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Heterocycles. XIII.[1] Reactions of 2-Amino-1,4-benzodiazepine 1-Oxides and 2-Amino-1,5-benzodiazocine 1-Oxides with Acetylenecarboxylates

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The reaction of 2-amino-1,5-benzodiazocine 1-oxides (**1**) with acetylenecarboxylates (**2**, **11**) afforded $C_{(10)}$-alkylated derivatives (**3**) *via* 3,3-sigmatropic rearrangement. Compounds **3** gave 10-alkoxycarbonylmethyl-1,5-benzodiazocines (**4**) when heated in ethanol. Heating of **3a**—**e** in pyridine, on the other hand, gave indole derivatives (**9**), which were converted into 7-benzoylindoles (**10a**—**e**) by acid hydrolysis.

The reaction of 2-amino-1,4-benzodiazepine 1-oxides (**13**) with acetylenedicarboxylates (**11**) also gave the rearranged products (**14**).

Keywords—— 1,4-benzodiazepines; 1,5-benzodiazocines; acetylenecarboxylates; amidine N-oxide; 3,3-sigmatropic rearrangement; indoles

A number of cycloaddition reactions of nitrones or heteroaromatic N-oxides with 1,3-dipolarophiles have been well documented.[3] They provide useful tools for the synthesis of various fused heterocycles; one such reaction is the reaction of 1,4-benzodiazepine 4-oxides with acetylenecarboxylates to give isoxazolo[2,3-*d*][1,4]benzodiazepine derivatives.[4] The 2-amino-1,5-benzodiazocine 1-oxides (**1**)[1] and the 2-amino-1,4-benzodiazepine 1-oxides (**13**)[1] were of interest to us from the viewpoint of reactivity at the amidine N-oxide moiety, since this moiety is regarded as a nitrone, though it may behave as the tautomeric hydroxyamidine.[5]

This paper deals with a new type of rearrangement observed with the amidine N-oxides **1** and **13** in the reaction with acetylenecarboxylates (**2**, **11**).[6]

When 2-amino-8-chloro-3,4-dihydro-6-phenyl-1,5-benzodiazocine 1-oxide (**1a**) was allowed to react with ethyl propiolate (**2**) in methanol at room temperature, a 1:1 adduct (**3a**) was obtained in good yield (79%). Compound **3a** was positive to the ferric chloride ($FeCl_3$) test and showed a strong, broad absorption band at 1630 cm^{-1} in the infrared (IR) spectrum, suggesting the presence of conjugate chelation of a β-dicarbonyl system.[7] The IR spectrum also showed the presence of amino and/or hydroxyl groups (broad bands at 3370 and 2900 cm^{-1}). In the nuclear magnetic resonance (NMR) spectrum of **3a** the newly introduced group appeared at 1.22 (3H, triplet, $C\underline{H}_3CH_2O$–), 4.10 (2H, quartet, $CH_3C\underline{H}_2O$–) and 8.60 ppm (1H, singlet, >C=C$\underline{H}$–(OH)), and seven aromatic protons were observed at 6.82—7.70 ppm.

1) Part XII: H. Natsugari, K. Meguro, and Y. Kuwada: *Chem. Pharm. Bull.* (Tokyo), **27**, 2608 (1979).
2) Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*
3) *a*) R. Huisgen, *Angew. Chem. Internat. Edi. Engl.*, **2**, 633 (1963); *b*) D. St. C. Black, R.F. Crozier, and V.C. Davis, *Synthesis*, **1975**, 205; *c*) R. Huisgen, *J. Org. Chem.*, **41**, 403 (1976).
4) *a*) M. Raban, E.H. Carlson, J. Szmuszkovicz, G. Slomp, C.G. Chidester, and D.J. Duchamp, *Tetrahedron Lett.*, **1975**, 139; *b*) T. Miyadera, Y. Kawano, T. Hata, C. Tamura, and R. Tachikawa, *Chem. Pharm. Bull.* (Tokyo), **25**, 3247 (1977); *c*) Sumitomo Chem. Co., Japan. Patent Spec., 93395 (1974).
5) Tautomerism of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 1,4-dioxide is discussed in the literature; R.Y. Ning, R.I. Fryer, and B.C. Sluboski, *J. Org. Chem.*, **42**, 3301 (1977).
6) Another rearrangement of an amidine N-oxide has recently been reported in the reaction of 2-aminothiazole 3-oxides with **11**; G. Entenmann, *Z. Naturforsh.*, **31b**, 251 (1976).
7) L.J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd Ed., John Wiley Sons, Inc., New York, 1958, p. 142.

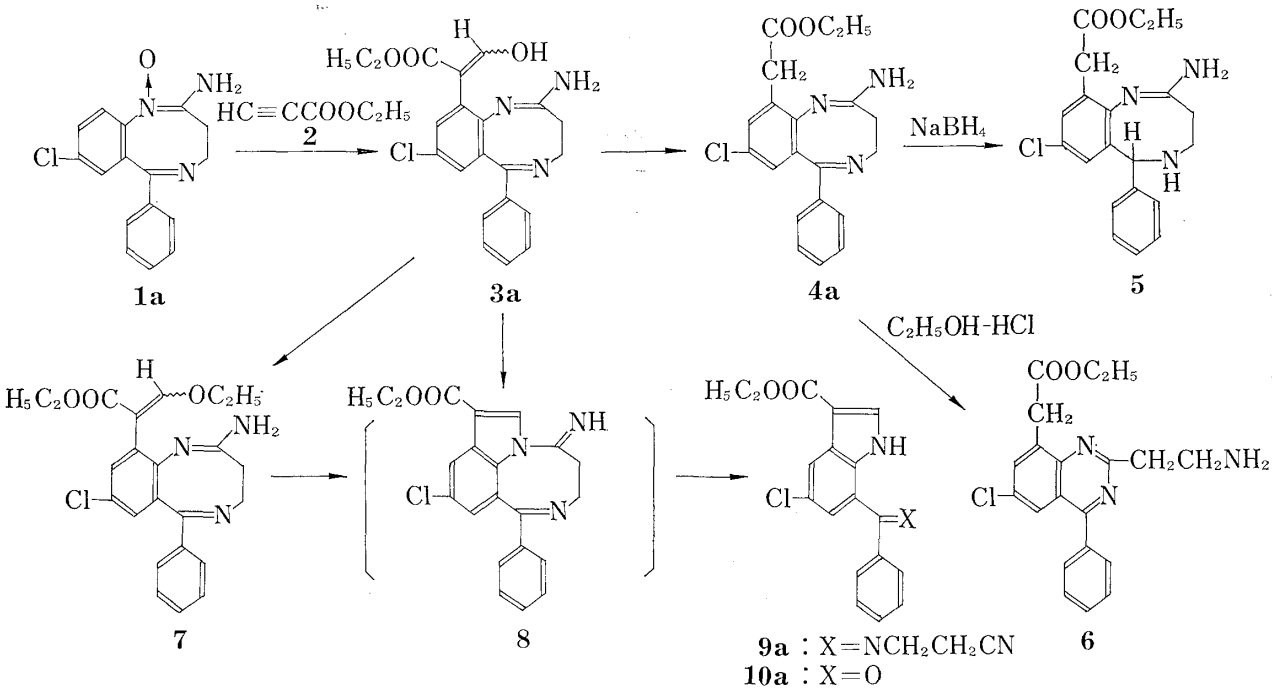


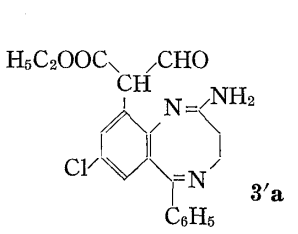
Chart 1

From these data and mechanistic considerations (*vide infra*), the structure of **3a** was assumed to be 2-amino-8-chloro-3,4-dihydro-10-(1-ethoxycarbonyl-2-hydroxyvinyl)-6-phenyl-1,5-benzodiazocine.[8] This was confirmed by the following chemical transformations (Chart 1).

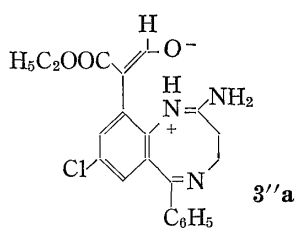
On heating in ethanol, **3a** gave the 10-ethoxycarbonylmethyl-1,5-benzodiazocine (**4a**) by retro-Claisen cleavage. The IR spectrum of **4a** showed bands at 3370, 3120 ($-NH_2$), 1720 (ester carbonyl) and 1660 cm^{-1} (>C=N–). In the NMR spectrum the newly formed $-\underline{CH_2}COOEt$ group appeared at 3.38 and 3.77 ppm as an AB quartet (J=16 Hz) and two aromatic protons ($C_{(7)}$–H and $C_{(9)}$–H) appeared at 6.80 and 7.18 ppm as two doublets (J=2 Hz). Compound **4a** underwent reactions characteristic of 2-amino-1,5-benzodiazocines, as reported in the preceding paper,[9] *i.e.*, reduction of **4a** with sodium borohydride gave the 2-amino-3,4,5,6-tetrahydro-1,5-benzodiazocine (**5**) and treatment of **4a** with alcoholic hydrogen chloride gave the 2-(2-aminoethyl)quinazoline (**6**).

On the other hand, heating of **3a** in pyridine gave the dehydrated product (**9a**) in quantitative yield. The IR spectrum of **9a** showed an absorption at 2240 cm^{-1} due to a nitrile group. Its NMR spectrum showed two doublets at 8.01 and 11.60 ppm (J=3 Hz) attributable to the C-2 proton and the N-1 proton of the indole, respectively. Compound **9a** gave the 7-benzoylindole-3-carboxylate (**10a**) on acid hydrolysis. These data are consistent with the proposed structure of **9a**. Formation of **9a** may be rationalized in terms of the dehydration of **3a** to the pyrrolobenzodiazocine (**8**), followed by opening of the diazocine ring.

8) The enolic structure was assigned to **3a**, but the tautomeric forms (*e.g.*, **3'a**, **3''a**) cannot be ruled out. Such tautomerism of an α-formylacetate moiety attached to heterocycles has been described in the literature, *e.g.*, *a*) H. Seidl and R. Huisgen, *Tetrahedron Lett.*, **1963**, 2023; *b*) S. Takahashi and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **12**, 1290 (1964); *c*) M. Hamana, K. Funakoshi, H. Shigyo, and Y. Kuchino, *ibid.*, **23**, 346 (1975).



3'a



3''a

9) H. Natsugari, K. Meguro, and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), **27**, 2589 (1979).

10) The stereochemistry of the vinyl moiety was not determined.

Reaction of **3a** with alcoholic hydrogen chloride gave the enol ether (**7**)[10] which also afforded **9a** on heating in pyridine.

Similar rearranged products (**3f** and **3g**) were obtained by the reaction of the diazocine 1-oxide (**1a**) with diethyl and dimethyl acetylenedicarboxylates (**11a** and **11b**). Compounds **3f** and **3g** gave the corresponding 10-alkoxycarbonylmethyl-2-amino-1,5-benzodiazocines (**4a** and **4b**) on heating in ethanol. However, heating of **3f** in pyridine did not give the indole derivative (**12**).[11]

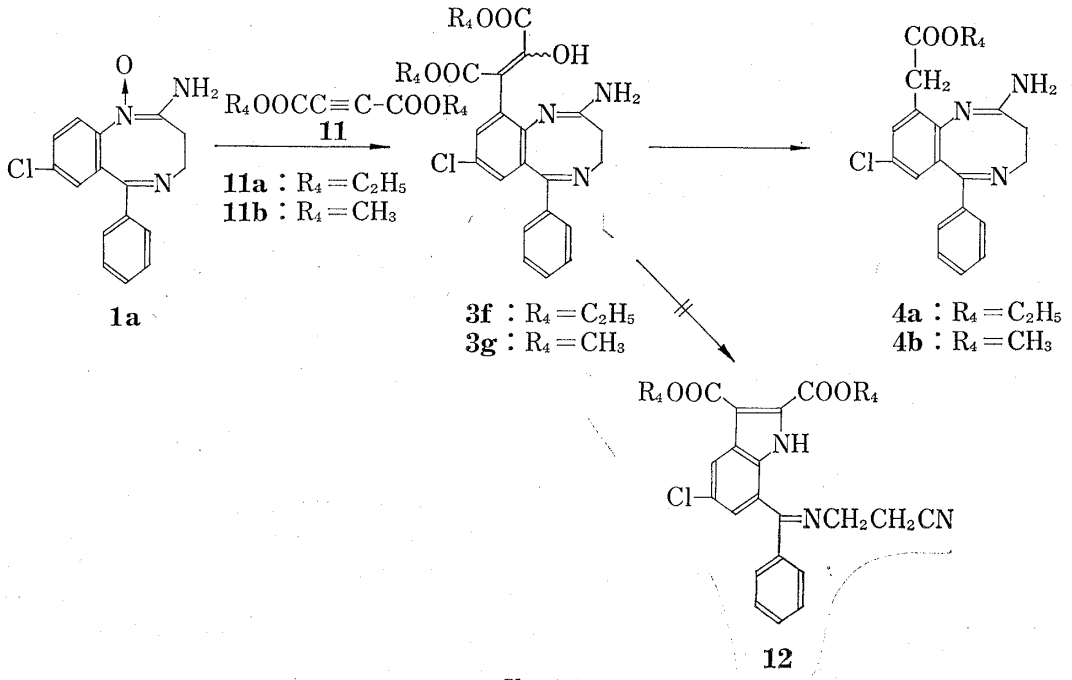


Chart 2

Similarly, compounds **3** and **4** bearing various substituents were prepared starting from 2-amino-1,5-benzodiazocine 1-oxides (**1**)[1] (Tables I and II). The indole derivatives **10a—e** were also prepared from the corresponding **3a—e** (Table III).

Reactions of 2-amino-1,4-benzodiazepine 1-oxides (**13**), which have the same partial structure as **1**, were also investigated. Treatment of **13a** with diethyl acetylenedicarboxylate (**11a**) gave the rearranged product (**14a**) in good yield. Reaction of **13b** with **11b** similarly

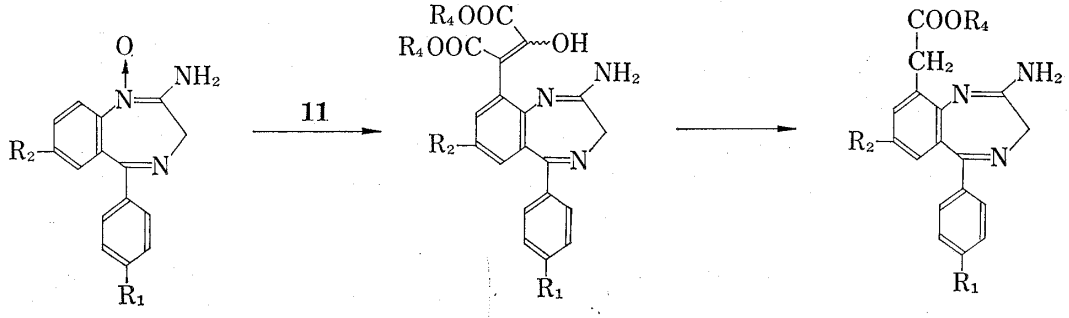
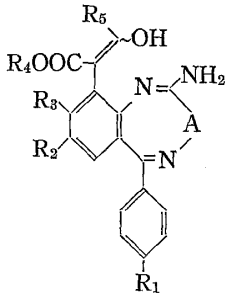


Chart 3

11) An unidentified crystalline product was isolated in poor yield.

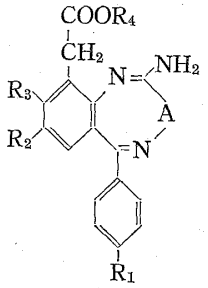
TABLE I.[a] 2-Amino-10-(1-alkoxycarbonyl-2-hydroxyvinyl)-3,4-dihydro-6-phenyl-1,5-benzodiazocines (**3**) and 2-Amino-9-(1-alkoxycarbonyl-2-hydroxyvinyl)-5-phenyl-3*H*-1,4-benzodiazepines (**14**)



Compd. No.	R_1	R_2	R_3	A	R_4	R_5	mp[b] (dec.) (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3a	H	Cl	H	$-CH_2CH_2-$	C_2H_5	H	205—207	79	$C_{21}H_{20}ClN_3O_3$	63.39	5.06	10.56	63.34	4.81	10.18
3b	H	H	H	$-CH_2CH_2-$	C_2H_5	H	190—191	66	$C_{21}H_{21}N_3O_3 \cdot 1/2CH_3OH$	68.05	6.10	11.07	67.99	5.96	11.29
3c	OCH_3	Cl	H	$-CH_2CH_2-$	C_2H_5	H	205—207	73	$C_{22}H_{22}ClN_3O_4$	61.75	5.18	9.82	61.62	5.30	9.51
3d	H	CH_3	H	$-C(CH_3)HCH_2-$	C_2H_5	H	197—198	94	$C_{22}H_{25}N_3O_3$	70.57	6.44	10.74	70.51	6.25	10.67
3e	Cl	Cl	H	$-C(CH_3)HCH_2-$	C_2H_5	H	197—198	75	$C_{22}H_{21}Cl_2N_3O_3 \cdot 1/2H_2O$	58.02	4.87	9.22	57.94	4.55	9.10
3f	H	Cl	H	$-CH_2CH_2-$	C_2H_5	$COOC_2H_5$	195—197	58	$C_{24}H_{24}ClN_3O_5$	61.33	5.14	8.94	61.34	5.06	9.10
3g	H	Cl	H	$-CH_2CH_2-$	CH_3	$COOCH_3$	212—214	68	$C_{22}H_{20}ClN_3O_5$	59.79	4.56	9.50	59.51	4.24	9.36
3h	H	CH_3	H	$-C(CH_3)HCH_2-$	CH_3	$COOCH_3$	210—212	69	$C_{24}H_{25}N_3O_5$	66.19	5.79	9.65	65.88	5.93	9.55
3i	H	OCH_3	OCH_3	$-CH_2CH_2-$	C_2H_5	$COOC_2H_5$	154—155	77	$C_{26}H_{29}N_3O_7$	63.03	5.90	8.48	62.65	5.81	8.28
14a	H	Cl	H	$-CH_2-$	C_2H_5	$COOC_2H_5$	208—209	79	$C_{23}H_{22}Cl_1N_3O_3 \cdot 1/2H_2O$	59.41	4.98	9.03	59.69	4.73	9.02
14b	OCH_3	Cl	H	$-CH_2-$	CH_3	$COOCH_3$	200—202	54	$C_{22}H_{20}ClN_3O_6$	57.70	4.40	9.17	57.35	4.31	8.80

a) For starting N-oxides see ref. 1.
b) All compounds were characterized without recrystallization due to their susceptibility to solvolysis.

TABLE II. 2-Amino-10-alkoxycarbonylmethyl-3,4-dihydro-6-phenyl-1,5-benzodiazocines (**4**) and 2-Amino-9-alkoxycarbonylmethyl-5-phenyl-3*H*-1,4-benzodiazepines (**15**)



Compd. No.	R_1	R_2	R_3	A	R_4	Recryst.[a] from	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
4a	H	Cl	H	$-CH_2CH_2-$	C_2H_5	D	194—195	94[b] 87[c]	$C_{20}H_{20}ClN_3O_2$	64.94	5.45	11.36	65.00	5.31	11.17
4b	H	Cl	H	$-CH_2CH_2-$	CH_3	A–H	192—194	92	$C_{19}H_{18}ClN_3O_2$	64.13	5.09	11.80	64.19	5.08	11.61
4c	H	H	H	$-CH_2CH_2-$	C_2H_5	M–H	152—154	85	$C_{20}H_{21}N_3O_2$	71.62	6.31	12.53	71.32	6.29	12.34
4d	OCH_3	Cl	H	$-CH_2CH_2-$	C_2H_5	E	227—228	99	$C_{21}H_{22}ClN_3O_3$	63.07	5.55	10.51	63.06	5.47	10.51
4e	H	CH_3	H	$-C_{(3)}(CH_3)HCH_2-$	C_2H_5	A–H	196—198	96	$C_{22}H_{25}N_3O_2$	72.70	6.93	11.56	72.77	6.91	11.52
4f	Cl	Cl	H	$-C_{(3)}(CH_3)HCH_2-$	C_2H_5	A	194—195	90	$C_{21}H_{21}ClN_3O_2$	60.29	5.06	10.04	60.36	5.02	9.91
4g	H	CH_3	H	$-C_{(3)}(CH_3)HCH_2-$	CH_3	A–H	194—195	89	$C_{21}H_{23}N_3O_2$	72.18	6.63	12.03	72.16	6.86	11.91
4h	H	OCH_3	OCH_3	$-CH_2CH_2-$	C_2H_5	A–H	191—192	82	$C_{22}H_{25}N_3O_2$	66.82	6.37	10.63	66.49	6.35	10.52
15a	H	Cl	H	$-CH_2-$	C_2H_5	M	228—230[d]	80	$C_{19}H_{18}ClN_3O_2$	64.13	5.09	11.80	64.16	4.91	11.73
15b	OCH_3	Cl	H	$-CH_2-$	CH_3	A–H	206—207[d]	84	$C_{19}H_{18}ClN_3O_3$	61.37	4.87	11.30	61.18	4.72	10.95

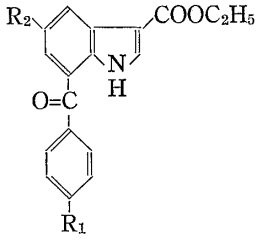
a) D, diethyl ether; A, acetone; H, hexane; M, methanol; E, ethanol.
b) From **3a**. *c*) From **3f**. *d*) Decomposition.

afforded **14b**. Compounds **14a** and **14b** were converted into a new type of 1,4-benzodiazepine derivatives (**15a** and **15b**) by heating in ethanol (Chart 3, Table II).

Treatment of **13a** with ethyl propiolate, however, did not give the rearranged product and **13a** was recovered.

A plausible reaction mechanism for the formation of **3** and **14** is a 3,3-sigmatropic rearrangement[12] of the intermediate adduct (**16**), as illustrated in Chart 4. The same type of

TABLE III. 7-Benzoyl-3-ethoxycarbonylindoles (**10**)



Compd. No.	R_1	R_2	Recryst.[a] from	Appearance	mp (°C)	Yield[b] (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
10a	H	Cl	E	Colorless needles	181—182	99	$C_{18}H_{14}ClNO_3$	65.95 (65.98	4.30 4.20	4.27 4.37)
10b	H	H	E	Colorless needles	178—179	97	$C_{18}H_{15}NO_3$	73.70 (73.67	5.15 4.98	4.78 4.78)
10c	OCH_3	Cl	A–H	Colorless needles	206—207	99	$C_{19}H_{16}ClNO_4$	63.78 (63.72	4.51 4.38	3.92 3.94)
10d	H	CH_3	E	Colorless needles	181—182	88	$C_{19}H_{17}NO_3 \cdot 1/2H_2O$	72.13 (72.40	5.73 5.44	4.42 4.29)
10e	Cl	Cl	E	Colorless needles	194—195	99	$C_{18}H_{13}Cl_2NO_3$	59.68 (59.85	3.61 3.49	3.86 3.92)

a) E, ethanol; A, acetone; H, hexane.
b) Overall (*i.e.*, **3**→**9**→**10**) yield based on the corresponding **3**.

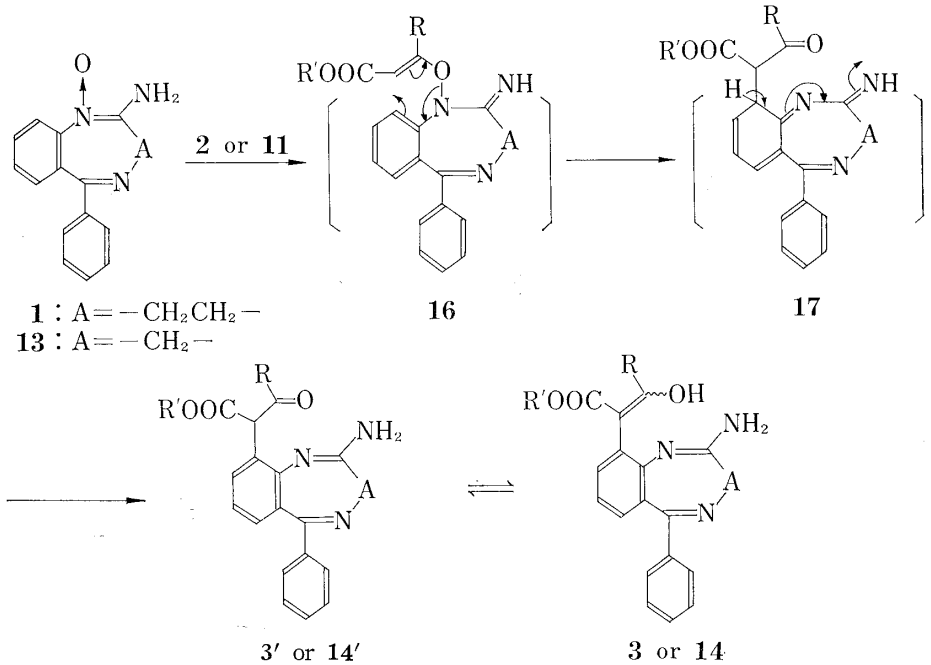


Chart 4

12) *a*) Y. Makisumi, *Yuki Gosei Kagaku Kyokai Shi*, **27**, 593 (1969); *b*) T. Hayashi, *ibid.*, **34**, 396 (1976).

reaction mechanism was proposed recently for the *ortho* alkylations observed with N-acyl-N-phenylhydroxylamines.[13] Reactions of N-phenylhydroxylamine which appear to involve rearrangements of this type have also been reported.[14] It is interesting that compounds **1** and **13** show reactivities similar to those of N-phenylhydroxylamine derivatives rather than those of nitrones in the reaction with acetylenecarboxylates.

Experimental[15]

2-Amino-8-chloro-3,4-dihydro-10-(1-ethoxycarbonyl-2-hydroxyvinyl)-6-phenyl-1,5-benzodiazocine (3a)——A solution of 4.0 g (13 mmol) of 2-amino-8-chloro-3,4-dihydro-6-phenyl-1,5-benzodiazocine 1-oxide (**1a**)[1] and 4.8 ml (47 mmol) of ethyl propiolate (**2**) in 50 ml of methanol was stirred at room temperature for 3 hr. The precipitate was collected by filtration and washed with ether to give colorless crystals (4.1 g). IR ν_{max}^{KBr} cm^{-1}: 3370 (b), 2900 (b), 1630 (b), 1530. NMR (DMSO-d_6) δ: 1.22 (3H, t, J=7 Hz, C$\underline{H}_3$CH$_2$O–), 2.6—4.2 (4H, b m, –CH$_2$C$\underline{H}_2$–), 4.10 (2H, q, J=7 Hz, CH$_3$C$\underline{H}_2$O–), 6.82 (1H, d, J=2 Hz, arom H), 7.1—7.7 (6H, m, arom H), 8.2 (1H, b, exchanged with D$_2$O), 8.60 (1H, s, –C$\underline{H}$(OH)). MS *m/e*: 397 (M$^+$), 379 (100%). $FeCl_3$ (+).

Compounds **3b**—**e** listed in Table I were similarly prepared from the corresponding **1** and **2**.

2-Amino-8-chloro-10-(1,2-diethoxycarbonyl-2-hydroxyvinyl)-3,4-dihydro-6-phenyl-1,5-benzodiazocine (3f)——A solution of 500 mg (1.7 mmol) of **1a** and 0.4 ml (2.5 mmol) of diethyl acetylenedicarboxylate (**11a**) in MeOH (5 ml)–ether (5 ml) was stirred at room temperature for 15 min. The precipitate was collected by filtration and washed with ether to give colorless crystals (450 mg). IR ν_{max}^{KBr} cm^{-1}: 3400—2800, 1720—1610. NMR (DMSO-d_6) δ: 1.20 (3H, t, J=7 Hz, C$\underline{H}_3$CH$_2$O), 1.28 (3H, t, J=7 Hz, C$\underline{H}_3$CH$_2$O–), 2.8—4.0 (4H, m, –CH$_2$C$\underline{H}_2$–), 3.8—4.2 (4H, m, 2×CH$_3$C$\underline{H}_2$O–), 6.84 (1H, d, J=2 Hz, arom H), 7.2—7.6 (6H, m, arom H), 8.7—9.0 (1H, b, exchanged with D$_2$O). $FeCl_3$ (+).

Compounds **3g**—**i** listed in Table I were similarly prepared from the corresponding **1** and **11**.

2-Amino-8-chloro-3,4-dihydro-10-(2-ethoxy-1-ethoxycarbonylvinyl)-6-phenyl-1,5-benzodiazocine (7)——A solution of 250 mg of **3a** in saturated ethanolic hydrogen chloride (3 ml) was stirred at room temperature for 1 hr. The mixture was poured into aq. $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with H$_2$O, dried and concentrated to give **7** as colorless crystals (235 mg, 88%), mp 155—157°. Recrystallization from ether gave colorless needles, mp 162—164°. *Anal.* Calcd. for $C_{23}H_{24}ClN_3O_3$: C, 64.85; H, 5.67; N, 9.86. Found: C, 64.61; H, 5.47; N, 9.81. IR ν_{max}^{KBr} cm^{-1}: 3450, 3070, 2950, 1703, 1660—1610. NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz, C$\underline{H}_3$CH$_2$O–), 1.32 (3H, t, J=7 Hz, C$\underline{H}_3$CH$_2$O–), 2.5—3.0 (2H, m, –CH$_2$–), 3.4—3.9 (2H, m, –CH$_2$–), 3.9—4.3 (4H, m, 2×–CH$_2$–), 4.62 (2H, b, NH$_2$), 6.78 (1H, d, J=2 Hz, arom H), 7.3—7.7 (6H, m, arom H), 7.47 (1H, s, =C$\underline{H}$(OC$_2$H$_5$)). $FeCl_3$ (–).

2-Amino-7-chloro-9-(1,2-diethoxycarbonyl-2-hydroxyvinyl)-5-phenyl-3*H*-1,4-benzodiazepine (14a)——A stirred and ice-cooled solution of 2.0 g (7.0 mmol) of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine 1-oxide (**13a**)[1] in 50 ml of MeOH was treated with 2.0 ml (12.5 mmol) of **11a**. The mixture was stirred for 15 min, then the precipitate was collected by filtration and washed with MeOH and ether to give colorless crystals (2.5 g). IR ν_{max}^{KBr} cm^{-1}: 3400—3100, 3100—2800, 1720—1610. NMR (DMSO-d_6) δ: 1.14 (3H, t, J=7 Hz, C$\underline{H}_3$CH$_2$O–), 1.25 (3H, t, J=7 Hz, C$\underline{H}_3$CH$_2$O–), 3.7—4.3 (4H, m, 2×CH$_3$C$\underline{H}_2$O–), 3.5—5.1 (2H, b, –CH$_2$–), 6.90 (1H, d, J=2 Hz, arom H), 7.2—7.7 (6H, m, arom H), 9.2—9.5 (1H, b, exchanged with D$_2$O). $FeCl_2$ (+).

2-Amino-7-chloro-9-(1,2-dimethoxycarbonyl-2-hydroxyvinyl)-5-(4-methoxyphenyl)-3*H*-1,4-benzodiazepine (14b)——A solution of 200 mg (0.6 mmol) of 2-amino-7-chloro-5-(4-methoxyphenyl)-3*H*-1,4-benzodiazepine 1-oxide (**13b**)[1] and 0.20 ml (1.6 mmol) of dimethyl acetylenedicarboxylate (**11b**) in 4 ml of MeOH was stirred at room temperature for 15 min. The precipitate was collected by filtration and washed

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15) All melting points were determined with a Yanagimoto micro melting point apparatus (a hot-stage type) and are uncorrected. IR spectra were measured on a Hitachi 215 spectrophotometer, NMR spectra on a Varian T-60 (60 MHz) or a Varian HA-100 (100 MHz) spectrometer using tetramethylsilane as an internal standard, ultraviolet (UV) spectra on a Perkin Elmer 450 spectrophotometer, and mass spectra (MS) on a Hitachi RMS-4 single-focussing mass spectrometer with a direct sample inlet system. The following abbreviations are used; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and b=broad. Extracted solutions were dried over Na_2SO_4.

with MeOH and ether to give colorless crystals (190 mg). IR ν_{max}^{KBr} cm^{-1}: 3400—3100, 3100—2800, 1715, 1680—1640. NMR (DMSO-d_6) δ: 3.46, 3.62, 3.76 (each 3H, s, $CH_3\times3$), 3.75 (1H, $C_{(3)}H$, overlapped with H_2O), 4.74 (1H, d, J=11 Hz, $C_{(3)}H$), 6.93, 7.44 (each 2H, d, J=9 Hz, arom H), 7.10, 7.54 (each 1H, d, J=2 Hz, arom H), 9.3—9.7 (1H, b, exchanged with D_2O). $FeCl_3$ (+).

2-Amino-8-chloro-3,4-dihydro-10-ethoxycarbonylmethyl-6-phenyl-1,5-benzodiazocine (4a)——a) From **3a**: A suspension of 2.0 g (5.0 mmol) of **3a** in 80 ml of EtOH was refluxed for 30 min. After removal of the solvent, the crystalline residue was collected by filtration and washed with ether to give colorless crystals (1.75 g, 94%), mp 191—192°. Recrystallization from ether gave colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 3370, 3120, 1720, 1660. NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$–), 2.6—2.8 (2H, m, $-C_{(3)}H_2$–), 3.38, 3.77 (each 1H, d, J=16 Hz, $-CH_2CO$–), 3.3—4.0 (2H, m, $-C_{(1)}H_2$–), 4.12 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$–), 4.75 (2H, b, NH_2), 6.80 (1H, d, J=2 Hz, arom H), 7.18 (1H, d, J=2 Hz, arom H), 7.2—7.7 (5H, m, arom H). MS *m/e*: 369 (M^+).

When the mother liquor was concentrated and the residue was purified by column chromatography on silica gel (10 g) using hexane–acetone (3: 2, v/v) as an eluent, compound **6** (*vide infra*) was obtained as colorless crystals (18 mg, 1%), mp 165—166°.

b) From **3f**: A suspension of 235 mg (0.5 mmol) of **3f** in 25 ml of EtOH was refluxed for 30 min. Removal of the solvent gave colorless crystals (160 mg, 87%), mp 192—193°. The IR spectrum was identical with that of **4a** obtained in a).

Compounds **4b**—**h** listed in Table II were similarly prepared from the corresponding **3**.

2-Amino-7-chloro-9-ethoxycarbonylmethyl-5-phenyl-3*H*-1,4-benzodiazepine (15a)——A suspension of 220 mg of **14a** in 20 ml of EtOH was refluxed for 30 min. Removal of the solvent gave colorless crystals (135 mg, 80%). Recrystallization from MeOH gave colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 3400, 3120, 1723, 1640. NMR (DMSO-d_6) δ: 1.18 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$–), 3.30 (2H, s, $-CH_2CO$–), 3.72 (2H, b, NH_2), 4.04 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$–), 4.2—5.0 (2H, b, $-CH_2$–), 6.97 (1H, d, J=2 Hz, arom H), 7.37 (1H, d, J=2 Hz, arom H), 7.41 (5H, s, arom H).

Compound **15b** was similarly prepared from **14b** (Table II).

2-Amino-8-chloro-10-ethoxycarbonylmethyl-6-phenyl-3,4,5,6-tetrahydro-1,5-benzodiazocine (5)——A solution of 200 mg of **4a** in 15 ml of MeOH was treated with 100 mg of $NaBH_4$. The mixture was stirred for 15 min then partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ layer was separated, washed with H_2O, dried and concentrated to give **5** as colorless crystals (180 mg, 90%). Recrystallization from acetone gave colorless crystals, mp 218—219°. *Anal.* Calcd. for $C_{20}H_{22}ClN_3O_2$: C, 64.59; H, 5.96; N, 11.29. Found: C, 64.92; H, 5.93; N, 11.40. IR ν_{max}^{KBr} cm^{-1}: 3470, 3320, 3100, 1720, 1655. NMR (DMSO-d_6) δ: 1.14 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$–), 1.5—3.4 (4H, m, $-CH_2CH_2$–), 3.25 (2H, b, NH_2), 3.40, 3.63 (each 1H, d, J=16 Hz, $-CH_2CO$–), 3.96 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$–), 4.32 (1H, s, $-C_{(6)}H$–), 6.24 (1H, s, $-N_{(5)}H$–), 6.38 (1H, d, J=2 Hz, arom H), 6.92 (1H, d, J=2 Hz, arom H), 7.18 (5H, s, arom H).

2-(2-Aminoethyl)-6-chloro-8-ethoxycarbonylmethyl-4-phenylquinazoline (6)——Compound **4a** (150 mg) was added to 5 ml of saturated ethanolic hydrogen chloride. The mixture was refluxed for 1 hr, poured into saturated aq. $NaHCO_3$ and extracted with AcOEt. The extract was washed with H_2O, dried and concentrated to give **6** as colorless crystals (120 mg, 80%). Recrystallization from ether-hexane gave colorless needles, mp 78—79°. *Anal.* Calcd. for $C_{20}H_{20}ClN_3O_2$: C, 64.94; H, 5.45; N, 11.36. Found: C, 65.13; H, 5.37; N, 11.32. IR ν_{max}^{KBr} cm^{-1}: 3400, 1735. NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$–), 1.66 (2H, b, NH_2), 3.29 (4H, s, $-C\underline{H}_2C\underline{H}_2NH_2$), 4.18 (2H, s, $-CH_2CO$–), 4.18 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$–), 7.4—7.8 (6H, m, arom H), 7.92 (1H, d, J=2 Hz, arom H). UV λ_{max}^{EtOH} nm (ε): 234 (44100), 272 (sh), 330 (6100).

3-[α-(5-Chloro-3-ethoxycarbonyl-7-indolyl)benzylidcneamino]propionitrile (9a)——a) From **3a**: A suspension of 2.10 g (53 mmol) of **3a** in 40 ml of dry pyridine was heated at 100° for 1.5 hr. After removal of the solvent, the residue was treated with ether to give **9a** as colorless crystals (2.0 g, quantitative). Recrystallization from acetone–hexane gave colorless needles, mp 164—165°. *Anal.* Calcd. for $C_{21}H_{18}ClN_3O_2$: C, 66.40; H, 4.77; N, 11.06. Found: C, 66.57; H, 4.53; N, 11.04. IR ν_{max}^{KBr} cm^{-1}: 3370, 2240, 1710. NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$–), 2.69, 3.60 (each 2H, t, J=6 Hz, $=NCH_2CH_2CN$), 4.36 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$–), 6.79 (1H, d, J=2 Hz, arom H), 7.1—7.6 (5H, m, arom H), 8.01 (1H, d, J=2 Hz, $C_{(2)}H$, collapsed to singlet on addition of D_2O), 8.44 (1H, d, J=2 Hz, arom H), 10.8 (1H, b, $N_{(1)}H$). MS *m/e*: 379 (M^+).

b) From **7**: A solution of 40 mg of **7** in 0.7 ml of pyridine was heated at 95° for 2 hr. After removal of the solvent, the residue was treated with ether to give **9a** as colorless crystals (20 mg, 56%). mp 162—163°. The IR spectrum was identical with that of **9a** obtained in a).

7-Benzoyl-5-chloro-3-ethoxycarbonylindole (10a)——A suspension of 2.0 g (53 mmol) of **9a** and 4 ml of conc. HCl in 50 ml of EtOH was refluxed for 15 min. After removal of the solvent, the crystalline residue was collected by filtration and washed with H_2O and EtOH to give colorless crystals (1.72 g, 99.5%), mp 174—175°. Recrystallization from EtOH gave colorless needles. IR ν_{max}^{KBr} cm^{-1}: 3295, 1700, 1632. NMR ($CDCl_3$) δ: 1.46 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$–), 4.42 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$–), 7.4—7.8 (6H, m, arom H), 8.02 (1H, d, J=3 Hz, $C_{(2)}H$, collapsed to a singlet on addition of D_2O), 8.44 (1H, d, J=2 Hz, arom H), 10.8 (1H, b, $N_{(1)}H$).

Compounds **10b**—**e** listed in Table III were prepared by heating the corresponding **3** in pyridine followed by hydrolysis of the oily 3-(α-indolylbenzylideneamino)propionitriles (**9**) with hydrochloric acid.

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