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Heterocycles. XIV.[1] Reactions of 2-Amino-5-phenyl-1,4-benzodiazepines and 2-Amino-6-phenyl-1,5-benzodiazocines with Diketene[2]

HIDEAKI NATSUGARI, KANJI MEGURO, and YUTAKA KUWADA

Central Research Division, Takeda Chemical Industries, Ltd.[3]

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The reaction of 2-amino-1,5-benzodiazocines (**1**) with diketene (**2**) gave two isomeric products **3** and **4**, whereas 2-amino-1,4-benzodiazepines (**16**) afforded 2-acetoacetamidodiazepines (**17**). Treatment of the acetoacetylated derivatives (**3**, **4**, **17**) with methanolic hydrogen chloride or thionyl chloride afforded the corresponding fused pyrimidine derivatives (**5**, **6**, **18**). Thermal dehydration of both **3a** and **4a**, on the other hand, gave the same cyclized compound (**5a**), indicating that acyl migration took place in the reaction of **4a**. Similarly, **17a** gave the rearranged product (**19a**).

Keywords——1,4-benzodiazepines; 1,5-benzodiazocines; diketene; pyrimido[1,2-*a*]-[1,4]benzodiazepines; pyrimido[1,2-*a*][1,5]benzodiazocines; amidine; acyl migration

Since the synthesis of 8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine[4] (estazolam), which was found to have depressive activities on the central nervous system superior to those of the known 1,4-benzodiazepines, our interest in seven- and eight-membered heterocycles has been focused on the synthesis of tricyclic compounds fused onto the "*a*" face of these heterocycles. In previous papers, syntheses and some reactions of 2-amino-1,4-benzodiazepines (**16**)[5] and 2-amino-1,5-benzodiazocines (**1**)[6] were reported, and our attention has also been directed to the high reactivity of their amidine moieties.

The amidine moiety is useful for the syntheses of various heterocycles. A typical example is the synthesis of fused pyrimidine derivatives from cyclic amidines by reaction with diketene (**2**).[7]

Kato *et al.*[7a] reported that the reaction of 2-aminopyridine (**A**) with **2** gave 2-acetoacetamidopyridine (**B**) as the major product and 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**E**) as a minor product, while it has been reported[8] that treatment of **B** with sulfuric acid gave **E** through dehydration accompanied by rearrangement (Chart 1). Interesting discussions[9] have also appeared concerning the structures of these products, which prompted us to investigate the reactions of **1** and **16** with **2**.

1) Part XIII: H. Natsugari and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), **27**, 2618 (1979).
2) A part of this work was presented at the 93rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1973, and is described in the following patent applications: Japan Patent Application 83476 (1971), 2722 (1972), and 115761 (1972).
3) Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*
4) K. Meguro and Y. Kuwada, *Tetrahedron Lett.*, **1970**, 4039; *idem*, *Chem. Pharm. Bull.* (Tokyo), **21**, 2375 (1973).
5) *a*) K. Meguro, H. Tawada, and Y. Kuwada, *Yakugaku Zasshi*, **93**, 1253 (1973); *b*) K. Meguro, H. Natsugari, H. Tawada, and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), **21**, 2366 (1973).
6) H. Natsugari, K. Meguro, and Y. Kuwada, *Chem. Pharm. Bull.* (Tokyo), **27**, 2589 (1979).
7) *a*) T. Kato, H. Yamanaka, T. Niitsuma, K. Wagatsuma, and M. Oizumi, *Chem. Pharm. Bull.* (Tokyo), **12**, 74 (1964); *b*) T. Kato, T. Chiba, and M. Daneshtalab, *Heterocycles*, **3**, 723 (1975).
8) R. Adams, *J. Am. Chem. Soc.*, **74**, 5491 (1952).
9) *a*) G. Stöckelmann, H. Specker, and W. Riepe, *Chem. Ber.*, **102**, 455 (1969); *b*) T. Kato, H. Yamanaka, N. Katagiri, and S. Masuda, *Chem. Pharm. Bull.* (Tokyo), **20**, 142 (1972); *c*) H.L. Yale, B. Toeplitz, J.Z. Gougoutas, and M. Puar, *J. Heterocyclic Chem.*, **10**, 123 (1973); *d*) H.L. Yale and E.R. Spitzmiller, *ibid.*, **14**, 637 (1977).

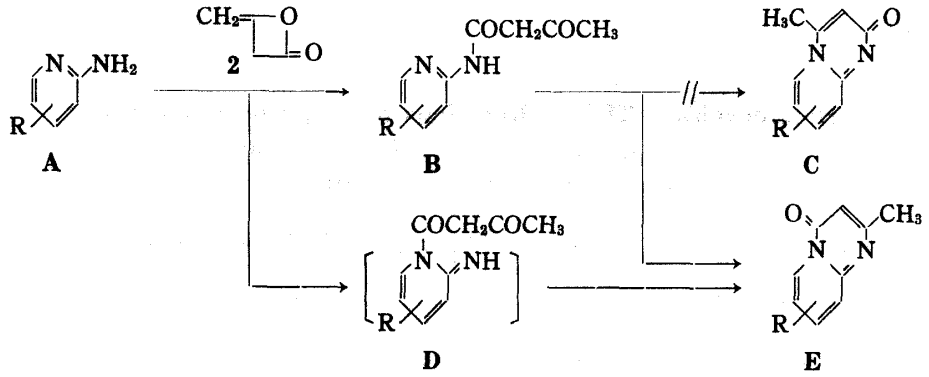


Chart 1

When 2-amino-8-chloro-3,4-dihydro-6-phenyl-1,5-benzodiazocine (**1a**) was allowed to react with **2** in benzene at room temperature, two isomeric products, **3a** (68%) and **4a** (31%), were obtained. The empirical formulae of both compounds correspond to that of a 1:1 adduct of **1a** and **2**. In the infrared (IR) spectra, **3a** showed two strong and sharp absorption bands at 1720 and 1660 cm^{-1}, whereas **4a** showed a strong and broad band at 1740—1620 cm^{-1}.

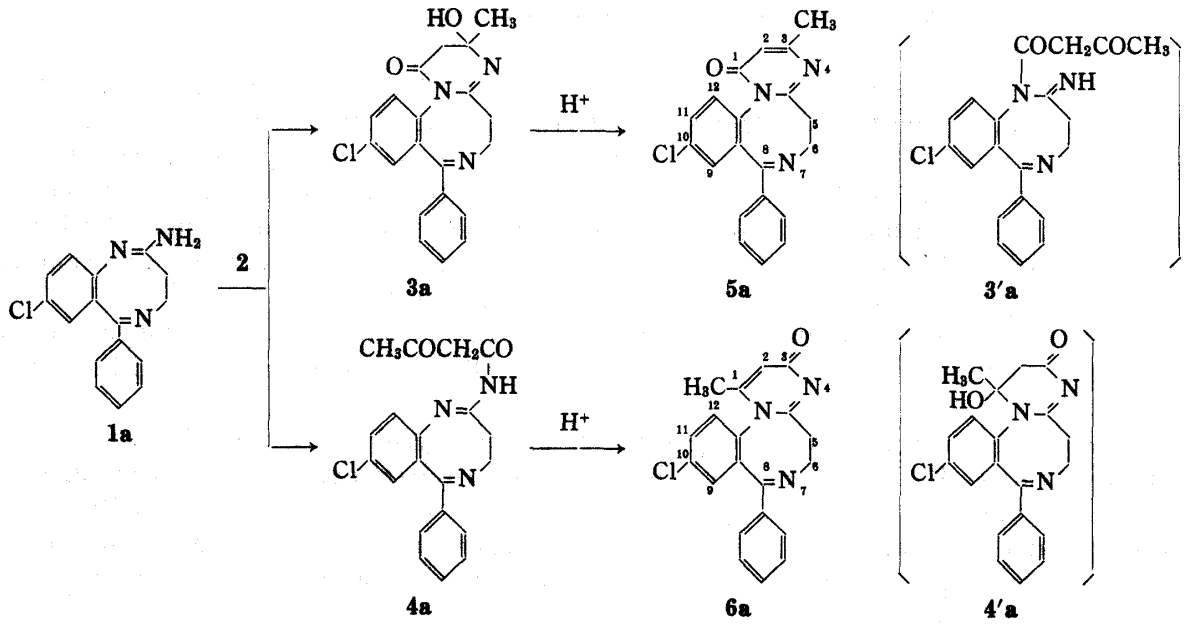


Chart 2

When **3a** and **4a** were treated with methanolic hydrogen chloride, with cooling, the dehydrated products **5a** and **6a** were obtained in 90% and 77% yields, respectively. Carbonyl stretching vibrations of **5a** and **6a** appeared at 1683 cm^{-1} and 1643 cm^{-1}, respectively; these values are compatible with those reported[9b] for pyrido[1,2-*a*]pyrimidin-4-ones (over 1675 cm^{-1}) and -2-ones (below 1657 cm^{-1}). The lower shift of the absorption band of **6a** is attributable to the conjugation of the carbonyl group with two double bonds.[10] The nuclear magnetic resonance (NMR) spectra of **5a** and **6a**, however, did not clearly differentiate their structures. No anisotropy effect of the carbonyl group at the $C_{(12)}$-proton was observed in **5a**, indicating lack of coplanarity of the carbonyl group and the adjacent benzene ring. The following chemical transformations were carried out to investigate the possibility of attaining coplanarity (Chart 3).

10) A. Le Berre and C. Renault, *Bull. Soc. Chim. France*, **1969**, 3139.

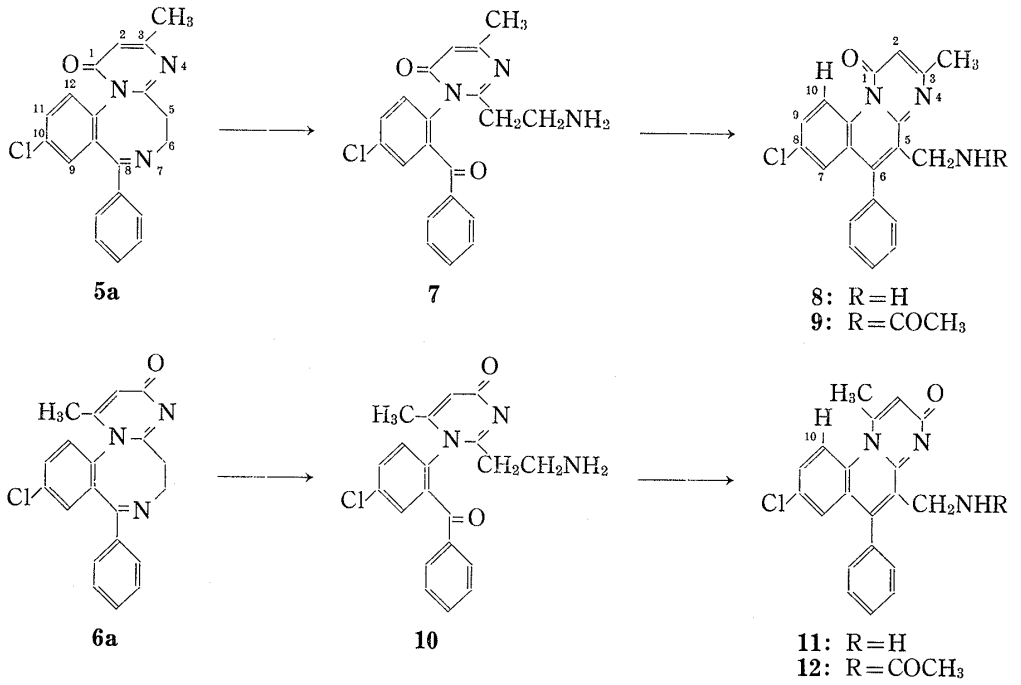


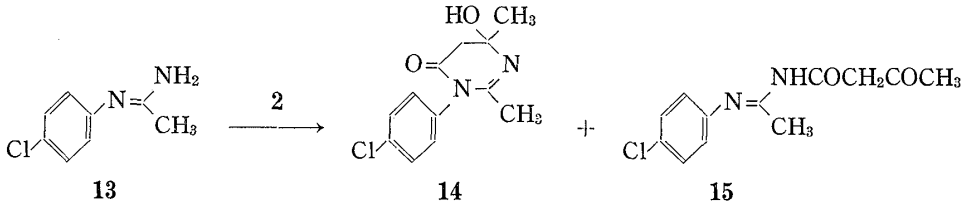
Chart 3

When **5a** was heated in dilute methanolic hydrogen chloride, the $C_{(8)}=N_{(7)}$ bond was cleaved to give **7**. Treatment of **7** with methanolic hydrogen chloride under more vigorous conditions afforded the 5-aminomethylpyrimido[1,2-*a*]quinolin-1-one (**8**); mp 220—221°, IR: 1680 cm^{-1}. Acetylation of **8** gave the 5-acetamidomethyl derivative (**9**); mp 287—289°, IR: 1680 (shoulder), 1670 cm^{-1}. Similarly, **6a** was transformed to the pyrimido[1,2-*a*]quinolin-3-one derivatives **11** (powder, IR: 1650 cm^{-1}) and **12** (mp 290—292°, IR: 1650 cm^{-1}) *via* the ring-opened compound (**10**). While the NMR spectra of **11** and **12** showed all the aromatic protons as indistinguishable multiplets at about 7.2 to 7.8 ppm, those of **8** and **9** gave clear signals of their $C_{(10)}$-protons as isolated doublets at much lower fields, 9.78 ppm (J=9 Hz) and 9.60 ppm (J=9 Hz), respectively. Thus, **5a** was confirmed to be the 1-one and **6a** to be the 3-one isomer.

Their precursors **3a** and **4a** were therefore shown to have structures with the acetoacetyl moiety on the $N_{(1)}$ and $C_{(2)}$-amino group, respectively. Compound **4a** showed a typical keto-enol character (about 5: 1) as exemplified by a positive ferric chloride ($FeCl_3$) test and the following NMR spectral data ($CDCl_3$, ppm): 1.95 (*ca.* 0.5 H, singlet, $C\underline{H}_3$ (OH)C=), 2.20 (*ca.* 2.5 H, singlet, CH_3CO–), 3.57 (*ca.* 1.6 H, singlet, –$COCH_2CO$–. exchanged with D_2O), and 5.10 (*ca.* 0.2 H, singlet, –$C\underline{H}$=C(OH)–, exchanged with D_2O). These results ruled out the alternative cyclic structure **4'a**.

Compound **3a**, on the other hand, was negative to $FeCl_3$, suggesting that a cyclic structure is more likely than the normal 1-acetoacetyl structure **3'a**. The NMR spectrum of **3a** exhibited a completely different pattern from that of **4a**. Although the $C_{(2)}$-methylene signal was not assigned because it appeared as a multiplet overlapping the $C_{(5)}$ and $C_{(6)}$-ethylene signals (2.4—3.5 ppm), the methyl protons appeared as two peaks with a relative intensity of 3: 1 at higher magnetic fields (0.95 ppm and 1.45 ppm, respectively) than those of **4a**. This unusual pattern of methyl signals may be rationalized by assuming the presence of conformational isomers,[11] although the spectrum was substantially unchanged even at elevat-

11) *a*) E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, "Conformational Analysis," Wiley-Interscience, New York, 1967, p. 243; *b*) B. Binsch, "Topics in Stereochemistry," Vol. 3, ed. by E.L. Eliel and N.L. Allinger, Wiley-Interscience, New York, 1968, p. 97; *c*) J.B. Lambert, "Topics in Stereochemistry," Vol. 6, ed. by E.L. Eliel and N.L. Allinger, Wiley-Interscience, New York, 1971, p. 19.



13 14 15

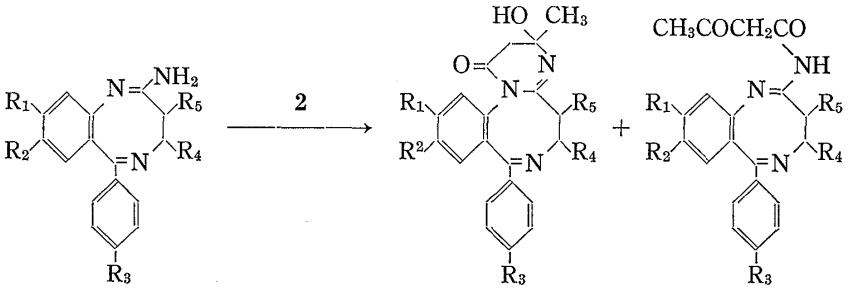
Chart 4

ed temperatures (up to *ca.* 80°[12]).

To resolve this ambiguity, the reaction of N-*p*-chlorophenylacetamidine (**13**), which has a partial structure of **1a**, with **2** was carried out as a model experiment (Chart 4). Two isomers, **14** (76%) and **15** (6%), were obtained. Compound **14** had characteristics very similar to those of **3a**; $FeCl_3$ (−), IR: 1720, 1660 cm^{-1}. Its NMR spectrum was compatible with the cyclic structure **14**, but the conformational isomer was not observed: 1.52, 1.86 ppm (each 3 H, singlet, $-CH_3\times2$), 2.83 ppm (2 H, singlet, $-CH_2-$), 4.5 ppm (1 H, broad, –OH), and 7.02, 7.40 ppm (each 2 H, doublet, $J=8$ Hz, aromatic protons). The unusual NMR behavior of **3a** may therefore be attributed to the sterically fixed tricyclic structure. The minor product **15** was closely related to **4a**; $FeCl_3$ (+), IR: 1635 cm^{-1} (broad, strong). Its NMR spectrum showed signals due to an acetoacetyl group (keto-enol=2.3:1), indicating that **15** is N-acetoacetyl-N′-*p*-chlorophenylacetamidine.

Other 2-amino-1,5-benzodiazocines (**1**) gave corresponding adducts (**3b—f** and **4b—f**) (Table I) on reaction with **2**. In these reactions compounds **3** were always major products regardless of the substituents of **1**. In the NMR spectra of **3b—f**, the $C_{(2)}$-methyl protons and $C_{(2)}$-methylene protons showed patterns similar to those observed with **3a**. The corre-

Table I. Reaction of 2-Amino-3,4-dihydro-6-phenyl-1,5-benzodiazocines (**1**) with Diketene (**2**)



1 3 4

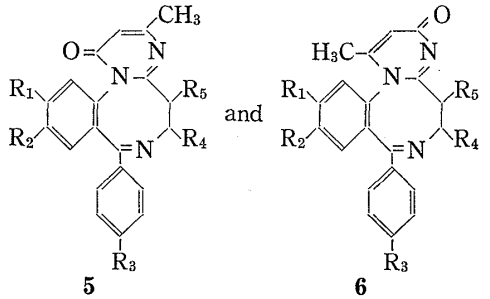
	R_1	R_2	R_3	R_4	R_5	**3**[a] mp[c] (°C)	**3**[a] Yield (%)	**4**[b] mp[c] (°C)	**4**[b] Yield (%)
a	H	Cl	H	H	H	149—150	68	158—159	31
b	H	H	H	H	H	130—132[d]	63	104—105	30
c	H	CH_3	H	H	H	155—156	68	149—150	27
d	CH_3O	CH_3O	H	H	H	160—162	72	—[e]	20
e	H	Cl	H	CH_3	H	155—157	51	—[e]	38
f	H	Cl	Cl	H	CH_3	142—144	38	152—154	28

a) Showed a negative $FeCl_3$ test.
b) Showed a positive $FeCl_3$ test.
c) Satisfactory elementary analyses (±0.4% for C, H, N) were obtained for the crystalline compounds listed herein.
d) Solvated with one-half mole of benzene.
e) Obtained as an oily product and used without purification in the subsequent reaction.

12) Decomposition occurs above this temperature (*vide infra*).

sponding pyrimido[1,2-*a*][1,5]benzodiazocin-1-ones (**5b—f**) and -3-ones (**6b—f**) (Table II) were also prepared from the adducts **3** and **4**, respectively. Transformation of **3f** to **5f** was carried out using thionyl chloride as a dehydrating agent. Among these compounds, **6e** and **6f** exhibited two sets of signals of $C_{(1)}$-methyl, $C_{(2)}$-olefin and $C_{(5\ or\ 6)}$-methyl protons in their NMR spectra with relative intensities of about 1:1 and 2:3, respectively (see "Experimental"). These findings suggest that conformational isomers are also present in **6e** and **6f**, as in the case of **3a**.[13]

TABLE II. Pyrimido[1,2-*a*][1,5]benzodiazocin-1-ones (**5**) and -3-ones (**6**)



5 **6**

	R_1	R_2	R_3	R_4	R_5	**5** mp (°C)	**5** Yield (%)	**5** IR $\nu_{C=O}$ (cm^{-1} in KBr)	**5** NMR ($C_{(2)}$–H) (ppm in $CDCl_3$)	**6** mp (°C)	**6** Yield (%)	**6** IR $\nu_{C=O}$ (cm^{-1} in KBr)	**6** NMR ($C_{(2)}$–H) (ppm in $CDCl_3$)
a	H	Cl	H	H	H	184—185	90[a] (36,[b] 32[c])	1683	6.10	263—265	77[a]	1643	5.86
b	H	H	H	H	H	169—170	83[a]	1690	6.10	265—267	75[a]	1640	5.89
c	H	CH_3	H	H	H	150—152	91[a]	1682	6.10	239—240	74[a]	1650	5.85
d	CH_3O	CH_3O	H	H	H	195—196	90[a]	1690	6.12	259—260	69[a]	1645	5.80
e	H	Cl	H	CH_3	H	191—193	89[a]	1685	6.12	271—273	80[a]	1645	5.76, 5.88[d]
f	H	Cl	Cl	H	CH_3	214—215	62[e]	1680	6.06	274—275	52[a]	1650	5.86 5.88[d]

	Formula	Analysis (%) Calcd. C	H	N	Found **5** C	H	N	Found **6** C	H	N
a	$C_{20}H_{16}ClN_3O$	68.67	4.61	12.01	68.65	4.52	11.93	68.39	4.65	11.69
b	$C_{20}H_{17}N_3O$	76.17	5.43	13.33	75.90	5.28	13.25	76.08	5.26	13.19
c	$C_{21}H_{19}N_3O$	76.57	5.81	12.76	76.71	5.80	12.81	76.57	5.75	12.99
d	$C_{22}H_{21}N_3O_3$	70.38	5.64	11.19	70.05	5.58	11.11			
	$C_{22}H_{21}N_3O_3 \cdot 1/2C_3H_6O$[f]	69.78	5.98	10.38				69.44	5.90	10.38
e	$C_{21}H_{18}ClN_3O$	69.32	4.98	11.54	69.38	4.96	11.60	69.53	4.95	11.50
f	$C_{21}H_{17}Cl_2N_3O$	63.32	4.30	10.55	63.04	4.21	10.46	63.04	3.98	10.52

a) By reaction with methanolic hydrogen chloride.
b) By thermolysis of **3a**.
c) By thermolysis of **4a**.
d) For other signals, see "Experimental."
e) By reaction of **3f** with $SOCl_2$.
f) Solvated with one-half mol of acetone.

13) The NMR spectrum ($CDCl_3$) of **6e** was substantially unchanged at elevated temperatures up to *ca.* 80°, indicating the presence of a high energy barrier between the conformers.

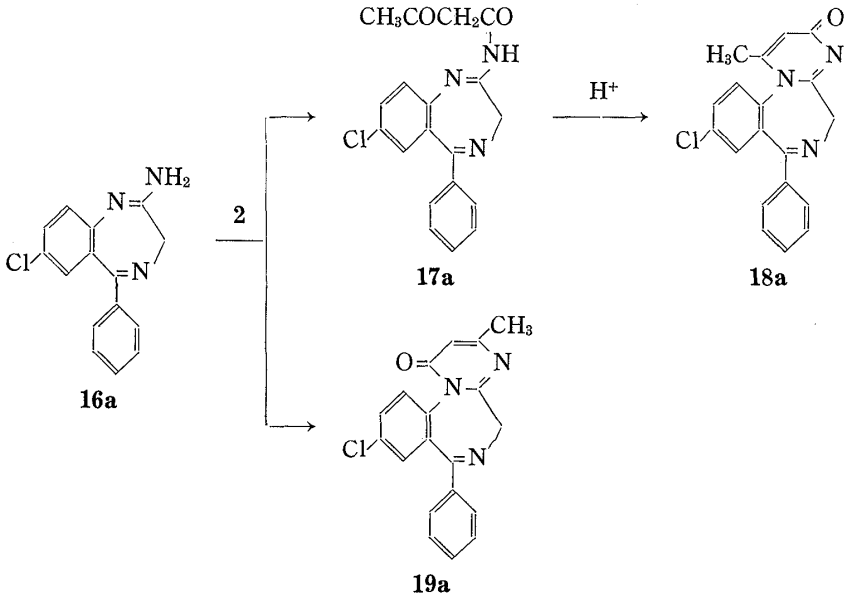
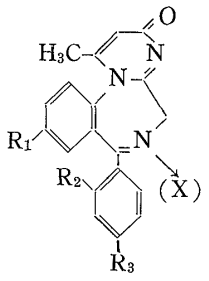


Chart 5

TABLE III. Pyrimido[1,2-*a*][1,4]benzodiazepin-3-ones (**18**)



18

Compd.	R_1	R_2	R_3	X	mp (°C)	Yield (%)	IR $\nu_{C=O}$ (cm^{-1} in KBr)	NMR ($C_{(2)}$–H) (ppm)	Formula	Analysis (%) Calcd. (Found) C	H	N
18a	Cl	H	H	—	232—234	89[a]	1650	6.03[b]	$C_{19}H_{14}ClN_3O$	67.96 (67.98	4.20 4.18	12.51 12.45)
18b	H	H	H	—	192—193	75[c]	1645	6.08[b]	$C_{19}H_{15}N_3O$	75.73 (75.69	5.02 4.93	13.95 13.93)
18c	CH_3	H	H	—	205—207	95[c]	1650	6.05[b]	$C_{20}H_{17}N_3O$	76.17 (75.83	5.43 5.55	13.33 13.24)
18d	Cl	H	OCH_3	—	249—250	75[c]	1640	6.03[b]	$C_{20}H_{16}N_3O_2$	65.66 (65.72	4.41 4.54	11.49 11.24)
18e	Cl	Cl	H	—	169—171	62[c]	1640	6.15[b]	$C_{19}H_{13}Cl_2N_3O \cdot 1/2H_2O$[d]	60.17 (59.85	3.72 3.68	11.08 10.98)
18f	Cl	H	H	0	243—245	97[a]	1640	6.15[e]	$C_{19}H_{14}ClN_3O_2$	64.87 (64.64	4.01 3.93	11.94 11.59)
18g	CF_3	H	H	0	250—251	74[a]	1660	6.04[b]	$C_{20}H_{14}F_3N_3O_2$	62.34 (61.94	3.66 3.61	10.90 11.09)
18h	NO_2	H	H	0	240—242	34[a]	1648	6.08[b]	$C_{19}H_{14}N_4O_4$	62.98 (62.93	3.89 3.74	15.46 15.10)

a) Based on the corresponding 2-acetoacetamido-1,4-benzodiazepine.
b) In $CDCl_3$ solution.
c) Overall yield based on the corresponding 2-amino-1,4-benzodiazepine.
d) MS *m/e*: 369 (M^+).
e) In DMSO-d_6 solution.

The reaction of 2-amino-1,4-benzodiazepines (**16**) with **2** was then investigated. When 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (**16a**) was allowed to react with **2** in chloroform at room temperature, the 2-acetoacetamido-1,4-benzodiazepine (**17a**) was obtained in 92% yield. The pyrimidodiazepine (**19a**) was also isolated in poor yield (1.3%), but its precursor, a 1-acetoacetylated derivative, was not obtained. Compound **17a** gave a positive $FeCl_3$ test and showed a broad and strong absorption band at 1630 cm^{-1} in the IR spectrum. The NMR spectrum of **17a** showed signals attributable to an acetoacetyl group (keto–enol=3.5:1). When **17a** was treated with methanolic hydrogen chloride, with cooling, the pyrimido[1,2-*a*][1,4]benzodiazepine (**18a**), which is isomeric with **19a**, was obtained in good yield (89%). Compound **18a** showed a carbonyl absorption at 1650 cm^{-1} in the IR spectrum and a $C_{(2)}$-olefin proton at 6.03 ppm in the NMR spectrum, while **19a** showed the carbonyl absorption and $C_{(2)}$-olefin proton at 1690 cm^{-1} and 6.25 ppm, respectively. By comparison of these data with those for compounds **3**—**6** the structures of **17a**, **18a** and **19a** were established as shown in Chart 5.

The reaction of 2-amino-1,4-benzodiazepines bearing various substituents (**16b**—**h**) with **2** also gave the corresponding 2-acetoacetamidodiazepines (**17b**—**h**) in good yields.[14] On treatment with methanolic hydrogen chloride, with cooling, **17b**—**h** afforded the corresponding pyrimido[1,2-*a*][1,4]benzodiazepin-3-ones (**18b**—**h**) in good yields (Table III).

It was noticed that heating of the acetoacetyl derivatives **3**, **4**, and **17** during recrystallization caused decomposition into two or three components. When **3a** was heated in dry

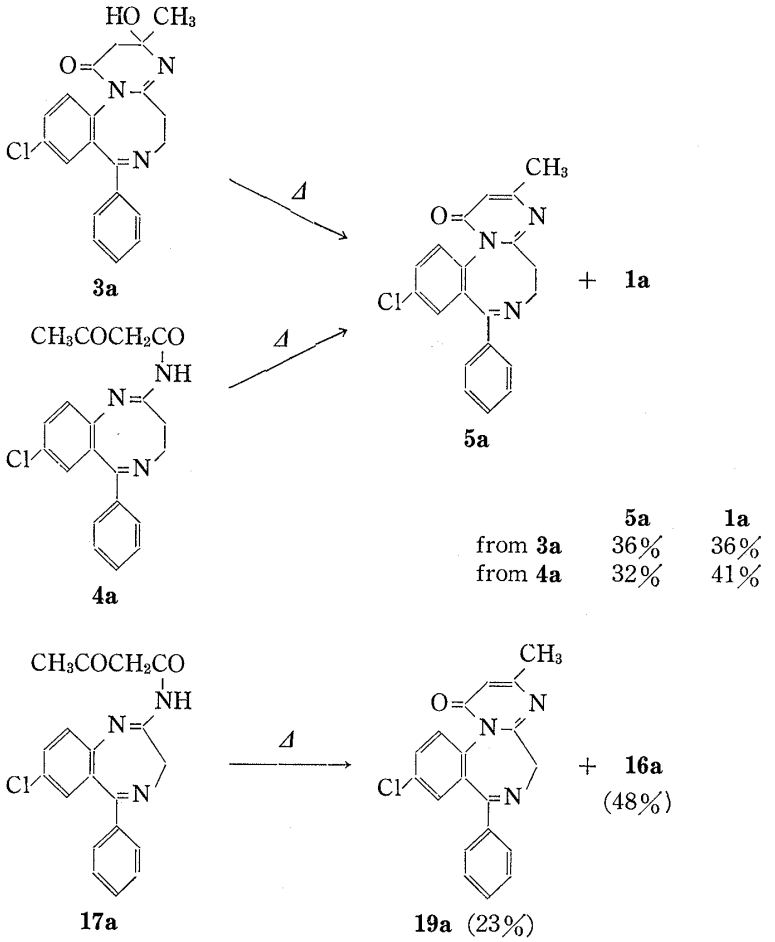


Chart 6

14) Isolation of the pyrimidobenzodiazepin-1-ones (**19**) was not attempted.

toluene, for example, **5a** (36%) and **1a** (36%) were obtained together with a small amount of **4a** (3%). On the other hand, **4a** unexpectedly gave the same products, **5a** and **1a**, in almost the same yields (32% and 41%, respectively) under similar conditions. Formation of the 3-one derivative (**6a**) could not be detected in this reaction. These experimental results can be rationalized in terms of an equilibrium **3a**$\rightleftarrows$**4a** through migration of the acetoacetyl residue. In the equilibrium mixture only **3a** undergoes thermal cyclization, and the water generated causes the fission of the acetoacetyl moiety to give **1a**. A similar phenomenon was observed in the thermolysis of **17a**, and the rearranged dehydrated compound (**19a**, 23%)[15] and **16a** (48%) were obtained.

The compounds prepared in this study were screened for biological activities, especially on the central nervous system (CNS); the pyrimido[1,2-*a*][1,4]benzodiazepines (**18**, **19**) exhibited a considerable depressive activity on the CNS.

Experimental[16]

Reaction of 2-Amino-3,4-dihydro-6-phenyl-1,5-benzodiazocine (1) with Diketene (2) (Table I)——A typical procedure is described for the reaction of **1a** with **2**.

A suspension of 5.0 g (17 mmol) of 2-amino-8-chloro-3,4-dihydro-6-phenyl-1,5-benzodiazocine (**1a**)[6] in 120 ml of benzene was treated with 3.0 g (36 mmol) of **2** and the mixture was stirred for 1.5 hr. The precipitated product was collected by filtration and washed with hexane and ether to give 10-chloro-3-hydroxy-3-methyl-8-phenyl-2,3,4,6-tetrahydro-1*H*-pyrimido[1,2-*a*][1,5]benzodiazocin-1-one (**3a**) as colorless crystals (4.52 g, 68%), mp 149—150°. $FeCl_3$ (−). IR ν_{max}^{KBr} cm^{-1}: 3110, 1720, 1660. NMR ($CDCl_3$) δ: 0.95 (*ca.* 2.2H, s, CH_3–), 1.45 (*ca.* 0.8H, s, CH_3–), 2.4—3.5 (5H, m, $-C_{(2)}H_2-$ and $-C_{(5)}H_2-C_{(6)}H(H)-$), 4.1—4.4 (1H, m, $-C_{(6)}H(H)-$), 7.1—7.6 (8H, m, arom. H). NMR (DMSO-d_6) δ: 0.80 (*ca.* 2.3H, s, CH_3–), 1.34 (*ca.* 0.7H, s, CH_3–), 2.2—3.5 (5H, m, $-C_{(2)}H_2-$ and $-C_{(5)}H_2-C_{(6)}H(H)-$), 4.0—4.3 (1H, m, $-C_{(6)}H(H)-$), 7.2—7.7 (8H, m, arom. H). UV λ_{max}^{EtOH} nm (ε): 247 (24300).

The filtrate and washings were combined and concentrated. Treatment of the residue with hexane–ether gave crude 2-acetoacetamido-8-chloro-3,4-dihydro-6-phenyl-1,5-benzodiazocine (**4a**) as colorless crystals (2.07 g, 31%), mp 147—150°. A part of this material (500 mg) was purified by silica gel (20 g) chromatography using $CHCl_3$–MeOH–AcOEt (85: 10: 5, v/v) as an eluent to give pure **4a** as colorless needles (430 mg), mp 158—159°. $FeCl_3$ (+). IR ν_{max}^{KBr} cm^{-1}: 3125, 1740—1620. NMR ($CDCl_3$) δ: 1.95 [*ca.* 0.5H, s, $C\underline{H}_3$-(OH)C=], 2.20 (*ca.* 2.5H, s, CH_3CO–), 2.8—4.2 (4H, m, $-CH_2CH_2-$), 3.57 (*ca.* 1.6H, s, $-CH_2CO-$, exchanged with D_2O), 5.10 (*ca.* 0.2H, s, $-C\underline{H}$=C(OH)CH_3, exchanged with D_2O), 6.9—7.8 (8H, m, arom. H). keto-enol= 5: 1. UV λ_{max}^{EtOH} nm (ε): 235 (28200).

Other compounds (**3b**—**f** and **4b**—**f**) listed in Table I were similarly prepared from the corresponding **1b**—**f** and **2**.

5,6-Dihydro-3-methyl-8-phenyl-1*H*-pyrimido[1,2-*a*][1,5]benzodiazocin-1-ones (5)——Typical procedures are described for **5a** and **5f**.

10-Chloro-5,6-dihydro-3-methyl-8-phenyl-1*H*-pyrimido[1,2-*a*][1,5]benzodiazocin-1-one (5a)——Method A (Acid-catalyzed Dehydration): A stirred suspension of 3.6 g (10 mmol) of **3a** in 100 ml of MeOH was treated with 5 ml of saturated methanolic hydrogen chloride, cooling with ice-salt. After stirring for 30 min, the mixture was poured into a solution of conc. NH_4OH (10 ml)–H_2O (150 ml) with ice cooling and extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated to give colorless crystals (3.05 g, 90%). Recrystallization from CH_2Cl_2–hexane gave colorless prisms. NMR ($CDCl_3$) δ: 2.18 (3H, s, CH_3–), 2.7—3.6 (3H, m, $-C_{(5)}H_2-C_{(6)}H(H)-$), 4.25—4.55 (1H, m, $-C_{(6)}H(H)-$), 6.10 (1H, s, $-C_{(2)}H-$), 7.2—7.6 (8H, m, arom. H). UV λ_{max}^{EtOH} nm (ε): 252 (13500). MS *m/e*: 349 (M^+).

15) An independent synthesis of **19a** by the reaction of **16a** with **2** followed by thermal cyclization was reported from Upjohn Co., Ltd. (Japan Patent Spec. 932 (1972)). Although the structure of the intermediate acetoacetyl derivative was not given in their report, it may be the same as our **17a**.

16) 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 or a Hitachi EPI-S2 spectrophotometer, NMR spectra on a Varian A-60 (60 MHz), a Varian T-60 (60 MHz) or a Varian HA-100 (100 MHz) NMR spectrometer using tetramethylsilane as an internal standard, ultraviolet (UV) spectra on a Perkin-Elmer 450 spectrophotometer, and mass spectra 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, m=multiplet, b=broad, sh=shoulder. Extracted solutions were dried over sodium sulfate.

10-Chloro-8-(4-chlorophenyl)-5,6-dihydro-3,5-dimethyl-1*H*-pyrimido[1,2-*a*][1,5]benzodiazocin-1-one (5f)——Method B (Dehydration with Thionyl Chloride): A solution of 250 mg (0.6 mmol) of 10-chloro-8-(4-chlorophenyl)-3-hydroxy-3-methyl-2,3,5,6-tetrahydro-1*H*-pyrimido[1,2-*a*][1,5]benzodiazocin-1-one (**3f**) in 15 ml of $CHCl_3$ was treated with 0.3 ml (4.2 mmol) of $SOCl_2$ at 60° for 1 hr. After cooling, the mixture was washed with saturated aq. $NaHCO_3$ and H_2O, dried and concentrated. The residue was purified by chromatography on silica gel (10 g) using $CHCl_3$ as an eluent. Removal of the solvent gave colorless crystals (148 mg, 62%), mp 209—210°. Recrystallization from acetone–hexane gave colorless prisms. NMR ($CDCl_3$) δ: 1.12 (3H, d, $J=6$ Hz, $C_{(5)}HC\underline{H}_3$), 2.17 (3H, s, $C_{(3)}$–CH_3), 2.74, 4.10 (each 1H, t, $J=10$ Hz, $-C_{(6)}H(H)-$), 3.6—3.95 (1H, m, $C_{(5)}\underline{H}(CH_3)$), 6.06 (1H, s, $C_{(2)}H$), 7.1—7.6 (7H, m, arom. H).

Other compounds (**5b**—**e**) listed in Table II were similarly prepared from the corresponding **3b**—**e** by Method A.

5,6-Dihydro-1-methyl-8-phenyl-3*H*-pyrimido[1,2-*a*][1,5]benzodiazocin-3-ones (6)——A typical procedure is described for **6a**.

10-Chloro-5,6-dihydro-1-methyl-8-phenyl-3*H*-pyrimido[1,2-*a*][1,5]benzodiazocin-3-one (6a)——A stirred suspension of 1.20 g of **4a** was treated with 1.5 ml of saturated methanolic hydrogen chloride, cooling with ice-salt. After stirring for 30 min, the mixture was poured into a mixture of conc. NH_4OH (5 ml)–H_2O (75 ml) with ice cooling and extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated to give colorless crystals (880 mg, 77%). Recrystallization from CH_2Cl_2–benzene gave colorless prisms. NMR ($CDCl_3$) δ: 1.84 (3H, s, CH_3–), 2.7—3.8 (3H, m, $-C_{(5)}H_2-C_{(6)}H(H)-$), 4.3—4.7 (1H, m, $-C_{(6)}H(H)-$), 5.86 (1H, s, $-C_{(2)}H-$), 7.2—7.7 (8H, m, arom. H). UV λ_{max}^{EtOH} nm (ε): 252.5 (30300). MS *m/e*: 349 (M^+).

Other compounds (**6b**—**f**) listed in Table II were similarly prepared from the corresponding **4b**—**h**. In the NMR spectra of **6e** and **6f**, $C_{(1)}$-methyl, $C_{(2)}$-olefin and $C_{(5\text{ or }6)}$-methyl protons are observed as follows: **6e**; 1.19, 1.53 (each 1.5 H, d, $J=6$ Hz, $C_{(6)}$–CH_3), 1.73, 1.97 (each 1.5H, s, $C_{(1)}$–CH_3), 5.76, 5.88 (each 0.5H, s, $C_{(2)}$–H). **6f**; 1.13, 1.25 (1.2H, 1.8H, respectively, d, $J=6$ Hz, $C_{(5)}$–CH_3), 1.71, 1.88 (1.2H, 1.8H, respectively, s, $C_{(1)}$–CH_3), 5.86, 5.88 (0.4H, 0.6H, respectively, s, $C_{(2)}$–H).

2-(2-Aminomethyl)-1-(2-benzoyl-4-chlorophenyl)-4-methylpyrimidin-6(1*H*)-one (7)——A suspension of 1.16 g of **5a** in 30 ml of MeOH was treated with 3 ml of saturated methanolic hydrogen chloride, and the mixture was refluxed for 1.5 hr. After removal of the solvent, the residual crystals were collected by filtration and washed with acetone to give the dihydrochloride of **7** as colorless crystals (1.2 g, 82%). Recrystallization from MeOH–acetone gave colorless prisms, mp 180° (sinter)—245° (dec.). *Anal.* Calcd. for $C_{20}H_{18}ClN_3O_2\cdot 2HCl$: C, 54.49; H, 4.57; N, 9.53. Found: C, 54.17; H, 4.23; N, 9.43. A part of this material was partitioned between saturated aq. $NaHCO_3$ and CH_2Cl_2. The CH_2Cl_2 layer was separated, washed with H_2O, dried and concentrated. The residue was recrystallized from CH_2Cl_2–hexane to give colorless prisms, mp 144—145°. *Anal.* Calcd. for $C_{20}H_{18}ClN_3O_2$: C, 65.30; H, 4.93; N, 11.42. Found: C, 65.26; H, 4.83; N, 11.37. IR ν_{max}^{KBr} cm^{-1}: 1680, 1658. NMR ($CDCl_3$) δ: 1.57 (2H, b, $-NH_2$), 2.25 (3H, s, $-CH_3$), 2.5—2.8, 2.9—3.3 (each 2H, m, $-CH_2CH_2-$), 6.06 (1H, s, =CH–), 7.2—7.8 (8H, m, arom. H).

5-Aminomethyl-8-chloro-3-methyl-6-phenyl-1*H*-pyrimido[1,2-*a*]quinolin-1-one (8)——A mixture of 1.2 g of the dihydrochloride of **7** and 25 ml of saturated methanolic hydrogen chloride was refluxed for 4 hr. The precipitated crystals were collected by filtration, washed with MeOH and ether, and partitioned between 10% NH_4OH and $CHCl_3$. The $CHCl_3$ layer was separated, washed with H_2O, dried and concentrated to give pale yellow crystals (650 mg, 68%), mp 214—215°. Recrystallization from CH_2Cl_2–hexane gave pale yellow needles, mp 220—221°. *Anal.* Calcd. for $C_{20}H_{16}ClN_3O$: C, 68.66; H, 4.61; N, 12.01. Found: C, 68.78; H, 4.47; N, 12.09. IR ν_{max}^{KBr} cm^{-1}: 1680. NMR ($CDCl_3$) δ: 1.7 (2H, b, $-NH_2$), 2.43 (3H, s, $-CH_3$), 3.86 (2H, b, $-CH_2-$), 6.40 (1H, s, =CH–), 7.2—7.7 (7H, m, arom. H), 9.78 (1H, d, $J=9$ Hz, $-C_{(10)}H-$).

5-Acetamidomethyl-8-chloro-3-methyl-6-phenyl-1*H*-pyrimido[1,2-*a*]quinolin-1-one (9)——A mixture of 200 mg of **8** and 1.5 ml of acetic anhydride was stirred at room temperature for 1 hr. The precipitated crystals were collected by filtration and washed successively with saturated aq. $NaHCO_3$, H_2O and acetone to give pale yellow crystals (210 mg, 94%), mp 283—285°. Recrystallization from MeOH–$CHCl_3$–AcOEt gave pale yellow prisms. *Anal.* Calcd. for $C_{22}H_{18}ClN_3O_2$: C, 67.43; H, 4.62; N, 10.72. Found: C, 67.54; H, 4.48; N, 10.71. IR ν_{max}^{KBr} cm^{-1}: 1680 (sh), 1670. NMR (CF_3COOH) δ: 2.26, 2.73 (each 3H, s, $-CH_3\times 2$), 4.8 (2H, b, $-CH_2-$), 6.77 (1H, s, =CH–), 7.3—8.2 (7H, m, arom. H), 9.60 (1H, d, $J=9$ Hz, $C_{(10)}$–H).

2-(2-Aminoethyl)-1-(2-benzoyl-4-chlorophenyl)-6-methylpyrimidin-4(1*H*)-one (10)——A mixture of 100 mg of **6a** and 1.5 ml of saturated methanolic hydrogen chloride was refluxed for 40 min. After removal of the solvent, the residue was poured into aq. ammonia and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried and concentrated. Treatment of the residue with ether gave pale yellow crystals (85 mg, 81%). Recrystallization from CH_2Cl_2–hexane gave pale yellow prisms, mp 185° (sinter)—210° (dec.). *Anal.* Calcd. for $C_{20}H_{18}ClN_3O_2\cdot 1/4CH_2Cl_2$: C, 62.50; H, 4.79; N, 10.80. Found: C, 62.53; H, 4.71; N, 10.64. IR ν_{max}^{KBr} cm^{-1}: 1660, 1640. NMR ($CDCl_3$) δ: 1.90 (3H, s, $-CH_3$), 2.2—3.2 (6H, m, $-NH_2$ and $-CH_2-CH_2-$), 6.00 (1H, s, =CH–), 7.4—7.9 (8H, m, arom. H).

5-Aminomethyl-8-chloro-1-methyl-6-phenyl-3*H*-pyrimido[1,2-*a*]quinolin-3-one (11)——A mixture of 250 mg of **10** and 3.5 ml of conc. H_2SO_4 was heated at 95° for 2 hr. After cooling, the mixture was poured into a mixture of conc. NH_4OH (20 ml) and H_2O (50 ml) with ice cooling, and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried and concentrated. Treatment of the residue with ether gave a

pale brown powder (185 mg, 78%). IR ν_{max}^{KBr} cm^{-1}: 1650. NMR ($CDCl_3$) δ: 2.3 (2H, b, $-NH_2$), 2.70 (3H, s, $-CH_3$), 3.80 (2H, s, $-CH_2-$), 6.30 (1H, s, =CH–), 7.2—7.8 (8H, m, arom. H).

This material was transformed into **12** without further purification.

5-Acetamidomethyl-8-chloro-1-methyl-6-phenyl-3*H*-pyrimido[1,2-*a*]quinolin-3-one (12)——A mixture of 185 mg of **11** and 1 ml of acetic anhydride was stirred at room temperature for 30 min. The mixture was partitioned between saturated aq. $NaHCO_3$ and $CHCl_3$. The $CHCl_3$ layer was separated, washed with H_2O, dried and concentrated. The residue was chromatographed on silica gel (15 g) using $CHCl_3$–MeOH–AcOEt (85: 10: 5, v/v) as an eluent to give pale yellow crystals (140 mg, 67%), mp 290—292° (dec.). *Anal.* Calcd. for $C_{22}H_{18}ClN_3O_2$: C, 67.43; H, 4.62; N, 10.72. Found: C, 67.16; H, 4.44; N, 10.54. IR ν_{max}^{KBr} cm^{-1}: 1650. NMR ($CDCl_3$) δ: 1.90, 2.75 (each 3H, s, $-CH_2\times 2$), 4.40 (2H, d, $J=6$ Hz, $-C\underline{H}_2NH-$), 6.42 (1H, s, =CH–), 7.2—7.7 (8H, m, arom. H).

N-*p*-Chlorophenylacetamidine (13)——A mixture of 2.55 g of *p*-chloroaniline, 4.1 ml of acetonitrile and 5.2 g of anhydrous $AlCl_3$ was refluxed for 30 min. After addition of another 3 ml of acetonitrile, the mixture was refluxed for a further 2.5 hr and cooled. Ice and 20% aq. NaOH were added and the whole mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried and concentrated. The residue was recrystallized from ether–hexane to give colorless prisms (2.7 g, 80%), mp 116—117° (lit. mp 116—117°,[17a] mp 112—115°[17b]). NMR ($CDCl_3$) δ: 1.93 (3H, s, $-CH_3$), 4.83 (2H, b, $-NH_2$), 6.73, 7.22 (each 2H, d, $J=$ 8 Hz, arom. H).

Reaction of N-*p*-Chlorophenylacetamidine (13) with Diketene (2)——A suspension of 505 mg (3.0 mmol) of **13** in 10 ml of benzene was treated with 0.52 ml (6.6 mmol) of **2** and the mixture was stirred for 15 min. The precipitate was collected by filtration and washed with benzene to give 1-(4-chlorophenyl)-4,5-dihydro-2,4-dimethyl-4-hydroxypyrimidin-6(1*H*)-one (**14**) as colorless crystals (580 mg, 76%), mp 132—134°. $FeCl_3$ (−). *Anal.* Calcd. for $C_{12}H_{13}ClN_2O_2$: C, 57.03; H, 5.18; N, 11.08. Found: C, 57.43; H, 5.05; N, 10.93. IR ν_{max}^{KBr} cm^{-1}: 3170, 1720, 1660. NMR ($CDCl_3$) δ: 1.52 (3H, s, $-CH_3$), 1.86 (3H, s, $-CH_3$), 2.83 (2H, s, $-CH_2-$, not exchanged with D_2O), 4.5 (1H, b, –OH), 7.02, 7.40 (each 2H, d, $J=8$ Hz, arom. H).

The filtrate and washings were combined and concentrated. The residue was chromatographed on silica gel (5 g) using acetone–hexane (3: 2, v/v) as an eluent to give N-acetoacetyl-N′-*p*-chlorophenylacetamidine (**15**) as colorless crystals (45 mg, 6%), mp 94—96°. $FeCl_3$ (+). *Anal.* Calcd. for $C_{12}H_{13}ClN_2O_2$: C, 57.03; H, 5.18; N, 11.08. Found: C, 57.09; H, 5.03; N, 10.94. IR ν_{max}^{KBr} cm^{-1}: 1635 (broad, strong). NMR ($CDCl_3$) δ: 1.95 (*ca.* 0.9H, s, $-CH_3$), 2.08 (*ca.* 2.1H, s, $-CH_3$), 2.20 (*ca.* 2.1H, s, $-CH_3$), 3.58 (*ca.* 1.4H, s, $-CH_2-$, exchanged with D_2O), 4.9 (*ca.* 0.3H, b, $-C\underline{H}=C(OH)CH_3$, exchanged with D_2O), 6.66, 7.22 (each 2H, d, $J=8$ Hz, arom. H). keto-enol = 2.3: 1.

Reaction of 2-Amino-5-phenyl-3*H*-1,4-benzodiazepine (16) with Diketene (2)——A typical procedure is described for the reaction of **16a** with **2**.

A suspension of 13.5 g (50 mmol) of 2-amino-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine (**16**)[5a] in 300 ml of $CHCl_3$ was treated with 7.5 ml (95 mmol) of **2**, and the mixture was stirred at room temperature for 2.5 hr. The solvent was evaporated off and the residue was treated with hexane–MeOH to give **17a** as pale yellow crystals (16.3 g, 92%), mp 148—148.5° (dec.). $FeCl_3$ (+). *Anal.* Calcd. for $C_{19}H_{16}ClN_3O_2$: C, 64.50; H, 4.56; N, 11.88. Found: C, 64.39; H, 4.47; N, 11.79. IR ν_{max}^{KBr} cm^{-1}: 1710 (weak), 1630 (broad, strong). NMR ($CDCl_3$) δ: 1.96 (*ca.* 0.7H, s, $C\underline{H}_3(OH)C=$), 2.25 (*ca.* 2.3H, s, CH_3CO-), 3.67 (*ca.* 1.6H, s, $-CH_2-$, exchanged with D_2O), 4.1—4.6 (2H, b, $-C_{(3)}H_2-$), 5.3 (*ca.* 0.2H, b, $-C\underline{H}=C(OH)CH_3$, exchanged with D_2O), 7.2—7.7 (8H, m, arom. H). keto-enol = 3.5: 1.

The mother liquor was concentrated and the residue was chromatographed on silica gel (40 g) using hexane–acetone (7: 3, v/v) as an eluent to yield 9-chloro-1,5-dihydro-3-methyl-7-phenylpyrimido[1,2-*a*][1,4]-benzodiazepin-1-one (**19a**) as colorless crystals (215 mg, 1.3%), mp 198—200°. Recrystallization from iso-Pr_2O gave colorless needles, mp 199—201°. *Anal.* Calcd. for $C_{19}H_{14}ClN_3O$: C, 67.96; H, 4.20; N, 12.51. Found: C, 68.09; H, 4.04; N, 12.63. IR ν_{max}^{KBr} cm^{-1}: 1690. NMR ($CDCl_3$) δ: 2.24 (3H, s, $-CH_3$), 4.00, 5.02 (each 1H, d, $J=11.0$ Hz, $-C_{(5)}H_2-$), 6.25 (1H, s, $-C_{(2)}H$), 7.2—7.8 (8H, m, arom. H). UV λ_{max}^{EtOH} nm (ε): 216 (44100). MS *m/e*: 335 (M^+).

Other 2-acetoacetamido-5-phenyl-3*H*-1,4-benzodiazepines (**17b—h**) were similarly prepared from the corresponding **16b—h** by reaction with **2** in $CHCl_3$, but isolation of pyrimido[1,2-*a*][1,4]benzodiazepin-1-one derivatives was not attempted. Compounds **17b—e** were obtained as oily materials and used in the subsequent reaction without purification. Compounds **17f—h** were obtained as crystals and characterized as follows: **17f**; mp 255—257° (dec.)., yield 78%. $FeCl_3$ (+). *Anal.* Calcd. for $C_{19}H_{16}ClN_3O_3$: C, 61.71; H, 4.36; N, 11.36. Found: C, 61.70; H, 4.00; N, 11.24. **17g**; mp 218—219° (dec.). yield 81%. $FeCl_3$ (+). *Anal.* Calcd. for $C_{20}H_{16}F_3N_3O_3$: C, 59.55; H, 4.00; N, 10.42. Found: C, 59.68; H, 3.94; N, 10.53. **17h**; mp 167—169° (dec.)., yield 83%. $FeCl_3$ (+). *Anal.* Calcd. for $C_{19}H_{16}N_4O_5$: C, 59.99; H, 4.21; N, 14.73. Found: C, 60.16; H, 4.06; N, 14.89.

3,5-Dihydro-1-methyl-7-phenylpyrimido[1,2-*a*][1,4]benzodiazepin-3-ones (18) (Table III)——A typical procedure is described for **18a.**

17) *a*) J.C. Gage, *J. Chem. Soc.*, **1949**, 221; *b*) S. Birtwell, *ibid.*, **1952**, 1279.

9-Chloro-3,5-dihydro-1-methyl-7-phenylpyrimido[1,2-*a*][1,4]benzodiazepin-3-one (18a)——A stirred suspension of 3.0 g (8 mmol) of **17a** in 35 ml of MeOH was treated with 5 ml of saturated methanolic hydrogen chloride, cooling with ice-salt. After stirring for 1 hr, the mixture was poured into a solution of conc. NH_4OH (20 ml)–H_2O (100 ml) with ice cooling and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried and concentrated. Treatment of the residue with ether gave colorless prisms (2.52 g, 89%). Recrystallization from CH_2Cl_2–iso-Pr_2O gave colorless needles. NMR ($CDCl_3$) δ: 2.12 (3H, s, $-CH_3$), 4.01, 5.01 (each 1H, d, $J=11.5$ Hz, $-C_{(5)}H_2-$), 6.03 (1H, s, $-C_{(2)}H-$), 7.2—7.8 (8H, m, arom. H). UV λ_{max}^{EtOH} nm (ε): 221 (31200), 263.5 (29300). MS *m/e*: 335 (M^+).

Other compounds (**18b**—**h**) listed in Table III were similarly prepared from the corresponding **17b**—**h**.

Thermolysis of 3a——A suspension of 735 mg of **3a** in 25 ml of dry toluene was refluxed for 1.5 hr. The solvent was removed and the residue was chromatographed on silica gel (15 g) using $CHCl_3$–MeOH–AcOEt (85: 10: 5, v/v) as an eluent. The first effluent, which was a mixture of two compounds, was re-chromatographed on silica gel (15 g) using hexane–acetone (7: 3, v/v) to give **4a** (mp 156—158°, yield 20 mg (3%)) and **5a** (mp 181—182°, yield 250 mg (36%)). The second fraction afforded **1a** (mp 209—213°, yield 205 mg (36%)). The IR spectra of these samples were identical with those of previously obtained **4a**, **5a** and **1a**, respectively.

Thermolysis of 4a——A suspension of 500 mg of **4a** in 18 ml of dry toluene was refluxed for 2 hr. The solvent was removed and the residue was chromatographed as described above to give **5a** (mp 180—183, yield 153 mg (32%)), and **1a** (mp 215—218°, yield 160 mg (41%)). The IR spectra of these samples were identical with those of previously obtained **5a** and **1a**, respectively. Although a small amount of unreacted **4a** was observed on TLC, it could not be isolated.

Thermolysis of 17a——A suspension of 15.0 g of **17a** in 600 ml of dry toluene was refluxed for 3.5 hr. The solvent was removed and the residue was treated with Et_2O to give **16a** (mp 235—238° (dec.), yield 4.6 g). The mother liquor was concentrated and the residue was chromatographed on silica gel (60 g) using $CHCl_3$–MeOH–AcOEt (85: 10: 5, v/v) as an eluent. The first eluate gave **19** (mp 203—205°, yield 3.3 g (23%)). The second eluate gave **16a** (mp 235—238° (dec.), yield 1.0 g, combined yield of **16a** 5.6 g (48%)). The IR spectra of these samples were identical with those of previously obtained **19a** and **16a**, respectively.

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