[Chem. Pharm. Bull. 27(11)2608—2617(1979)]

UDC 547.891.2.04 : 547.895.04

Heterocycles. XII.[1] Synthesis of 2-Amino-5-phenyl-1,4-benzodiazepine 1-Oxides and 2-Amino-6-phenyl-1,5-benzodiazocine 1-Oxides and Their Reactions with Acylating Agents

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(Received February 28, 1979)

When 2-amino-3,4-dihydro-6-phenyl-1,5-benzodiazocines (**1**) and 2-amino-5-phenyl-3*H*-1,4-benzodiazepines (**5**) were treated with *m*-chloroperbenzoic acid, oxidation occurred selectively at the 1-position giving the corresponding 1-oxides (**2** and **6**), which are a novel class of derivatives of the diazocines and the diazepines.

Although reaction of **2** with phosgene afforded the oxadiazolone derivative (**4**) in high yield, rearrangement of the diazepine oxide (**6**) occurred upon treatment with phosgene in the presence of imidazoles to form the 3-imidazolyl compound (**9**). When **6a** was treated with acetic anhydride, rearrangement also occurred to give the 3-oxo compound (**8**).

Keywords——1,4-benzodiazepines; 1,5-benzodiazocines; 3-imidazolyl-1,4-benzodiazepines; 1,2,4-oxadiazolo[2,3-*a*][1,5]benzodiazocines; *m*-chloroperbenzoic acid; amidine N-oxide; rearrangement of 2-amino-1,4-benzodiazepine 1-oxides

In the course of our studies on seven- and eight-membered heterocycles, facile syntheses of 2-amino-3*H*-1,4-benzodiazepines (**5**)[3] and 2-amino-3,4-dihydro-1,5-benzodiazocines (**1**)[1] were achieved. The reactivity of the amidine moiety of these species permitted various modifications of the heterocycles, including the synthesis of *s*-triazolo[4,3-*a*][1,4]benzodiazepines[4] which possess strong depressive activity on the central nervous system. Our subsequent interest was directed towards the preparation and reactions of 1-oxides of the diazocine (**1**) and the diazepine (**5**) since few reports[5] have appeared on the 1-oxide derivative of the 1,4-benzodiazepine or 1,5-benzodiazocine ring system despite considerable work in this field of chemistry.

Thus, the oxidation of **1** and **5** with *m*-chloroperbenzoic acid (MCPBA) to obtain the 1-oxides (**2** and **6**) was investigated.[6] When 2-amino-8-chloro-3,4-dihydro-6-phenyl-1,5-benzodiazocine (**1a**)[1] was treated with a slight excess of MCPBA in diethyl ether at room temperature, a colorless crystalline substance whose analytical data were consistent with a 1:1 adduct of **1a** and MCPBA was obtained in almost quantitative yield. This adduct was proved to be the *m*-chlorobenzoic acid salt of **2a** by treatment with a base. Compound **2a** was positive in the ferric chloride ($FeCl_3$) test, indicating the presence of an amidoxime group. Treatment of **2a** with phosphorus trichloride (PCl_3) regenerated **1a**. Hydrolysis of **2a** with

1) Part XI: H. Natsugari, K. Meguro, and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), **27**, 2589 (1979).
2) Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*
3) K. Meguro, H. Tawada, and Y. Kuwada, *Yakugaku Zasshi*, **93**, 1253 (1973).
4) K. Meguro and Y. Kuwada, *Tetrahedron Lett.*, **1970**, 4039; *idem*, *Chem. Pharm. Bull.* (Tokyo), **21**, 2375 (1973).
5) *a*) 2-Amino-5-oxo-3*H*-1,4-benzodiazepine 1-oxide has been prepared by reductive cyclization of α-(2-nitrobenzoyl)aminoacetonitrile; M. Julia, N. Hurion, and H.D. Tam, *Chimie Therap.*, **5**, 343 (1973); *b*) After completion of our study (Japan Patent Application, 113600 (1972)) some reactions of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 1,4-dioxide (**6f**) were reported; R.Y. Ning, R.I. Fryer, and B. S. Sluboski, *J. Org. Chem.*, **42**, 3301 (1977).
6) Oxidation of cyclic amidines such as 2-aminopyridines and 2-aminoisoquinoline with MCPBA has been reported to give the corresponding 1-oxides; L.W. Deady, *Synth. Commun.*, **7**, 509 (1977).

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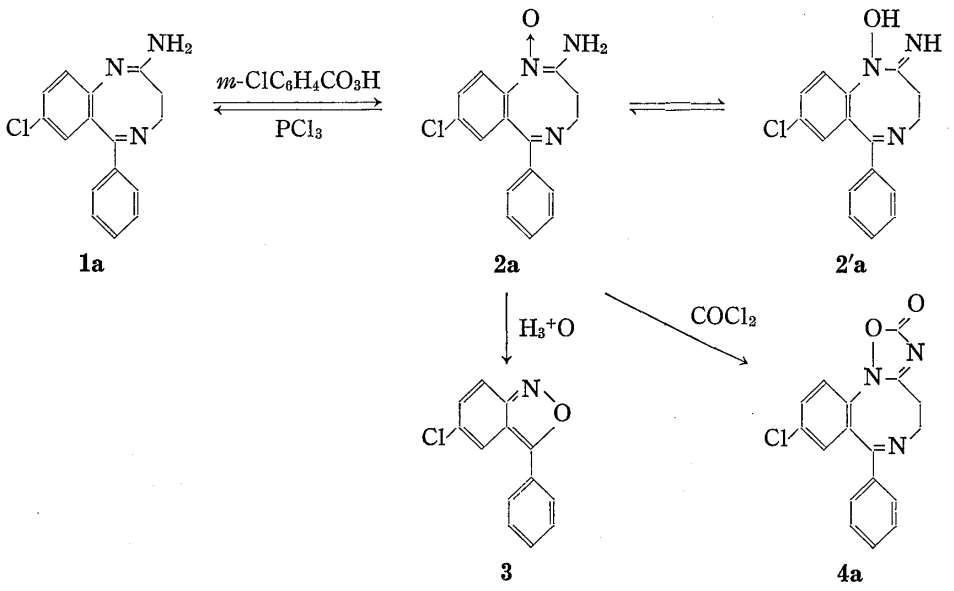
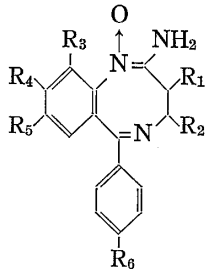


Chart 1

TABLE I. 2-Amino-3,4-dihydro-1,5-benzodiazocine 1-Oxides (2)



Compd. No.	R_1	R_2	R_3	R_4	R_5	R_6	Recryst.[a] from	mp[b] (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
2a	H	H	H	H	Cl	H	H_2O	144—145	81,[c] 82[d]	$C_{16}H_{14}ClN_3O \cdot 1/4H_2O$	63.16 (63.03)	4.81 4.77	13.81 13.76)
2b	H	H	H	H	H	H	M-A	122—123	66[d]	$C_{16}H_{15}N_3O \cdot CH_3OH$	68.66 (68.82)	6.44 6.22	14.13 14.37)
2c	H	H	H	CH_3O	CH_3O	H	M-E	196—198	74[e]	$C_{18}H_{19}N_3O_3 \cdot 1/2H_2O$	64.65 (64.33)	6.03 5.71	12.57 12.33)
2d	H	H	CH_3O	H	Cl	H	M-A	157—159	75[d]	$C_{17}H_{16}ClN_3O_2 \cdot CH_3OH$	59.74 (59.59	5.57 5.27	11.61 11.48)
2e	H	H	H	H	Cl	CH_3O	M-A	138—139	75[d]	$C_{17}H_{16}ClN_3O_2 \cdot H_2O$	58.70 (58.36	5.22 5.08	12.08 11.76)
2f	CH_3	H	H	H	Cl	Cl	M-E	141—142	83[d]	$C_{17}H_{15}Cl_2N_3O \cdot CH_3OH$	56.85 (56.49	5.03 4.73	11.05 11.47)
2g	CH_3	H	H	H	Cl	H	M-A	202—203	73[e]	$C_{17}H_{16}ClN_3O$	65.06 (64.77	5.14 4.86	13.39 13.14)
2h	H	CH_3	H	H	Cl	H	M-A	215—216	72[e]	$C_{17}H_{16}ClN_3O \cdot H_2O$	61.53 (61.79	5.46 5.58	12.66 12.34)
2i	CH_3	H	H	H	CH_3	H	M-A	138—140	73[d]	$C_{18}H_{19}N_3O \cdot H_2O$	69.43 (69.65	6.80 6.62	13.50 13.13)

a) M: methanol; A: acetone; E: ethyl acetate.
b) All compounds melted with decomposition.
c) By Method a (see "Experimental"). The *m*-chlorobenzoates of **2** were isolated as crystals (**2a**: see "Experimental"; **2c**: mp 188—189°, colorless needles (from MeOH), *Anal.* Calcd: C, 59.26; H, 4.35; N, 8.64. Found: C, 59.16; H, 4.23; N, 8.37; **2g**: mp 183—184°, colorless needles, (from acetone), *Anal.* Calcd.: C, 61.28; H, 4.50; N, 8.93. Found: C, 60.98; H, 4.39; N, 8.85).
d) By Method b (see "Experimental").
e) By Method c (see "Experimental").

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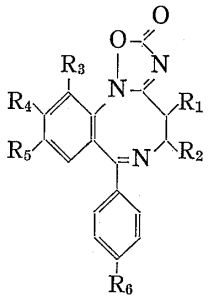
Table II. 4,5-Dihydro-2*H*-1,2,4-oxadiazolo[2,3-*a*][1,5]benzodiazocin-2-ones (**4**)



Compd. No.[a]	Recryst.[b] from	mp[c] (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
4a	A–H	171—172	[d]	$C_{17}H_{12}ClN_3O_2$	62.67 (62.89	3.71 4.02	12.89 12.67)
4b	A–H	171—172	92[e]	$C_{17}H_{13}N_3O_2$	70.09 (70.10	4.50 4.26	14.43 14.34)
4c	A–H	150—152	67[e]	$C_{19}H_{17}N_3O_4$	64.95 (64.78	4.88 5.05	11.96 12.17)
4d	A	200—201	51[f]	$C_{18}H_{14}ClN_3O_3$	60.76 (60.85	3.97 3.95	11.81 12.05)
4e	A	188—189	98[f]	$C_{18}H_{14}ClN_3O_3$	60.76 (60.95	3.97 3.79	11.81 11.37)
4f	A	154—155	90[e]	$C_{18}H_{13}Cl_2N_3O_2$	57.76 (58.03	3.50 3.42	11.22 11.23)
4g	M	147—148	78[g]	$C_{18}H_{14}ClN_3O_2$	63.62 (63.48	4.15 4.05	12.36 12.33)
4h	M	177—178	72[g]	$C_{18}H_{14}ClN_3O_2$	63.62 (63.71	4.15 4.01	12.36 12.19)
4i	A–H	143—145	73[e]	$C_{19}H_{17}N_3O_2$	71.45 (71.16	5.37 5.23	13.16 12.96)

a) For the substituents (R_1—R_6), see Table I.
b) A: acetone; H: hexane; M: methanol.
c) All compounds melted with decomposition.
d) See "Experimental."
e) By Method c (see "Experimental").
f) By Method b (see "Experimental").
g) By Method a (see "Experimantal").

an acid gave the known 2,1-benzisoxazole (**3**)[7] in good yield. The formation of **3**, apparently *via* 5-chloro-2-hydroxyaminobenzophenone, confirms the $N_{(1)}$-oxide structure of **2a**. It is interesting that the oxidation occurred selectively at the 1-position in spite of the presence of the basic nitrogen atom at the 5-position.

Compound **2a** was easily cyclized by treatment with phosgene in the presence of a base to the oxadiazolo[2,3-*a*][1,5]benzodiazocin-2-one (**4a**), which showed a carbonyl absorption band at 1780 cm^{-1} in the infrared (IR) spectrum (KBr). Compound **4a** was also formed by reaction of **2a** with N,N′-carbonylbis(2-methylimidazole) or methyl isocyanate (Chart 1).

Other 1-oxides (**2b—i**, Table I) were similarly obtained from the corresponding **1**[1] by reaction with MCPBA. Oxadiazolone derivatives (**4b—i**, Table II) were also prepared in the manner described above.

2-Amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (**5a**), which has the same partial structure as **1**, also afforded the 1-oxide (**6a**) in 75% yield on treatment with MCPBA in the presence of a base. Compound **6a** had chemical properties similar to those of **2a**; it was

7) R.B. Davis and L.C. Pizzini, *J. Org. Chem.*, **25**, 1884 (1960).

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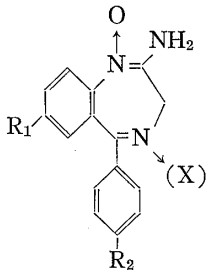
TABLE III. 2-Amino-3*H*-1,4-benzodiazepine 1-Oxides (**6**)



Compd. No.	R_1	R_2	X	Recryst.[a] from	mp[b] (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
6a	Cl	H	—	M–E	159—160	75	$C_{15}H_{12}ClN_3O \cdot 1/2H_2O$	61.12 (60.83	4.44 4.63	14.25 14.31)
6b	H	H	—	M–A	145—147	74	$C_{15}H_{13}N_3O \cdot 1/2H_2O$	69.21 (68.83	5.42 5.36	16.15 16.12)
6c	CH_3	H	—	M–A	161—163	75	$C_{16}H_{15}N_3O \cdot 1/3H_2O$	70.82 (70.94	5.82 5.62	15.48 15.08)
6d	CH_3O	H	—	M–A	158—161	70	$C_{16}H_{15}N_3O_2 \cdot 1/2H_2O$	66.19 (66.16	5.56 5.84	14.48 14.09)
6e	Cl	CH_3O	—	M–A	158—160	67	$C_{16}H_{14}ClN_3O_2 \cdot 2/3H_2O$	58.74 (58.52	4.72 4.57	12.84 12.63)
6f	Cl	H	O	M–E	210—211[c]	53	$C_{15}H_{12}ClN_3O_2$	59.71 (59.75	4.01 3.89	13.94 13.94)

a) M: methanol; E: ethyl acetate; A: acetone.
b) All compounds melted with decomposition.
c) Lit.[5b] mp 220°.

positive in the $FeCl_3$ test and afforded **5a** and **3** on treatment with PCl_3 and on acid hydrolysis, respectively. Direct comparison also revealed that **6a** was different in every respect from the possible isomers, 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**7**)[8] and 7-chloro-2-hydroxyamino-5-phenyl-3*H*-1,4-benzodiazepine.[9] Thus, compound **6a** was confirmed to be the 1-oxide of **5a**.

Other 2-amino-1,4-benzodiazepines (**5**)[3] afforded the corresponding 1-oxides (**6**) similarly by reaction with MCPBA, and the 4-oxide (**7**)[8] was also oxidized to the dioxide (**6f**)[5b] (Table III).

The diazocine 1-oxides (**2**) and the diazepine 1-oxides (**6**) may exist as the tautomeric hydroxyamidine forms **2′** and **6′**, respectively, but this has not yet been studied in detail.

Reaction of the 1-oxides (**2**, **6**) with acetic anhydride was of interest, since the 4-oxides of the 1,4-benzodiazepine series undergo[10] a Polonovski-type rearrangement on treatment with acetic anhydride; *e.g.*, reaction of the 2-amino-3*H*-1,4-benzodiazepine 4-oxide (**7**) with acetic anhydride[10b] affords 3-substituted products such as the 2-acetamido-3*H*-1,4-benzodiazepin-3-one (**8**) and 2-acetamido-3-acetoxy-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine.

Reaction of **2** with acetic anhydride, however, resulted in the formation of a complex mixture from which no products could be isolated. On the other hand, reaction of **6a** with excess acetic anhydride at 100° gave a crystalline compound (**8**) with an empirical formula of $C_{17}H_{12}ClN_3O_2$. Compound **8** showed carbonyl absorptions at 1712 and 1685 cm^{-1} in the

8) L.H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).
9) *a*) K. Meguro, H. Natsugari, H. Tawada, and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2366 (1973); *b*) J.B. Hester, Jr. and A.D. Rudzik, *J. Med. Chem.*, **17**, 293 (1974).
10) *a*) S.C. Bell and S.J. Childress, *J. Org. Chem.*, **27**, 1691 (1962); *b*) S.C. Bell, C. Gochman, and S.J. Childress, *ibid.*, **28**, 3010 (1963).

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IR spectrum (KBr) and signals due to acetyl protons at 2.16 ppm, aromatic protons at 7.4—7.8 ppm and an amide (NH) proton at 11.5 ppm in the nuclear magnetic resonance (NMR) spectrum. The structure **8** was deduced from these spectral data and finally confirmed by direct comparison with an authentic sample prepared from **7**.[10b]

It is interesting that **6a** and **7** furnished the same compound (**8**), although the reaction pathway, especially the mechanism of the oxidation process to form the ketone, has not been elucidated.

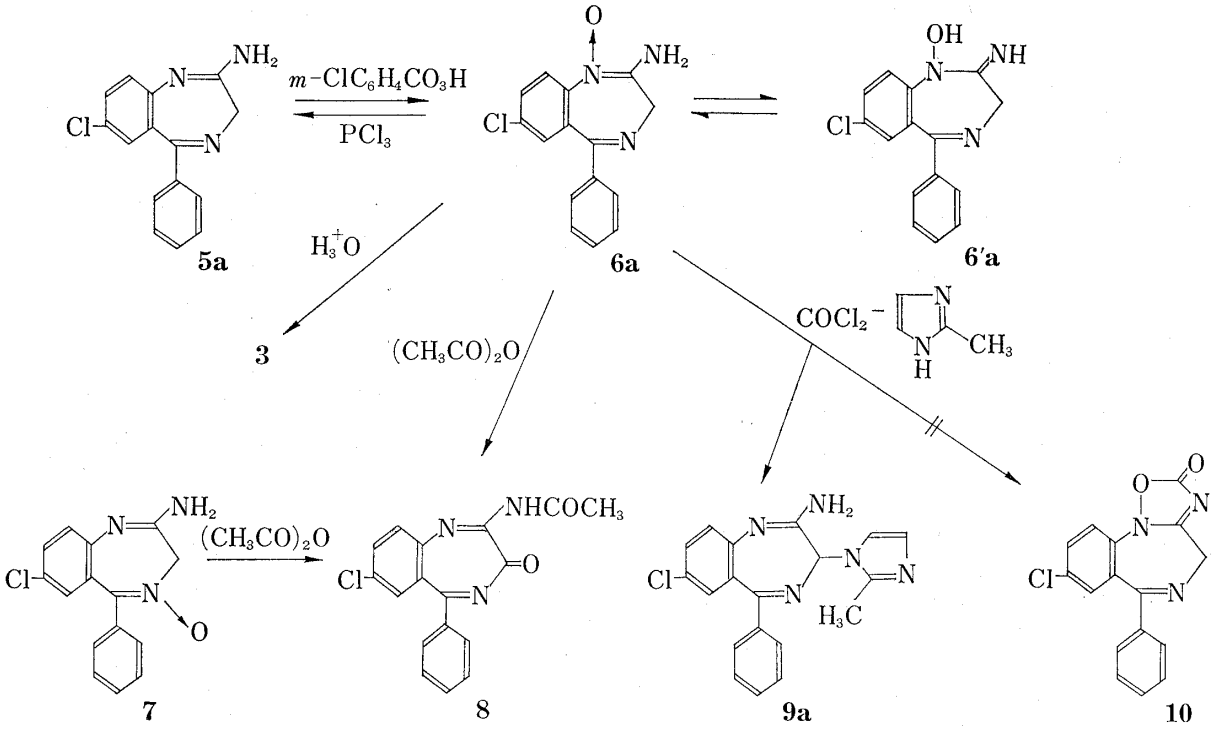

Chart 2

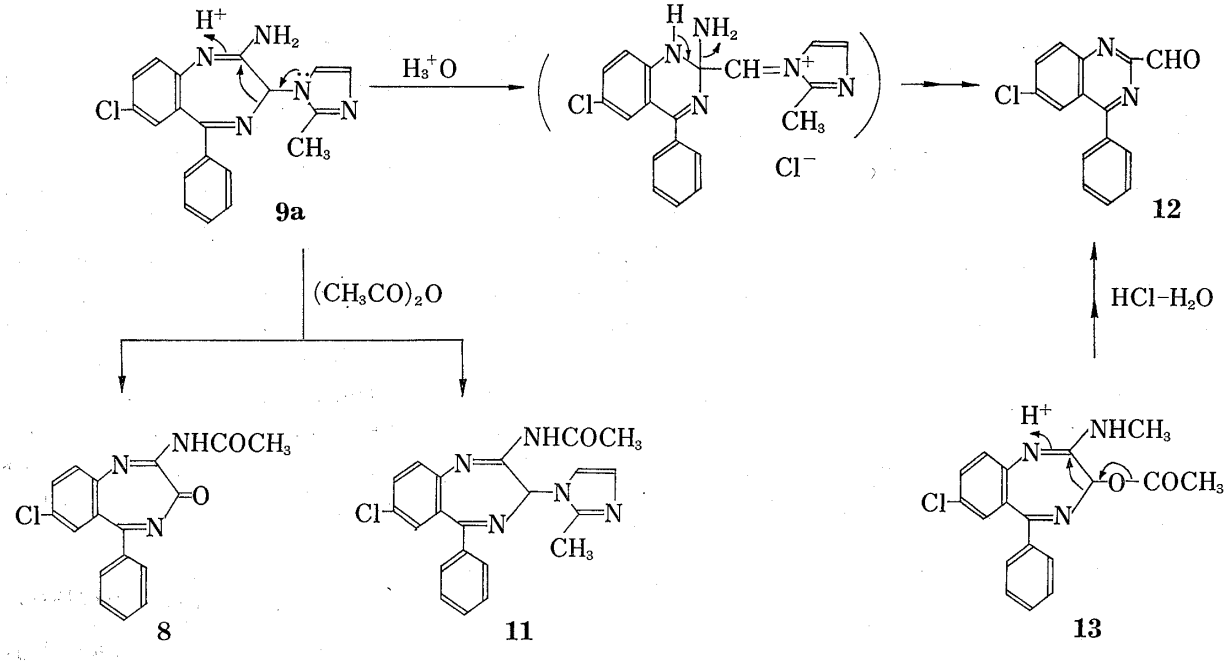

Chart 3

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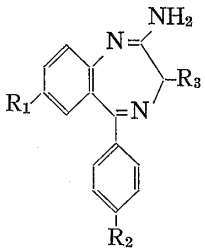
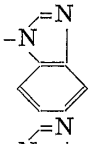
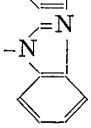
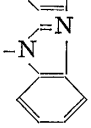
In order to obtain a new tricyclic benzodiazepine, oxadiazolo[2,3-*a*][1,4]benzodiazepin-2-one (**10**), reaction of **6a** with phosgene was attempted. When **6a** was treated with phosgene in the presence of triethylamine under the conditions used for the cyclization of **2a** to **4a**, a complicated reaction occurred and no crystalline product could be isolated. However, a clean reaction took place at room temperature when 2-methylimidazole was used as a base or when **6a** was treated with N,N′-carbonylbis(2-methylimidazole). The product, obtained as colorless crystals, had the empirical formula $C_{19}H_{16}ClN_5$, indicating that this compound contains an imidazole moiety. Its NMR spectrum, which showed signals at 2.20 ppm (3H, singlet), 5.28 ppm (1H, singlet) and 6.9—7.7 ppm (10H, multiplet), is consistent with the structure **9a**. Confirmation of the structure **9a** was provided by the following reactions.

Table IV. 2-Amino-3-(1-imidazolyl)-1,4-benzodiazepine (**9**)



Compd. No.	R_1	R_2	R_3	Recryst.[a] from	mp[b] (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
9a	Cl	H		M	270—271	60,[c] 62[d]	$C_{19}H_{16}ClN_5$	65.23 (65.13	4.61 4.52	20.02 20.18)
9b	Cl	H		M–C	265—266	78,[c] 39[e]	$C_{18}H_{14}ClN_5$	64.38 (64.27	4.20 4.42	20.86 20.46)
9c	Cl	H		M–C	285—286	70[c]	$C_{22}H_{16}ClN_5$	68.47 (68.15	4.18 4.25	18.15 17.95)
9d	H	H		M	258—261	73[c]	$C_{18}H_{15}N_5$	71.74 (71.75	5.02 4.91	23.24 23.11)
9e	CH_3	H		M	253—254	59[c]	$C_{21}H_{21}N_5$	73.44 (73.46	6.16 6.00	20.39 20.36)
9f	CH_3	H		M–D	270—273	92[c]	$C_{23}H_{19}N_5$	75.59 (75.31	5.24 5.14	19.17 18.96)
9g	CH_3O	H		M	250—252	79[c]	$C_{20}H_{19}N_5O \cdot 1/2H_2O$	68.21 (68.50	5.85 5.54	19.37 19.29)
9h	Cl	CH_3O		M	250—252	55[c]	$C_{21}H_{20}ClN_5O$	64.03 (63.80	5.11 4.84	17.78 17.74)
9i	Cl	CH_3O		M–C	302—303	82[c]	$C_{23}H_{18}ClN_5O$	66.42 (66.06	4.36 4.32	16.84 16.97)

a) M: methanol; C: chloroform; D: dichloromethane.
b) All compounds melted with decomposition.
c) By Method a (or c) (see "Experimental").
d) By Method b (see "Experimental").
e) By Method d (see "Experimental").

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Treatment of **9a** with acetic anhydride at 95—100° for 1—2 minutes afforded the monoacetylated compound (**11**), whereas **9a** gave **8** on prolonged heating in acetic anhydride. The formation of **8** indicates that **9a** retains the 1,4-benzodiazepine skeleton and that the imidazole moiety might be at the 3-position. Acid hydrolysis of **9a** afforded the quinazoline 2-carboxaldehyde (**12**), as in the hydrolysis of the 3-acetoxy-2-methylamino-3*H*-1,4-benzodiazepine (**13**).[11] This similarity in behavior on acid treatment suggests that the both compounds **9a** and **13** have closely related structures permitting the formation of **12** through the reaction pathways depicted in Chart 3.

3-Imidazolylbenzodiazepines (**9**) (Table IV) were also obtained from **6** by reaction with imidazoles (imidazole, 2-methylimidazole, 2-ethylimidazole and benzimidazole) in the presence of phosgene. Attempted rearrangement of **6** using primary and secondary amines (*e.g.*, methylamine and dimethylamine) in the presence of phosgene failed.

The rearrangement of **6** to **9** apparently proceeded in two steps. When the reactions of **6a** with phosgene-imidazoles or with N,N′-carbonylbis(2-methylimidazole) were monitored by thin layer chromatography (TLC), a common intermediate was first formed, regardless of the reagents used, and was then converted into the individual products. Although the intermediate was unstable and could not be isolated, IR measurements of the reaction mixture of **6a** with N,N′-carbonylbis(2-methylimidazole) in chloroform indicated that the intermediate was the oxadiazolo[2,3-*a*][1,4]benzodiazepin-2-one (**10**); a strong carbonyl absorption at 1790 cm^{-1} was observed in the initial stage of the reaction and then disappeared gradually. Conversion of **10** to **9** presumably proceeds *via* the tautomer **10′**.

Heating of **6a** with imidazole in the absence of phosgene also gave **9b**, although the yield was rather low (39%) and the reaction did not occur at room temperature. This reaction probably proceeds *via* the tautomer **6″a** (Chart 4).

The oxadiazolone (**4**) in the diazocine series did not react with imidazoles (*vide supra*) despite our previous finding that the $C_{(3)}$-methylene of the 2-amino-1,5-benzodiazocine (**1**) is rather active.[4] This suggests that the methylene group of the diazocine series (**2** or **4**) is much less active than that of the diazepine (**6** or **10**).

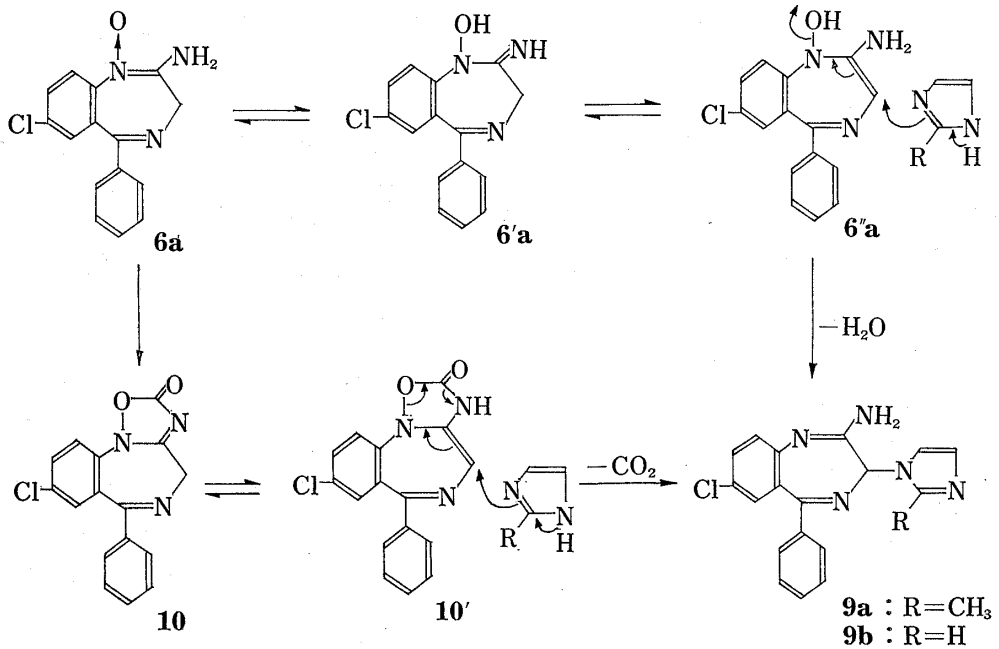

Chart 4

11) L.H. Sternbach, E. Reeder, A. Stempel, and A.I. Rachlin, *J. Org. Chem.*, **29**, 332 (1964).

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Experimental[12]

2-Amino-3,4-dihydro-1,5-benzodiazocine 1-Oxides (2) (Table I)——Typical procedures are described for **2a** and **2h**.

2-Amino-8-chloro-3,4-dihydro-6-phenyl-1,5-benzodiazocine 1-Oxide (2a)——Method a: A suspension of 10.6 g (37 mmol) of 2-amino-8-chloro-3,4-dihydro-6-phenyl-1,5-benzodiazocine (**1a**)[1] in 200 ml of ether was treated with a solution of 10.0 g (53 mmol) of MCPBA (85%) in 100 ml of ether. The mixture was stirred for 30 min at room temperature. The colorless crystals formed were collected by filtration and washed with ether to yield 17.0 g (99.5%) of *m*-chlorobenzoate of **2a**; mp 90—95°. Recrystallization from acetone–ether gave colorless needles, mp 95—97°. *Anal.* Calcd. for $C_{16}H_{14}ClN_3O \cdot C_7H_5ClO_2$: C, 60.53; H, 4.19; N, 9.20. Found: C, 60.20; H, 4.19; N, 9.06. $FeCl_3$ (+). This salt (8.0 g) was charged on a column packed with Amberlite IRA-400 (OH^-) (250 ml) and eluted with MeOH. The solvent was evaporated off to give **2a** as colorless crystals (4.3 g). MS *m/e*: 299 (M^+). $FeCl_3$ (+).

Method b: A suspension of 6.0 g (21 mmol) of **1a** and 120 ml of Amberlite IRA-400 (OH^-) in 150 ml of MeOH was treated with 6.5 g (34 mmol) of MCPBA (85%). The mixture was stirred for 30 min at room temperature. The ion exchange resin was removed by filtration and the filtrate was concentrated to afford **2a** as colorless crystals (5.3 g). The IR spectrum of this sample was identical with that of **2a** obtained by Method a.

2-Amino-8-chloro-3,4-dihydro-4-methyl-6-phenyl-1,5-benzodiazocine 1-Oxide (2h)——Method c: A stirred and ice-cooled suspension of 50.0 g (0.17 mol) of 2-amino-8-chloro-3,4-dihydro-4-methyl-6-phenyl-1,5-benzodiazocine (**1h**)[1] in 800 ml of ether was treated with 44.5 g (0.24 mol) of MCPBA (85%) and the mixture was stirred for 10 min. After removal of the solvent, the residue was added to 600 ml of conc. NH_4OH under ice cooling. The precipitate was collected by filtration and washed successively with H_2O, acetone and ether to give **2h** as crystals (40.2 g, 72%), mp 213—215° (dec.). Recrystallization from MeOH–acetone gave pale yellow prisms. $FeCl_3$ (+).

Other compounds listed in Table I were similarly prepared from the corresponding **1**[1] by Method a or b.

2-Amino-3*H*-1,4-benzodiazepine 1-Oxides (6) (Table III)——A typical procedure is described for **6a**.

2-Amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 1-Oxide (6a)——A suspension of 5.0 g (19 mmol) of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (**5a**) and 50 ml of Amberlite IRA-400 (OH^-) in 150 ml of MeOH was treated with 5.0 g (26 mmol) of MCPBA (85%). The mixture was stirred for 30 min at room temperature. The ion exchange resin was removed by filtration and the filtrate was concentrated. Treatment of the residue with ether gave pale yellow crystals (4.1 g, 75%). Recrystallization from MeOH–AcOEt gave pale yellow flakes. $FeCl_3$ (+).

Other compounds listed in Table III were similarly prepared from the corresponding **5**.

Deoxygenation of 2a——PCl_3 (0.3 ml) was added to a solution of 300 mg of **2a** in 15 ml of $CHCl_3$. The mixture was refluxed for 5 min. After removal of the solvent, 1 N NaOH was added to the residue. Colorless crystals formed were collected by filtration and washed successively with H_2O, acetone and ether to give **1a** (240 mg, 88%). Recrystallization from acetone gave colorless needles, mp 219—221° (dec.). The IR spectrum of this sample was identical with that of authentic **1a**.[1]

Deoxygenation of 6a——PCl_3 (0.2 ml) was added to a suspension of 200 mg of **6a** in 10 ml of $CHCl_3$. The mixture was refluxed for 15 min. After removal of the solvent, the residue was partitioned between $CHCl_3$ and 1 N NaOH. The $CHCl_3$ layer was washed with H_2O, dried and concentrated to give **5a** as colorless crystals (95 mg, 50%), mp 233—235° (dec.). The IR spectrum of this sample was identical with that of authentic **5a**.[3]

Acid Hydrolysis of 2a——A mixture of 100 mg of **2a** and 2 ml of hydrochloric acid (*ca.* 18%) was heated at 95—100° for 1.5 hr. After cooling, crystals formed were collected by filtration and washed with H_2O and EtOH to give 5-chloro-3-phenyl-2,1-benzisoxazole (**3**) (50 mg, 67%), mp 113—115° (lit.[7] mp 115—117°). The IR spectrum of this sample was identical with that of an authentic sample prepared by the known method.[7]

Acid Hydrolysis of 6a——A mixture of 100 mg of **6a** and 2 ml of hydrochloric acid (*ca.* 18%) was heated at 95—100° for 1.5 hr. After cooling, crystals formed were collected by filtration and washed with H_2O and EtOH to give **3** (57 mg, 71%), mp 113—115° (lit.[7] mp 115—117°). The IR spectrum of this sample was identical with that of an authentic sample.[7]

4,5-Dihydro-2*H*-1,2,4-oxadiazolo[2,3-*a*][1,5]benzodiazocin-2-ones (4) (Table II)——Typical procedures are described for **4a**.

12) All melting points were determined with a Yanagimoto micro melting point apparatus (a hot-stage type) and are uncorrected. IR spectra were measured with a Hitachi 215 spectrophotometer, NMR spectra with a Varian T-60 (60 MHz) or a Varian HA-100 (100 MHz) spectrometer using tetramethylsilane as an internal standard, and mass spectra (MS) with a Hitachi RMS-4 single focusing mass spectrometer with a direct sample inlet system. The following abbreviations are used; s=singlet, m=multiplet and b=broad. Extracted solutions were dried over Na_2SO_4.

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9-Chloro-4,5-dihydro-7-phenyl-2*H*-1,2,4-oxadiazolo[2,3-*a*][1,5]benzodiazocin-2-one (**4a**)——Method a: A mixture of 30 ml (30 mmol) of 10% $COCl_2$ in toluene and 130 ml of $CHCl_3$ was added dropwise to a stirred and ice-cooled solution of 7.0 g (23 mmol) of **2a** and 7 ml (51 mmol) of Et_3N in 200 ml of $CHCl_3$. After stirring for 1 hr, the mixture was washed with H_2O, dried and evaporated down to give **4a** as colorless crystals (5.2 g, 69%), mp 165—168° (dec.). Recrystallization from acetone–hexane gave colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 1780 (C=O). MS *m/e*: 325 (M^+).

Method b: A mixture of 1 ml (1.0 mmol) of 10% $COCl_2$ in toluene and 2 ml of $CHCl_3$ was added dropwise to a stirred solution of 150 mg (0.5 mmol) of **2a** and 240 mg (2.9 mmol) of 2-methylimidazole in 5 ml of $CHCl_3$. The mixture was stirred for 1 hr at room temperature, washed with H_2O, dried and concentrated to give **4a** as colorless crystals (125 mg, 78%), mp 167—169° (dec.).

Method c: A solution of 150 mg (0.5 mmol) of **2a** and 130 mg (0.7 mmol) of N,N′-carbonylbis(2-methylimidazole) in 6 ml of dry tetrahydrofuran was refluxed for 15 min. After removal of the solvent, H_2O was added to the residue. Colorless crystals formed were collected by filtration, then washed successively with H_2O and acetone to give **4a** (130 mg, 80%), mp 166—168° (dec.).

Method d: A mixture of 150 mg (0.5 mmol) of **2a**, 0.06 ml (1.0 mmol) of methyl isocyanate and 5 ml of dry benzene was refluxed for 2 hr. After stirring for 1 hr, the mixture was partitioned between H_2O and AcOEt. The organic layer was separated, washed with H_2O, dried and concentrated to give **4a** as colorless crystals (9.5 g, 78%), mp 172—173° (dec.). The IR spectra of the compounds obtained by Methods b—d were identical with that of **4a** obtained by Method a.

Other compounds (**4b—i**) were similarly prepared from the corresponding **2** by Method a, b or c.

2-Amino-3-(1-imidazolyl)-5-phenyl-3*H*-1,4-benzodiazepines (**9**) (**Table IV**)——Typical procedures are described for **9a** and **9b**.

2-Amino-7-chloro-3-(2-methyl-1-imidazolyl)-5-phenyl-3*H*-1,4-benzodiazepine (**9a**)——Method a: A solution of 570 mg (2.0 mmol) of **6a** and 820 mg (10.0 mmol) of 2-methylimidazole in 50 ml of $CHCl_3$ was treated with 3 ml (3.0 mmol) of 10% $COCl_2$ in toluene. After stirring for 2 hr at room temperature, the mixture was washed with aq. $NaHCO_3$ and H_2O, dried and concentrated to give **9a** as colorless crystals (420 mg, 60%). Recrystallization from MeOH gave colorless prisms. MS *m/e*: 349 (M^+), 268 (100%). IR ν_{max}^{KBr} cm^{-1}: 3500—2900 (b), 1655 (C=N). NMR (DMSO-d_6) δ: 2.20 (3H, s, CH_3), 5.28 (1H, s, $C_{(3)}H$), 6.9—7.7 (10H, m, phenyl H and two imidazole H).

Method b: A solution of 145 mg (0.5 mmol) of **6a** and 190 mg (1.0 mmol) of N,N′-carbonylbis(2-methylimidazole) in 20 ml of $CHCl_3$ was stirred for 4 hr at room temperature. The solution was washed with H_2O, dried and concentrated to give **9a** as colorless crystals (110 mg, 62%), mp 271—273° (dec.). The IR spectrum of this sample was identical with that of **9a** obtained by Method a.

2-Amino-7-chloro-3-(1-imidazolyl)-5-phenyl-3*H*-1,4-benzodiazepine (**9b**)——Method c: A solution of 285 mg (1.0 mmol) of **6a** and 470 mg (6.9 mmol) of imidazole in 25 ml $CHCl_3$ was treated with 1.5 ml (1.5 mmol) of 10% $COCl_2$ in toluene. After stirring for 2 hr at room temperature, the mixture was washed with aq. $NaHCO_3$ and H_2O, dried and concentrated to give **9b** as colorless crystals (260 mg, 78%), mp 263—265° (dec.). Recrystallization from MeOH–$CHCl_3$ gave colorless needles. IR ν_{max}^{KBr} cm^{-1}: 3500—2900 (b), 1650 (C=N). NMR (DMSO-d_6) δ: 5.50 (1H, s, $C_{(3)}H$), 7.0—7.6 (10H, m, phenyl H and two imidazole H), 8.03 (1H, s, one imidazole ($C_{(2)}$)H).

Method d: A solution of 50 mg (0.2 mmol) of **6a** and 70 mg (1.0 mmol) of imidazole in 3 ml of $CHCl_3$ was refluxed for 2.5 hr. The solution was washed with H_2O, dried and concentrated. The residue was treated with MeOH to give **9b** as colorless crystals (23 mg, 39%), mp 263—265° (dec.). The IR spectrum of this sample was identical with that of **9b** obtained by Method c.

Other compounds (**9c—i**) listed in Table IV were similarly prepared from the corresponding **6** and imidazoles by Method a or c.

Acid Hydrolysis of 9a——A mixture of 150 mg of **9a** and 6 ml of 50% H_2SO_4 was heated at 95° for 30 min. After cooling, the mixture was neutralized with 1 N NaOH and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried and concentrated. The residue was chromatographed on silica gel (6 g), eluting with benzene, then hexane–acetone (4: 1, v/v). From the benzene eluate, 2-amino-5-chlorobenzophenone was obtained as yellow crystals (20 mg, mp 96—97°, lit.[13] 100°). From the hexane–acetone eluate, 6-chloro-4-phenylquinazoline-2-carboxaldehyde (**12**) was obtained as colorless crystals (23 mg, mp 175—177°, lit.[11] mp 177—178°). The IR spectra of these compounds were identical with those of authentic samples prepared by the reported procedures.

2-Acetamido-7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-3-one (**8**)——From 6a: A mixture of 300 mg of **6a** and 14 ml of acetic anhydride was heated at 100° for 3.5 hr. After cooling, the colorless crystals formed were collected by filtration and washed with ether to give **8** (125 mg, 37%). Recrystallization from acetone gave colorless needles, mp 232—233° (dec.). (lit.[10b] 239—240° (dec.)). *Anal.* Calcd. for $C_{17}H_{12}ClN_3O_2$: C, 62.67; H, 3.71; N, 12.90. Found: C, 62.76; H, 3.95; N, 12.73. IR ν_{max}^{KBr} cm^{-1}: 1712, 1685 (C=O). NMR (DMSO-d_6) δ: 2.16 (3H, s, CH_3CO–), 7.4—7.8 (8H, m, arom. H), 11.5 (1H, b, NHCO). The IR and NMR spectra of this sample were identical with those of a sample prepared by the reported procedure.[10b]

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From **9a**: A mixture of 100 mg of **9a** and 1 ml of acetic anhydride was heated at 95° for 2 hr. After cooling, the colorless needles formed were collected by filtration to give **8** (35 mg, 38%), mp 230—231° (dec.).

2-Acetamido-7-chloro-3-(2-methyl-1-imidazolyl)-5-phenyl-3*H*-1,4-benzodiazepine (**11**)——A mixture of 200 mg of **9a** and 1.5 ml of acetic anhydride was heated at 95° until the mixture became clear (*ca.* 1—2 min). The solution was concentrated, then the residue was diluted with saturated aq. $NaHCO_3$ and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried and concentrated to give pale yellow crystals (165 mg, 74%), mp 199—201° (dec.). Recrystallization from MeOH gave pale yellow prisms, mp 206—207° (dec.). *Anal.* Calcd. for $C_{21}H_{18}ClN_5O \cdot CH_3OH$: C, 62.33; H, 5.23; N, 16.52. Found: C, 62.47; H, 4.90; N, 16.60. IR ν_{max}^{KBr} cm^{-1}: 1715 (C=O). NMR (DMSO-d_6) δ: 2.10, 2.21 (each 3H, s, CH_3 and CH_3CO), 5.40 (1H, s, $C_{(3)}H$).

Acknowledgement We are very grateful to Dr. E. Ohmura of this Division for his encouragement throughout this work. Thanks are also due to the members of the Analytical Section of this Division for microanalyses and measurements of NMR and mass spectra.

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