	120		

II, III and IV, respectively. The perspective views of the molecules in the crystals can be seen in Fig. 1, 2 and 3. Bond distances and angles are shown in Tables V, VI and VII. The estimated standard deviations for bond distances and angles are 0.03 Å and 1.8°.

Four least-squares planes were calculated for the structure III (Plane 1 to 4), 3 planes for the structure C (Plane 1′ to 3′) and 4 planes for the structure E (Plane 1″ to 4″). The

Table VI. Bond Distances and Angles of VII (C)

Bond distances (angstrom)

Cl—C(2)	1.66	N(2)-C(7)	1.27	C(4)-C(5)	1.33	C(14)-C(19)	1.38
O(1)-N(4)	1.46	N(3)-C(8)	1.49	C(4)-C(7)	1.46	C(15)-C(16)	1.40
O(1)-C(10)	1.28	N(3)-C(12)	1.40	C(5)-C(6)	1.38	C(16)-C(17)	1.42
O(2)-C(10)	1.17	N(4)-C(9)	1.22	C(7)-C(14)	1.46	C(17)-C(18)	1.35
O(3)-C(12)	1.20	C(1)-C(2)	1.35	C(8)-C(9)	1.54	C(18)-C(19)	1.39
N(1)-C(5)	1.36	C(1)-C(6)	1.37	C(10)-C(11)	1.50		
N(1)-C(9)	1.34	C(2)-C(3)	1.41	C(12)-C(13)	1.50		
N(2)-N(3)	1.38	C(3)-C(4)	1.37	C(14)-C(15)	1.37		

Bond angles (degree)

N(4)-O(1)-C(10)	113	C(1)-C(2)-C(3)	126	N(2)-C(7)-C(14)	112	O(3)-C(12)-C(13)	124
C(5)-N(1)-C(9)	119	C(2)-C(3)-C(4)	117	C(4)-C(7)-C(14)	118	N(3)-C(12)-C(13)	119
N(3)-N(2)-C(7)	118	C(3)-C(4)-C(5)	117	N(3)-C(8)-C(9)	107	C(7)-C(14)-C(15)	121
N(2)-N(3)-C(8)	124	C(3)-C(4)-C(7)	116	N(1)-C(9)-N(4)	126	C(7)-C(14)-C(19)	122
N(2)-N(3)-C(12)	114	C(5)-C(4)-C(7)	126	N(1)-C(9)-C(8)	121	C(15)-C(14)-C(19)	117
C(8)-N(3)-C(12)	119	N(1)-C(5)-C(4)	116	N(4)-C(9)-C(8)	112	C(14)-C(15)-C(16)	120
O(1)-N(4)-C(9)	105	N(1)-C(5)-C(6)	117	O(1)-C(10)-O(2)	119	C(15)-C(16)-C(17)	122
C(6)-C(1)-C(2)	116	C(4)-C(5)-C(6)	127	O(1)-C(10)-C(11)	112	C(16)-C(17)-C(18)	118
Cl—C(2)-C(1)	117	C(1)-C(6)-C(5)	117	O(2)-C(10)-C(11)	129	C(17)-C(18)-C(19)	120
Cl—C(2)-C(3)	117	N(2)-C(7)-C(4)	128	O(3)-C(12)-N(3)	117	C(14)-C(19)-C(18)	123

Table VII. Bond Distances and Angles of IX (E)

Bond distances (angstrom)

Cl—C(1)	1.75	N(2)-C(7)	1.28	C(2)-C(3)	1.40	C(9)-C(10)	1.41
O(1)-C(14)	1.38	N(3)-C(14)	1.38	C(3)-C(4)	1.41	C(10)-C(11)	1.39
O(1)-C(16)	1.37	N(3)-C(18)	1.37	C(3)-C(7)	1.48	C(11)-C(12)	1.38
O(2)-C(18)	1.22	N(4)-C(4)	1.46	C(4)-C(5)	1.36	C(12)-C(13)	1.44
O(3)-C(20)	1.23	N(4)-C(15)	1.37	C(5)-C(6)	1.40	C(14)-C(15)	1.32
N(1)-C(15)	1.41	N(4)-C(20)	1.39	C(7)-C(8)	1.49	C(16)-C(17)	1.47
N(1)-C(16)	1.29	C(1)-C(2)	1.37	C(8)-C(9)	1.39	C(18)-C(19)	1.51
N(2)-N(3)	1.47	C(1)-C(6)	1.38	C(8)-C(13)	1.41	C(20)-C(21)	1.51

Bond angles (degree)

C(14)-O(1)-C(16)	105	C(1)-C(2)-C(3)	117	C(7)-C(8)-C(9)	119	N(1)-C(15)-C(14)	109
C(15)-N(1)-C(16)	109	N(2)-C(3)-C(4)	118	C(7)-C(8)-C(13)	117	N(4)-C(15)-C(14)	127
N(3)-N(2)-C(7)	111	C(2)-C(3)-C(7)	120	C(9)-C(8)-C(13)	124	O(1)-C(16)-N(1)	112
N(2)-N(3)-C(14)	114	C(4)-C(3)-C(7)	122	C(8)-C(9)-C(10)	116	O(1)-C(16)-C(17)	117
N(2)-N(3)-C(18)	118	N(4)-C(4)-C(3)	118	C(9)-C(10)-C(11)	123	N(1)-C(16)-C(17)	130
C(14)-N(3)-C(18)	127	N(4)-C(4)-C(5)	120	C(10)-C(11)-C(12)	120	O(2)-C(18)-N(3)	119
C(4)-N(4)-C(15)	113	C(3)-C(4)-C(5)	122	C(11)-C(12)-C(13)	121	O(2)-C(18)-C(19)	124
C(4)-N(4)-C(20)	121	C(4)-C(5)-C(6)	121	C(8)-C(13)-C(12)	116	N(3)-C(18)-C(19)	117
C(15)-N(4)-C(20)	122	C(1)-C(6)-C(5)	116	O(1)-C(14)-N(3)	119	O(3)-C(20)-N(4)	119
Cl—C(1)-C(2)	118	N(2)-C(7)-C(3)	124	O(1)-C(14)-C(15)	108	O(3)-C(20)-C(21)	122
Cl—C(1)-C(6)	118	N(2)-C(7)-C(8)	118	N(3)-C(14)-C(15)	132	N(4)-C(20)-C(21)	119
C(2)-C(1)-C(6)	125	C(3)-C(7)-C(8)	118	N(1)-C(15)-N(4)	124		

equations for Plane 1 to 4 are referred to the orthogonalized coordinates (in Angstrom) parallel to the crystallographic axes of III, while the equations of Plane 1′ to 3′ and 1″ to 4″ are referred to the orthogonalized coordinates parallel to *a*, *b* and *c** axes of C and E, respectively. They are listed in Table VIII together with atoms used for the calculation. Fig. 4, 5 and 6 illustrate these planes and deviations of atoms in Å$\times 10^2$ units from them. The interplanar angles are listed in Table IX.

TABLE VIII. Least-Squares Planes

	Equations	Atoms for which least-squares planes are calculated
III 1	$0.7314X-0.2242Y+0.6440Z=5.2397$	Cl, C(1), C(2), C(3), C(4), C(5), C(6)
2	$0.8285X+0.2534Y-0.4994Z=-0.2547$	C(11), C(12), C(13), C(14), C(15), C(16)
3	$0.8362X+0.4424Y+0.3242Z=6.3383$	N(2), C(4), C(7), C(8), C(11)
4	$0.8065X-0.5826Y+0.1008Z=1.4867$	N(1), N(3), N(4), C(9), C(10)
C 1′	$-0.5142X+0.7491Y-0.4177Z=-7.3583$	Cl, C(1), C(2), C(3), C(4), C(5), C(6)
2′	$0.0893X+0.8005Y+0.5926Z=5.9027$	C(14), C(15), C(16), C(17), C(18), C(19)
3′	$-0.2195X+0.5619Y+0.7975Z=4.7668$	N(2), N(3), C(4), C(7), C(14)
E 1″	$0.2939X+0.4342Y+0.8515Z=5.0847$	C(1), C(2), C(3), C(4), C(5), C(6)
2″	$0.7611X+0.6457Y-0.0606Z=0.8596$	C(8), C(9), C(10), C(11), C(12), C(13)
3″	$0.9174X+0.3855Y+0.0989Z=0.7010$	N(2), N(3), C(3), C(7), C(8)
4″	$-0.1267X+0.9830Y-0.1327Z=1.3395$	O(1), N(1), C(14), C(15), C(16)

TABLE IX. Dihedral Angles between Least-Squares Planes

III		plane 4	plane 3	plane 2
	plane 1	142°	136°	103°
	plane 2	118°	50°	
	plane 3	117°		
VII		plane 3′	plane 2′	
	plane 1′	102°	108°	
	plane 2′	25°		
IX		plane 4″	plane 3″	plane 2″
	plane 1″	106°	121°	117°
	plane 2″	123°	20°	
	plane 3″	104°		

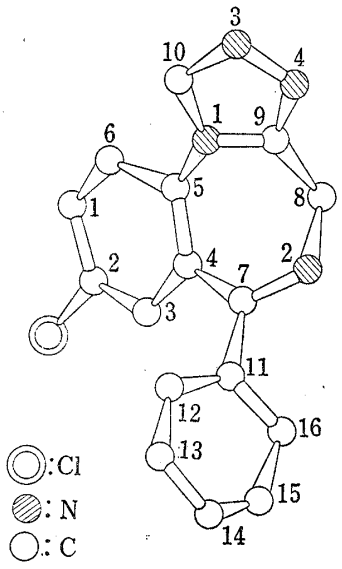


Fig. 1. Perspective Views of the Molecule III projected along the *a* Axis of the Unit-cell

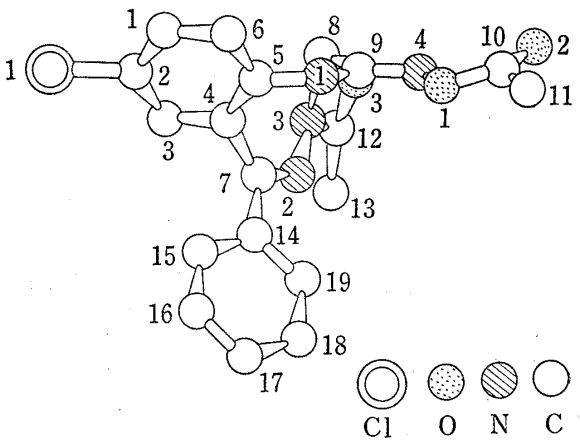


Fig. 2. Perspective Views of the Molecule VII (C) projected along the *b* Axis of the Unit-cell

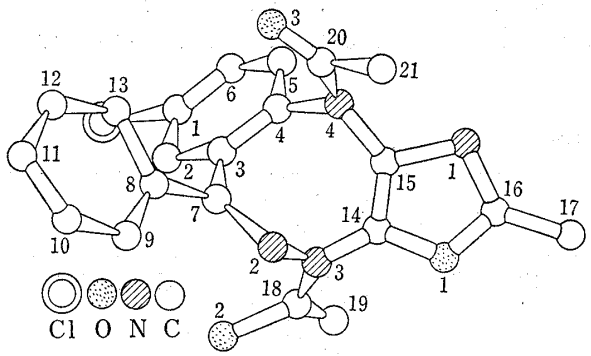


Fig. 3. Perspective Views of the Molecule IX (E) projected along the *b* Axis of the Unit-cell

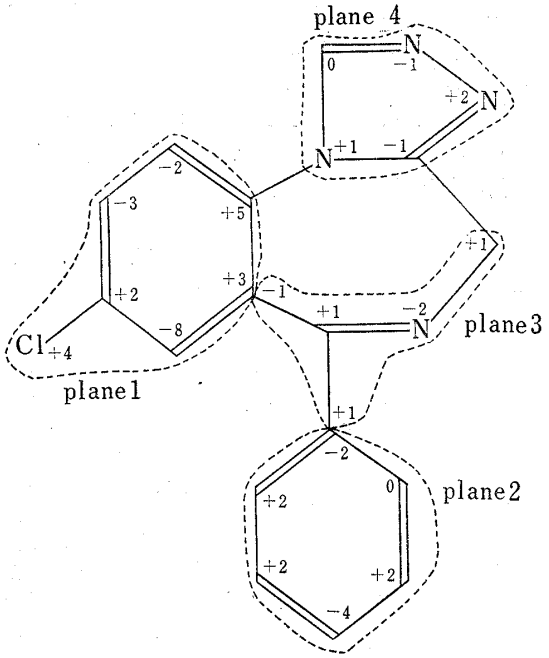


Fig. 4. Least-Squares Planes of III

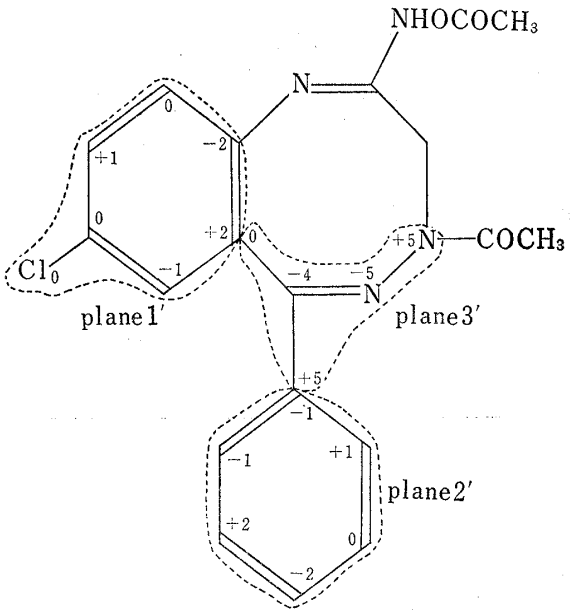


Fig. 5. Least-Squares Planes of VII (C)

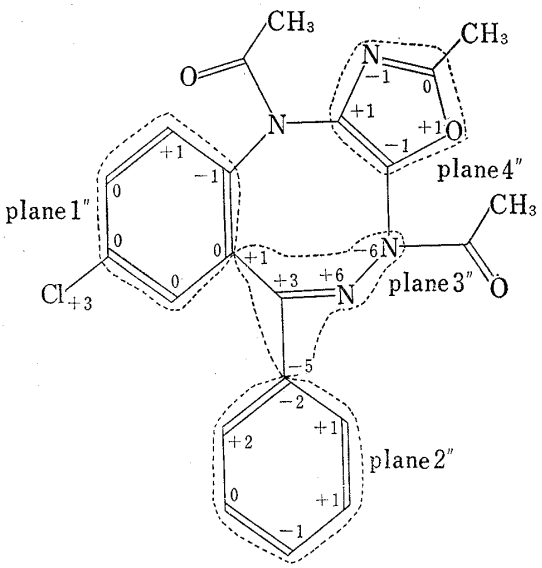


Fig. 6. Least-Squares Planes of IX (E)

Discussion

From the present analysis, III was determined to be 8-chloro-6-phenyl-4*H*-*s*-triazolo-[4,3-*a*][1,4]benzodiazepine. The structure of II was confirmed by its conversion into III. Compounds C and E were determined not to be 1,4-benzodiazepine derivatives, but to be 2-acetoxyamino-4-acetyl-8-chloro-3,4-dihydro-6-phenyl-1,4,5-benzotriazocine (VII) and 8-chloro-4,11-diacetyl-4,11-dihydro-2-methyl-6-phenyl oxazolo[4,5-*b*][1,4,5]benzotriazocine (IX), respectively. Formation of VII from IV may be explained by assuming the following reaction processes. Cleavage of 3,4-double bond in IV by the attack of hydrazine at C_4 followed by ring expansion will cause the formation of an eight-membered ring containing three nitrogen atoms, *i.e.* compound V. It is uncertain whether chlorine atom in the chloromethyl group is presubstituted by hydrazine or not. Acetylation of V with acetic anhydride will

give VII. From these considerations, the structure of A will be revised to be 2-hydroxyamino-8-chloro-3,4-dihydro-6-phenyl-1,4,5-benzotriazocine (V) and, therefore, those of B and D should be VI and VIII. These structures were also compatible with chemical and spectroscopic evidences.[3] Thus, an interesting ring expansion of a quinazoline derivative into a 1,4,5-benzotriazocine was evidenced for the first time by the present investigations. It is assumed that another rearrangement took place on conversion of V into IX (Chart 3). Similar rearrangement was reported in the case of 1-tetralone oxime with acetic anhydride.[10]

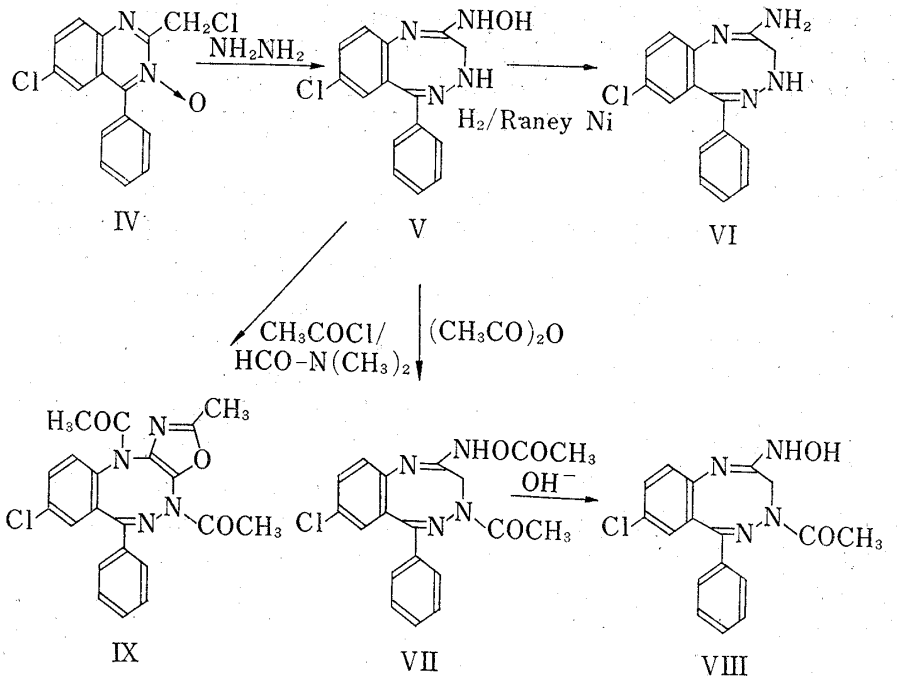


Chart 3

Conformation of III, VII and IX

Crystal and molecular structures of some 1,4-benzodiazepine derivatives, X,[5] XI[6] and XII,[7] have previously been reported. The conformation of III elucidated in the present analysis is nearly compatible with those reported therein. Seven-membered rings in these 1,4-benzodiazepine derivatives are similar to each other in conformations in spite of their differences in location of double bonds and fused rings. These diazepine rings can be described approximately as boat forms, in which taking N_1-C_2 and N_4-C_5 as the bottom of the boat, C_3 will be the bow and the two carbon atoms fused in the benzene ring construct the stern.

The conformations of eight-membered rings in the 1,4,5-benzotriazocines, VII and IX, are also similar to each other and are in boat forms, although the eight-membered ring of IX is more distorted than that of VII owing to the steric hindrance imposed by closing the five-membered ring.

Phenyl and chlorophenyl groups in III, VII and IX are all reasonably planar within the experimental errors. The atoms contained in the triazole ring of III and those in the oxazole ring of IX are also completely coplanar. The least-squares planes involving the (C7)=N(2) bond in III, VII and IX are not coplanar with their adjacent chlorophenyl groups and make angles of 136°, 102° and 121° with them, respectively.

Camerman and Camerman have determined crystal and molecular structures of diazepam (XII) and diphenylhydantoin (XIII).[7] Although these compounds are not closely related chemically, their molecular conformations, especially the relative arrangement of the two

10) N.V. Vorozhtsov and V.A. Koptiug, *J. Gen. Chem.* (U.S.S.R.) (Eng. Transl.), **28**, 1697 (1958).

aromatic rings and the positioning of electron-donating groups in each molecule, exhibit marked similarities. They have suggested from these observations that a conformational approach to the search for antiepilepsy agents may be useful in developing new and more effective therapeutics.[7]

Fig. 7 shows projections of the molecules III, VII, IX and XII[11] on each of the least-squares planes for their chlorophenyl groups. The conformations of the molecules III, VII, IX and XII can easily be compared with one another by superposing the structures in the figure.

By the superposition of the chlorophenyl groups of III and XII, the benzene ring attached to C(7) in III and the corresponding ring in XII take similar positions in space. Positions and orientations of the bonds connecting the benzene ring with the seven-membered ring in III and XII are also similar. In addition, the position of N(4) in III is close spatial proximity to the carbonyl oxygen in XII.

These conformational similarities are understood further from Table X, in which intramolecular distances between heteroatoms and the centers of aromatic rings are given. Such structural resemblances may result in the related pharmacological properties of III and XII.[12]

The arrangement of the two aromatic rings and the relative positioning of electron-donating groups in VII and IX are different from those in III or XII. As can be seen from Fig. 7, the relationship between the two aromatic rings in VII and IX, especially the orientation of the bonds connecting the aromatic ring with the eight-membered ring (C(7)–C(14) in VII and C(7)–C(8) in IX), is apparently different from that of the corresponding bonds found in III and XII. Distances between the centers of the two aromatic rings in VII and IX (4.84 and 4.89 Å, respectively) are shorter than the corresponding distances in III and XII (4.92 and 5.00 Å), while distances between the chlorine atom and the phenyl group in VII and IX (6.44 and 6.30 Å) are longer than those in III and XII (5.98 and 6.08 Å). It is obvious that the differences of distances arise mostly from the different orientations of the bonds emanating from benzene rings. Moreover in VII and IX, no electron-donating atoms are located at the spatial position which is occupied by the carbonyl group in XII or the C=N group in III. The position of N(2) atom in VII or IX is also different from the position of the corresponding nitrogen atom in XII or III. These distinctions are clearly seen from distances given in Table X.

It is interesting that the resemblance found in 1,4-benzodiazepines and the differences between 1,4-benzodiazepines and 1,4,5-benzotriazocines in their conformations seem to account for similarities and dissimilarities of their pharmacological properties. These findings also

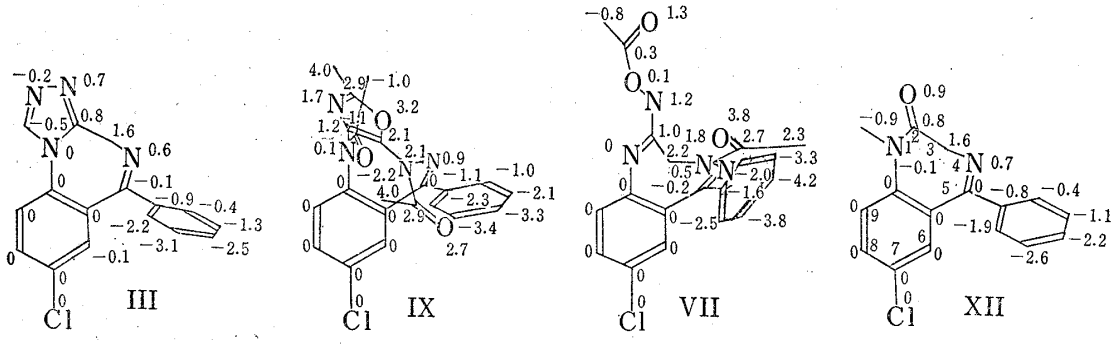


Fig. 7. Projections of Molecules of III, VII, IX and XII on Each of Their Least-Squares Planes of Chlorophenyl Groups

The molecules are seen with chlorophenyl groups oriented in the same perspective. Displacements of atoms from the least-squares planes in Å units are also shown.

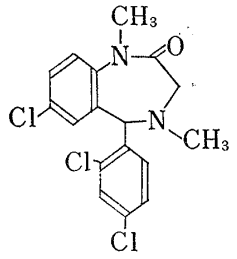
11) The figure of the structure XII is obtained from the atomic coordinates in the literature.[7]

12) R. Nakajima, C. Hattori and Y. Nagawa, *Japan. J. Pharmacol.*, **21**, 489 (1971); R. Nakajima, Y. Take, R. Moriya, Y. Saji, T. Yui and Y. Nagawa, *ibid.*, 497 (1971).

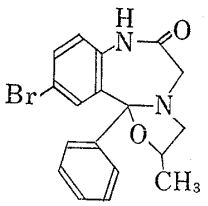
suggest that conformational structure may be one of the important factors in determining the activities of drugs.

Table X. Distances (Å) between Aromatic Ring Centers and N(4) and N(2) in III and Comparable Distances in VII, IX and XII

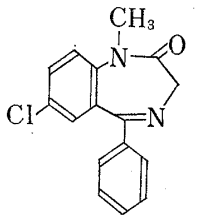
Groups or atoms in III	III	XII	VII	IX
C(1)-C(6)——C(11)-C(16)	4.92	5.00	4.84	4.89
C(1)-C(6)——N(4)	4.94	4.91	4.70	4.78
C(1)-C(6)——N(2)	3.88	3.76	3.84	3.77
Cl————C(11)-C(16)	5.98	6.08	6.44	6.30
Cl————N(4)	8.03	7.98	7.57	7.72
Cl————N(2)	6.32	6.23	5.96	6.09
C(11)-C(16)——N(4)	6.70	6.68	5.81	7.16
C(11)-C(16)——N(2)	3.68	3.64	3.55	3.66
N(4)————N(2)	3.47	3.35	3.51	4.29



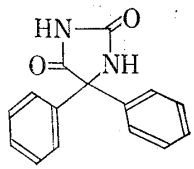
X



XI



XII



XIII

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