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4-Oxo-1,2,3,4-tetrahydroquinazoline. IV.[1] Reactions of 2-Chloromethyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines

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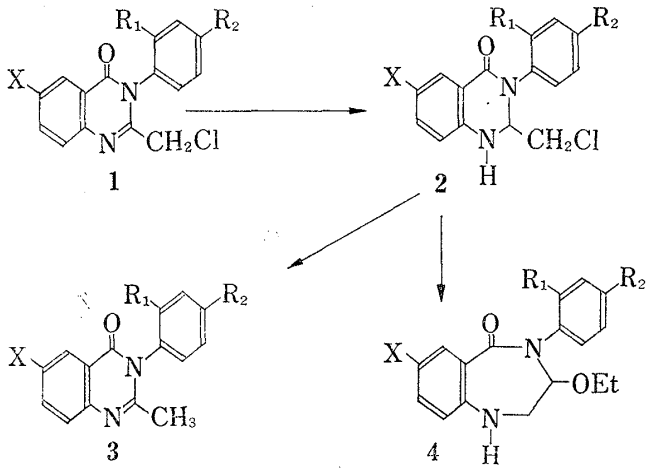
Ring expansion reaction and dehydrochlorination reaction of substituted-2-chloromethyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines (**2a**—**g**) were investigated. The required starting materials **2a**—**g** were prepared from the corresponding 4(3*H*)quinazolines (**1a**—**g**) by $NaBH_4$ reduction in excellent yields. **2a**—**f** were easily converted to dehydrochlorination products **3a**—**f** in $CHCl_3$ at room temperature. On the other hand, treatments of **2a**—**f** with EtONa in EtOH afforded ring expansion products **4a**—**f**. The mechanism of the ring expansion reaction was proved by the isolation of an intermediate, azirinoquinazoline (**7**). The investigation was extended to the reactions of azirinoquinazoline (**7**) with nucleophiles. The reactions with $NaBH_4$, MeOH, AcOH, PhSH, and EtSH proceeded analogously to give benzodiazepines (**8**, **9**, **10**, **11**, and **12**).

It is a general approach for the development of more potent drugs and antimetabolite to replace the hydrogen with a halogen atom, especially fluorine atom, in a known biologically active compound. In line with this idea, we have investigated the synthesis of the fluorinated 4(3*H*)-quinazolinones and 4-oxo-1,2,3,4-tetrahydroquinazolines, and succeeded in synthesizing a powerful choleretic agent, 1-morpholinoacetyl-2-fluoromethyl-3-phenyl-4-oxo-1,2,3,4--tetrahydroquinazoline,[1] and a hypnotic agent, 2-fluoromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone,[3] by the introduction of a fluorine atom into the C-2 methyl group of the corresponding mother compounds. During the course of the study, some of the substituted-2-chloromethyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines were found to be very unstable in chloroform solution even at room temperature. The susceptibility of the compounds suggested the possibilities of the dehydrochlorination to a substituted 2-methyl-4(3*H*)-quinazolinone and of the ring expansion to a benzodiazepine *via* an intermediary azirinoquinazoline. This prompted us to investigate the mode of the reactions of the substituted 2-chloromethyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines (**2a**—**g**) with nucleophiles. The present paper describes the dehydrochlorination and the ring enlargement reaction of the substituted-2-chloromethyl-3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines.

We have already reported a convenient synthesis of 4-oxo-1,2,3,4-tetrahydroquinazolines from the corresponding 4(3*H*)-quinazolinones by reduction with $NaBH_4$.[1,4] This method was applied to the preparation of **2a**—**g**. Thus, reductions of 2-chloromethyl-3-phenyl-4(3H)-quinazolinone hydrochloride (**1a**·HCl) and BF_3 adducts of the substituted-2-chloromethyl-3-aryl-4(3*H*)-quinazolinones (**1b**—**g**) with $NaBH_4$ gave **2a**—**g** in excellent yields. Difficulty in the purification of some of **2a**—**g** was encountered owing to their instability in the solution. When a solution of 2-chloromethyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (**2a**) in $CHCl_3$ was allowed to stand at room temperature, the colorless needles of 2-methyl-3-phenyl-4(3*H*)-quinazolinone hydrochloride (**3a**·HCl) precipitated in quantitative yield in 12 hours. However, any change could not be observed with the ethanol solution. This tendency of

1) Part III: K. Okumura, Y. Yamada, T. Oine, J. Tani, T. Ochiai, and I. Inoue, *J. Med. Chem.*, **15**, 518 (1972).
2) Location: *962, Kashimacho, Higashiyodogawa-ku, Osaka.*
3) T. Ochiai, R. Ishida, S. Nurimoto, I. Inoue, and Y. Kowa, *Japan. J. Pharmacol.*, **22**, 431 (1972).
4) K. Okumura, T. Oine, Y. Yamada, G. Hayashi, and N. Nakama, *J. Med. Chem.*, **11**, 348 (1968).

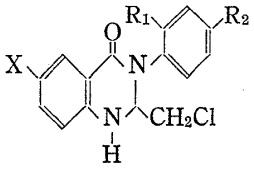


	X	R_1	R_2
a :	H	H	H
b :	OCH_3	H	CH_3
c :	Cl	H	H
d :	Cl	CH_3	H
e :	Cl	CH_3	CH_3
f :	Cl	Cl	H
g :	NO_2	H	H

Chart 1

the stability which would depend largely on the polarity of the solvent was also shown with other analogs (**2b**—**f**). The stability of **2a**—**g** in the nonprotic solvent, $CHCl_3$, was remarkably affected by the substituents at the 6 position and on the 3(N)-phenyl group. For example, 2-chloromethyl-3-(4-methylphenyl)-6-methoxy-4-oxo-1,2,3,4-tetrahydroquinazoline (**2b**) was very unstable in $CHCl_3$ and changed immediately into 2-methyl-3-(4-methylphenyl)-6-methoxy-4(3*H*)-quinazolinone hydrochloride (**3b**·HCl). The formation of 4(3*H*)-quinazolinone can be explained by the β-elimination of hydrogenchloride from the 4-oxo-1,2,3,4-tetrahydroquinazoline and the subsequent proton migration. On the contrary, 2-chloromethyl-3-phenyl-6-nitro-4-oxo-1,2,3,4-tetrahydroquinazoline (**2g**) exhibited a remarkable stability in $CHCl_3$ even at the reflux temperature.

Table I. Tetrahydroquinazolines (**2a**—**g**)



	X	R_1	R_2	Yield (%)	mp °C	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2a	H	H	H	86	141—143[a]	$C_{15}H_{13}ON_2Cl$	66.06	4.80	10.27	66.27	4.81	10.56
2b	OCH_3	H	CH_3	92	174—176[b]	$C_{17}H_{17}O_2N_2Cl$	64.45	5.40	8.84	64.58	5.50	8.71
2c	Cl	H	H	90	164—165[c]	$C_{15}H_{12}ON_2Cl_2$	58.64	3.93	9.12	58.49	4.03	9.45
2d	Cl	CH_3	H	93	181—182[c]	$C_{16}H_{14}ON_2Cl_2$	59.82	4.39	8.72	59.75	4.49	8.56
2e	Cl	CH_3	CH_3	80	136—139[c]	$C_{17}H_{16}ON_2Cl_2$	60.90	4.81	8.35	61.01	4.79	8.22
2f	Cl	Cl	H	81	183—185[d]	$C_{15}H_{11}ON_2Cl_3$	52.73	3.24	8.20	52.98	3.28	7.98
2g	NO_2	H	H	99	233—235[e]	$C_{15}H_{12}O_3N_3Cl$	56.87	3.81	13.22	57.22	3.84	13.23

a) colorless plates (from iso-PrOH) *b*) not recrystallized
c) colorless prisms (from EtOH) *d*) colorless prisms (from MeOH)
e) pale yellow prisms (from dioxane)

The semiquantitative determination of the dehydrochlorination reactivity in $CDCl_3$ by nuclear magnetic resonance (NMR) spectroscopy gave a reactivity order: **2b**$\gg$**2e**$>$**2d**$>$**2a**$\approx$**2c**$>$**2f**$\gg$**2g**, for the compounds **2a**—**g**. From these data, it can be said that the more the number of electron donating group, the more the elimination reaction is accelerated. The

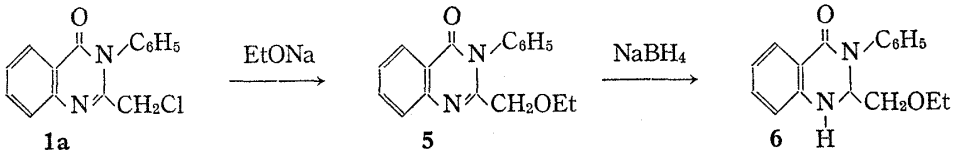
Table II. Relative Reactivities of Tetrahydroquinazolines (2a—g)

Compd.	Relative reactivity[a]	Compd.	Relative reactivity[a]
2a	33	**2e**	61
2b	100[b]	**2f**	12
2c	32	**2g**	0[c]
2d	56		

a) Relative reactivities were determined by NMR spectroscopy (in $CDCl_3$). Each sample (0.15 mmoles) was dissolved in $CDCl_3$ (0.7 ml). After 20 hr, an aliquot of DMSO-d_6 was added to dissolve the precipitates, and the spectra were determined using acetone as an internal stoichiometric standard. The value was represented by the yields of **3a**—**g**·HCl.
b) **2b** changed immediately into **3b**·HCl.
c) No dehydrochlorination was observed.

reactivity seems to depend on the basicity of the compound which may function as a base in the proton abstraction at C-2. It is well known that the base strength of the amines varies with the properties of the solvents (the dielectric constant and the solvating properties) in the complex manner, and as a result the basicity of an amine is more enhanced in $CHCl_3$ than in EtOH.[5] The marked stability of the 6-nitro derivative **2g** is compatible with this explanation.

On the other hand, treatment of **2a** with EtONa in EtOH afforded a product to which structure **4a** was assigned on the basis of the mechanistic consideration and the spectral data. There are three posible pathways; the first one is the direct displacement of the chlorine atom with ethoxy group; the second is the formation of an intermediate, azirinoquinazoline, and the subsequent ring opening by the fission of the 1(N)-2(C) bond, giving compound **6**; the third is the ring opening of the azirinoquinazoline to benzodiazepine. Since the similar ring enlargements[6] have already been known, one may expect a same type of the reaction in this case. The NMR spectrum in $CDCl_3$ showed the signals of an ethoxy group in the usual region, a multiplet at δ 3.75 which overlapped with the methylene quartet of the ethoxyl, and a deformed triplet at δ 5.02. The multiplet at δ 3.75 for two protons and the deformed triplet at δ 5.02 for one proton may be assigned to the endocyclic methylene and methine protons in the seven membered ring. A slight change in the signal pattern at δ 3.75 on exchange with D_2O and the chemical shift of the methine proton (δ 5.02) supported, not so conclusively, the assigned structure (**4a**). Further confirmation was made on the discordance of the product with an authentic sample of 2-ethoxymethyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (**6**) prepared from 2-ethoxymethyl-3-phenyl-4(3*H*)-quinazolinone (**5**). The exclusive occurrence of the ring expansion in the reaction with the strong base EtONa in EtOH may be rationalized by an explanation that the N-1 proton of the 2-chloromethyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline was first abstracted by the ethoxide ion to give an anion which suppressed the second abstraction of the proton at C-2 for the β-elimination. The ring expansion reaction of **2b**—**f** proceeded in the same fashion to give the benzodiazepines (**4b**—**f**).

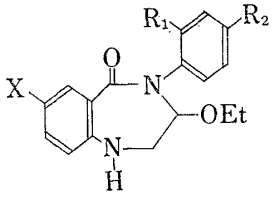


1a **5** **6**

Chart 2

5) R.G. Pearson, and D.C. Vogelsong, *J. Am. Chem. Soc.*, **80**, 1038 (1958).
6) R.F. Childs, and A.W. Johnson, *Chem. Commun.*, **1965**, 95; M. Anderson, and A.W. Johnson, *J. Chem. Soc.*, **1951**, 2411, and earlier papers; G.F. Field, W.J. Zally, and L.H. Sternbach, *J. Am. Chem. Soc.*, **89**, 332 (1967); L.H. Sternbach, *Angew. Chem. Intern. Ed. Engl.* **10**, 34 (1971).

Table III. Benzodiazepines (**4a**—**g**)



	X	R_1	R_2	Yield (%)	mp °C	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
4a	H	H	H	85	163—165[a]	$C_{17}H_{18}O_2N_2$	72.32	6.43	9.92	71.92	6.39	9.91
4b	OCH_3	H	CH_3	67	125—128[b]	$C_{19}H_{22}O_3N_2$	69.92	6.79	8.58	70.03	6.82	8.57
4c	Cl	H	H	76	176—177[a]	$C_{17}H_{17}O_2N_2Cl$	64.45	5.40	8.84	64.33	5.62	8.82
4d	Cl	CH_3	H	88	174—176[a]	$C_{18}H_{19}O_2N_2Cl$	65.37	5.78	8.46	65.17	5.84	8.43
4e	Cl	CH_3	CH_3	76	176—179[a]	$C_{19}H_{21}O_2N_2Cl$	66.17	6.14	8.12	66.41	6.01	7.99
4f	Cl	Cl	H	28	132—133[b]	$C_{17}H_{16}O_2N_2Cl_2$	58.13	4.59	7.98	58.43	4.36	8.01
4g	NO_2	H	H	19[c]	234—236[d]	$C_{17}H_{17}O_4N_3$	62.37	5.24	12.84	62.61	5.13	12.94

a) colorless prisms (from EtOH) *b*) colorless prisms (from iso-PrOH)
c) prepared by method B *d*) pale yellow needles (from THF)

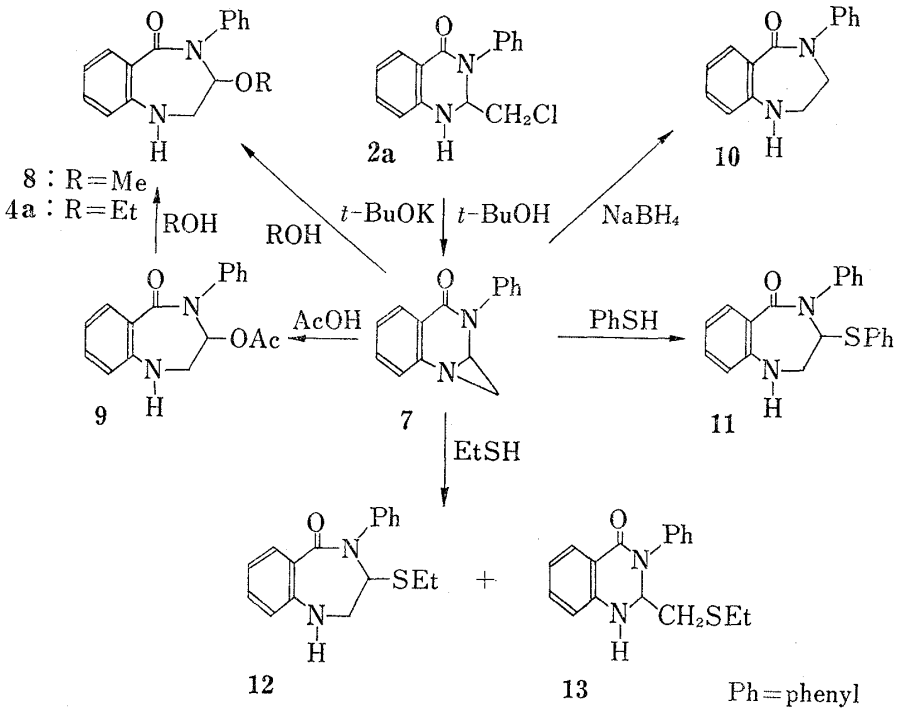


Chart 3

In the case of 6-nitro derivative (**2g**), an isolable product was 2-methyl-3-phenyl-6-nitro-4(3*H*)-quinazolinone (**3g**). However, treatment of **2g** with diazabicycloundecene in boiling THF·EtOH gave 3-ethoxy-4-phenyl-7-nitro-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-5-one (**4g**) in 19% yield. Meanwhile, Sternbach and his co-workers[7] have reported a ring expansion of 2-chloromethyl-2-methyl-4-oxo-1,2,3,4-tetrahydroquinazoline to a benzodiazepine, and proposed a plausible reaction mechanism which involves the intermediate formation of an

7) G.F. Field, W.J. Zally, and L.H. Sternbach, *J. Org. Chem.*, **36**, 777 (1971).

azirinoquinazoline from the consideration of their earlier findings in the chemistry of quinazoline, though they could not isolate the intermediate. Accordingly, our efforts were directed toward the identification of the azirinoquinazoline in our present investigation in order to provide the clear cut evidence for the mechanism of this type of the reaction. The examination of the reaction by thin-layer chromatography (TLC) showed the transient formation of a product which gradually disappeared as the reaction proceeded. This suggested that the isolation of the intermediate might be possible, if the reaction were run with *t*-BuOK in a less nucleophilic solvent. Treatment of **2a** with *t*-BuOK in *t*-BuOH and the careful work up of the reaction mixture gave a crystalline product, mp 96—98°, in 42.4% yield. The structure was assigned 4-phenyl-5-oxo-1,3,4,5-tetrahydro-2*H*-azirino[1,2-*a*]quinazoline (**7**) by its spectral data and chemical behavior. The NMR spectrum of **7** in $CDCl_3$ showed two doublets at δ 1.95 and 2.68 (J=3 Hz) assignable to the methylene protons of the aziridine ring, a triplet at α 4.28 (J=3 Hz) indicative of the methine proton and a multiplet in the aromatic region. The high-field part of the spectrum may be attributed to an ABX pattern in which the geminal coupling constant of the azirinomethylene group is fortuitously zero. Azirinoquinazoline **7** was easily converted to the benzodiazepine (**4a**) in good yield by treatment with EtOH. Reduction of **7** with $NaBH_4$ in Diglyme gave 4-phenyl-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-5-one (**10**) in 50.7% yield. These results confirmed the proposed mechanism for the ring enlargement reaction.

The investigation was extended to the reaction with other nucleophiles. The reactions with MeOH, AcOH, and PhSH proceeded analogously to give 3-methoxy-4-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**8**), 3-acetoxy-4-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**9**) and 3-phenylthio-4-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**11**), respectively. However, treatment of **7** with EtSH afforded 2-ethylthiomethyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (**13**) as a major product which was resulted from the ring opening of the aziridine ring to a different direction, and 3-ethylthio-4-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**12**) as a minor product. These two different courses of the reaction can be explained by Leonard's proposal[8] on the ring opening of aziridinium compounds; weak nucleophiles bring about S_N1 type ring opening so that benzodiazepines are obtained, while strong nucleophiles tend to approach the aziridine ring from the less hindered side in S_N2 manner to afford 4-oxo-1,2,3,4-tetrahydroquinazolines. 3-Acetoxybenzodiazepine (**9**) was fairly reactive, and therefore treatment of **9** with EtOH gave **4a** in high

Table IV. Infrared Spectra

Tetrahydroquinazolines		Benzodiazepines	
Compd.	$\nu_{C=O}$ cm^{-1}	Compd.	$\nu_{C=O}$ cm^{-1}
2a	1643	**4a**	1620
2b	1640	**4b**	1605
2c	1645	**4c**	1614
2d	1645	**4d**	1610
2e	1640	**4e**	1610
2f	1646	**4f**	1615
2g	1640	**4g**	1615
6	1640	**8**	1610
13	1632	**12**	1620
		9	1620
		10	1610
		11	1612

8) N.J. Leonard, and D.A. Durand, *J. Org. Chem.*, 33, 1322 (1968).

yield. The structures of the compounds (**8**—**13**) were determined by elemental analysis and spectrometry.

The carbonyl absorptions (streching vibration) of the 3-aryl-4-oxo-1,2,3,4-tetrahydroquinazolines and the benzodiazepines in infrared (IR) spectrum are presented in Table IV. Inspection of the table reveals that the carbonyls of the benzodiazepines absorb at longer wave length than those of the 4-oxo-1,2,3,4-tetrahydroquinazolines. The great differences in the carbonyl absorptions between the 4-oxo-1,2,3,4-tetrahydroquinazolines and the benzodiazepines provide a convenient diagnosis for differentiation of 4-oxo-1,2,3,4-tetrahydroquinazoline and 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine.

Experimental[9]

2-Chloromethyl-4(3*H*)-quinazolinones (1)——2-Chloromethyl-3-phenyl-4(3*H*)-quinazolinone (**1a**) was prepared from 2-aminobenzanilide by the method of P.A. Petyunin.[10] Other new 4(3*H*)-quinazolinones (**1b**—**g**) were obtained in the same manner.

2-Chloromethyl-3-(4-methylphenyl)-6-methoxy-4(3*H*)-quinazolinone (**1b**) was obtained as colorless plates (iso-PrOH), mp 164—166°. Yield 63.0%. *Anal.* Calcd. for $C_{17}H_{15}O_2N_2Cl$: C, 64.86; H, 4.80; N, 8.90; Cl, 11.26. Found: C, 64.84; H, 4.92; N, 8.83; Cl, 11.07.

2-Chloromethyl-3-phenyl-6-chloro-4(3*H*)-quinazolinone (**1c**) was obtained as colorless prisms (EtOH), mp 184—186°. Yield 65.3%. *Anal.* Calcd. for $C_{15}H_{10}ON_2Cl_2$: C, 59.04; H, 3.30; N, 9.18; Cl, 23.24. Found: C, 58.84; H, 3.56; N, 9.14; Cl, 23.32.

2-Chloromethyl-3-(2-methylphenyl)-6-chloro-4(3*H*)-quinazolinone (**1d**) was obtained as colorless prisms (benzene), mp 203—204°. Yield 67.7%. *Anal.* Calcd. for $C_{16}H_{12}ON_2Cl_2$: C, 60.20; H, 3.78; N, 8.77; Cl, 22.21. Found: C, 60.25; H, 3.77; N, 8.73; Cl, 21.73.

2-Chloromethyl-3-(2,4-dimethylphenyl)-6-chloro-4(3*H*)-quinazolinone (**1e**) was obtained as colorless prisms (EtOH), mp 198—199.5°. Yield 73.7%. *Anal.* Calcd. for $C_{17}H_{14}ON_2Cl_2$: C, 61.27; H, 4.23; N, 8.40; Cl, 21.28. Found: C, 61.30; H, 4.21; N, 8.24; Cl, 21.47.

2-Chloromethyl-3-(2-chlorophenyl)-6-chloro-4(3*H*)-quinazolinone (**1f**) was obtained as colorless prisms (EtOH), mp 212—213°. Yield 83.7%. *Anal.* Calcd. for $C_{15}H_9ON_2Cl_3$: C, 53.04; H, 2.67; N, 8.24; Cl, 31.32. Found: C, 53.07; H, 2.66; N, 8.14; Cl, 31.13.

2-Chloromethyl-3-phenyl-6-nitro-4(3*H*)-quinazolinone (**1g**) was obtained as colorless prisms (dioxane), mp 228—230°. Yield 63.7%. *Anal.* Calcd. for $C_{15}H_{10}O_3N_3Cl$: C, 57.06; H, 3.19; N, 13.31; Cl, 11.23. Found: C, 57.27; H, 3.34; N, 13.42; Cl, 11.42.

2-Ethoxymethyl-3-phenyl-4(3*H*)-quinazolinone (**5**)——To a freshly prepared solution of EtONa (11 mmoles) in EtOH (30 ml) was added 2-chloromethyl-3-phenyl-4(3*H*)-quinazolinone (**1a**, 2.7 g, 9.6 mmoles) and the mixture was stirred at room temperature for 17 hr. The mixture was concentrated under reduced pressure and the residue was dissolved in benzene. The benzene solution was washed with H_2O, dried (Na_2SO_4), and concentrated to give crude **5** as an oil. NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz), 3.34 (2H, q, J=7 Hz), 4.15 (2H, s), 7.1—8.4 (9H, m). This was crystallized as the hydrochloride. Recrystallization from acetone–ether gave a pure sample (1.7 g) as colorless prisms, mp 178—180° (decomp.). *Anal.* Calcd. for $C_{17}H_{17}O_2N_2Cl$: C, 64.45; H, 5.41; N, 8.84; Cl, 11.19. Found: C, 64.29; H, 5.42; N, 8.87; Cl, 11.14.

2-Chloromethyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (**2a**)——To a stirred suspension of 2-chloromethyl-3-phenyl-4(3*H*)-quinazolinone hydrochloride (**1a**–HCl, 1.5 g, 5 mmoles) in THF (30 ml) was added a solution of $NaBH_4$ (0.23 g, 6 mmoles) in Diglyme (10 ml) at 3—5° during 2 hr. The mixture was stirred for 30 min at the same temperature. H_2O (5 ml) was added to the mixture and the solvent was evaporated under reduced pressure. The residue was treated with H_2O (100 ml) to give a crystalline product. The product was collected by filtration to give almost pure **2a** (1.3 g, 86%), mp 141—146°. Recrystallization from iso-PrOH gave an analytically pure sample as colorless plates, mp 141—143°. NMR ($CDCl_3$) δ: 3.61 (1H, d.d, J=11 Hz, J=4 Hz), 3.88 (1H, d.d, J=11 Hz, J=9 Hz), 5.14 (1H, d.d, J=9 Hz, J=4 Hz), 5.42 (1H, br. s), 6.6—8.1 (4H, m), 7.40 (5H, s).

2-Chloromethyl-3-(2-chlorophenyl)-6-chloro-4-oxo-1,2,3,4-tetrahydroquinazoline (**2f**)——To a solution of 2-chloromethyl-3-(2-chlorophenyl)-6-chloro-4(3*H*)-quinazolinone (**1f**, 40 g, 0.118 mole) in THF (700 ml) was added gradually BF_3–ether (16.72 g, 0.118 mole) at room temperature and the mixture was stirred for 30 min. A solution of $NaBH_4$ (3.31 g, 0.088 mole) in Diglyme (60 ml) was added to the resulting mixture

9) Melting points are uncorrected and were determined on a Yamato apparatus MP-1. The NMR spectra were determined on a Hitachi Perkin-Elmer R-20A instrument (Me_4Si). Mass spectra were measured on a Hitachi RMS-4 spectrometer. IR spectra were determined on a Shimadzu IR-27G spectrometer and ultraviolet (UV) spectra on a Hitachi EPS-2U spectrometer.

10) P.A. Petyunin, and Y.V. Kozhevinkov, *Khim. Geterotsikl. Soedin.*, **1967**, 415 [*C.A.*, **70**, 87739q (1969)].

with stirring during 40 min at 0——5° and stirring was continued at room temperature for 1.3 hr. H_2O (60 ml) was added to the mixture until H_2 evolution ceased (for *ca.* 1 hr). The solvent was evaporated under reduced pressure and the residue was poured into H_2O (500 ml) to give a crystalline product. The crystals were collected by filtration and washed with iso-Pr_2O to give almost pure **2f** (32.6 g, 81.2%), mp 183—185°. Recrystallization from EtOH afforded an analytically pure sample as colorless prisms, mp 182—183°. NMR ($CDCl_3$) δ: 3.77 (2H, m), 5.05 (1H, d.d, J=9 Hz, J=4 Hz), 5.15 (1H, br), 6.6—8.0 (7H, m).

Other substituted 2-chloromethyl-4-oxo-1,2,3,4-tetrahydroquinazolines (**2b—g**) were prepared from the corresponding 4(3*H*)-quinazolinone (**1b—g**) in the same manner, and their physical constants and yields were shown in Table I.

Dehydrochlorination of 2-Chloromethyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (2a)——A solution of **2a** (300 mg) in $CHCl_3$ (5 ml) was stirred at room temperature for 12 hr. The crystals that had precipitated were collected by filtration to give almost pure 2-methyl-3-phenyl-4(3*H*)-quinazolinone hydrochloride (**3a**–HCl, 275 mg, 91.7%), mp 255—261° (decomp.). IR spectrum of this product was identical with that of an authentic sample of **3a**–HCl.

Dehydrochlorination of 2-Chloromethyl-3-phenyl-6-nitro-4-oxo-1,2,3,4-tetrahydroquinazoline (2g)——To a freshly prepared solution of EtONa (3 mmoles) in EtOH was added portionwise **2g** (0.95 g, 3 mmoles) at 0—2° for 30 min. The mixture was stirred at same temperature for 1 hr and at room temperature for 4 hr. The crystals that had precipitated were collected by filtration to give almost pure 2-methyl-3-phenyl-6-nitro-4(3*H*)-quinazolinone (**3g**, 670 mg, 79.5%), mp 210—214°. Recrystallization from THF afforded pure **3g** as yellow prisms, mp 213—215°, (lit.,[11] mp 223—224°).

2-Ethoxymethyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (6)——To a stirred suspension of 2-ethoxymethyl-3-phenyl-4(3*H*)-quinazolinone hydrochloride (**5**·HCl, 630 mg, 2 mmoles) in THF (10 ml) was added a solution of $NaBH_4$ (82 mg, 2.2 mmoles) in Diglyme (5 ml) at 0—3° during 2 hr. The mixture was stirred for 30 min at the same temperature and H_2O (3 ml) was added to the mixture. The solution was concentrated under reduced pressure. The residue was poured into H_2O (100 ml) and the precipitate was collected by filtration to give crude product (490 mg), mp 102—105°. Recrystallization from iso-PrOH afforded a pure sample as colorless prisms (430 mg, 72.0%), mp 106—108°. UV λ_{max}^{EtOH} nm ($\varepsilon\times10^{-3}$): 227 (34.7), 248 (sh), 350 (2.8). Mass Spectrum *m/e*: 282 (M^+). NMR ($CDCl_3$) δ: 1.10 (t, 3H, J=7 Hz), 3.2—3.9 (4H, m), 4.9—5.2 (2H, m), 6.6—8.1 (9H, m). *Anal.* Calcd. for $C_{17}H_{18}O_2N_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 71.96; H, 6.44; N, 9.93.

3-Ethoxybenzodiazepines (4). Method A. 3-Ethoxy-4-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (4a)——To a freshly prepared solution of EtONa (0.054 mole) in EtOH (150 ml) was added finely pulverized **2a** (13.6 g, 0.05 mole) at 0——5°. The mixture was stirred at the same temperature for 1 hr and then at 15—25° for 4 hr. The solvent was evaporated under reduced pressure and the residue was treated with H_2O (200 ml) to give a crystalline product. This was collected by filtration to afford crude **4a** (13 g). Recrystallization from EtOH (100 ml) gave pure sample as colorless prisms, mp 163—165°. UV λ_{max}^{EtOH} nm ($\varepsilon\times10^{-3}$): 227 (34.3), 260 (sh), 344 (5.7). Mass Spectrum *m/e*: 282 (M^+). NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7 Hz), 3.3—3.9 (4H, m), 4.50 (1H, br. s), 5.01 (1H, t, J=3 Hz), 6.5—8.1 (9H, m). *Anal.* Calcd. for $C_{17}H_{18}O_2N_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 71.92; H, 6.39; N, 9.91.

Method B. 3-Ethoxy-4-phenyl-7-nitro-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (4g)——To a stirred solution of 2-chloromethyl-3-phenyl-6-nitro-4-oxo-1,2,3,4-tetrahydroquinazoline (**2g**, 1.9 g, 6 mmoles) in a mixture of THF (250 ml) and EtOH (150 ml) was added a solution of 1,8-diazabicyclo[5·4·0]undec-7-ene (1.2 g) in THF (30 ml) at 50—52° during 1 hr. The mixture was refluxed for 3.5 hr and the solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (200 ml) and the solution was washed with H_2O, dried ($MgSO_4$) and concentrated to dryness under reduced pressure. The residue was dissolved in $CHCl_3$ (10 ml) and the solution was allowed to stand at room temperature. The resulting crystals were collected by filtration to give crude **4g**. Recrystallization from THF gave pure sample as pale yellow needles, (370 mg, 19%), mp 234—236°. NMR (DMSO-d_6) δ: 0.99 (3H, t, J=7 Hz), 3.4—4.0 (4H, m), 5.13 (1H, m), 6.85 (1H, d, J=10 Hz), 7.40 (5H, br. s), 8.00 (1H, d.d, J=10 Hz, J=3 Hz), 8.20 (1H, br. s), 8.77 (1H, d, J=3 Hz). *Anal.* Calcd. for $C_{17}H_{17}O_4N_3$: C, 62.37; H. 5.24; N, 12.84. Found: C, 62.61; H, 5.13; N, 12.94.

4-Phenyl-5-oxo-1,3,4,5-tetrahydro-2*H*-azirino [1,2-*a*] quinazoline (7)——To a freshly prepared solution of *t*-BuOK (5.5 mmoles) in *t*-BuOH (20 ml) was added **2a** (1.36 g, 5 mmoles) and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the residue was dissolved in CCl_4 (30 ml) at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was crystallized by trituration with ether and the crystals were collected by filtration to give **7** (0.5 g, 42.4%), mp 96—98°. IR ν_{max}^{Nujol} cm^{-1}: 1668, 1605, 1580, 1492. NMR ($CDCl_3$) δ: 1.95 (1H, d, J=3 Hz), 2.68 (1H, d, J=3 Hz), 4.28 (1H, t, J=3 Hz), 7.0—8.2 (9H, m).

11) Olin Mathieson Chem. Corp., Fr. Patent 1367738 (1964) [*C.A.*, **62**, 1672a (1965)].

Reaction of Azirinoquinazoline (7) with Nucleophiles——1) With EtOH: A solution of **7** (200 mg) in EtOH (10 ml) was warmed at 50—60° for 30 min. The solution was concentrated under reduced pressure to give a paste which was crystallized by trituration with iso-PrOH. The crystals were collected by filtration to afford almost pure **4a**, (0.15 g, 62.6%), mp 161—163°. The product was identical in all criteria with the sample **4a** obtained directly from **2a**.

2) With $NaBH_4$: To a freshly prepared solution of *t*-BuOK (5.5 mmoles) in *t*-BuOH (20 ml) was added **2a** (1.36 g, 5 mmoles) and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the residue was extracted with CCl_4 (30 ml). The extract was concentrated to dryness. The residual paste was dissolved in Diglyme (20 ml). To the solution was added dropwise a solution of $NaBH_4$ (0.11 g, 2.7 mmoles) in Diglyme (10 ml) under ice cooling during 1 hr and the mixture was stirred at room temperature for 1 hr. The mixture was poured into H_2O (300 ml) and crystals that had formed were collected by filtration to give crude 4-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**10**, 1.0 g), mp 205—215°. Recrystallization from EtOH gave a pure sample as colorless needles (0.6 g, 50.7%), mp 223—224°. UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$): 220 (26.4), 260 (sh), 340 (3.7). NMR (DMSO-d_6) δ: 3.4—3.7 (2H, m) 3.75—4.0 (2H, m), 6.2—6.5 (1H, m), 6.5—7.8 (9H, m). *Anal.* Calcd. for $C_{15}H_{14}ON_2$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.23; H, 5.99; N, 11.62.

3) With MeOH: The solution of **7** in *t*-BuOH was prepared from potassium (0.22 g, 5.5 mmoles), *t*-BuOH (20 ml) and **2a** (1.36 g, 5 mmoles). To the solution was added MeOH (1 ml) and the mixture was stirred at room temperature for 1 hr and at 60° for 2 hr. After cooling, the insoluble material was filtered off and the filtrate was concentrated. The residue was dissolved in MeOH (30 ml) and the solution was warmed at 50—60° for 1 hr. After cooling, the precipitates was collected by filtration to give crude 3-methoxy-4-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**8**, 0.9 g, 66.9%), mp 226—227° (decomp.). Recrystallization from MeOH gave pure sample as colorless leaflets, mp 227—231° (decomp.). UV λ_{max}^{MeOH} nm ($\varepsilon \times 10^{-3}$): 227 (34.8), 260 (sh), 344 (4.3). NMR (DMSO-d_6) δ: 3.30 (3H, s), 3.55—3.85 (2H, m), 4.85—5.0 (1H, m), 6.35—7.90 (10H, m). *Anal.* Calcd. for $C_{16}H_{16}O_2N_2$: C, 71.62; H, 6.02; N, 10.44. Found: C, 71.28: H, 6.15; N, 10.42.

4) With AcOH: The solution of **7** in *t*-BuOH was prepared from potassium (0.44 g, 11 mmoles), *t*-BuOH (40 ml) and **2a** (2.72 g, 10 mmoles). To the solution was added AcOH (3.0 g) and the mixture was stirred at room temperature overnight. The solid that had precipitated was collected by filtration and dissolved in $CHCl_3$ (30 ml). The insoluble material was filtered off and the filtrate was concentrated to dryness. The residue was triturated with ether and the crystals were collected by filtration to give crude product (2.2 g, 74.5%), mp 144—146° (decomp.). Recrystallization from benzene gave 3-acetoxy-4-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**9**) as colorless needles, mp 162—164° (decomp.). UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$): 228.5 (26.8), 257 (sh), 346 (4.8). NMR ($CDCl_3$) δ: 1.97 (3H, s), 3.57 (1H, d.d, J=14 Hz, J=2 Hz), 3.87 (1H, d.d, J=14 Hz, J=6 Hz), 6.13 (1H, d.d, J=6 Hz, J=2 Hz), 4.84 (1H, br. s), 6.5—8.3 (9H, m). *Anal.* Calcd. for $C_{17}H_{16}O_3N_2$: C, 68.90; H, 5.44; N, 9.45. Calcd.: C, 68.71; H, 5.60; N, 9.57.

5) With PhSH: The solution of **7** in *t*-BuOH was prepared from potassium (0.22 g, 5.5 mmoles), *t*-BuOH (25 ml) and **2a** (1.36 g, 5 mmoles). To the solution was added PhSH (1.0 g) and the mixture was stirred at room temperature for 1 hr and at 40° for 30 min. The mixture was concentrated to dryness and the residue was dissolved in $CHCl_3$ (100 ml). The insoluble solid was removed by filtration and the filtrate was concentrated. The residue was crystallized by trituration with iso-PrOH and the crystals were collected by filtration. Recrystallization from EtOH gave 3-phenylthio-4-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**11**) as colorless prisms (1.05 g, 60.7%), mp 183—185°. UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$) 231 (36.9), 262 (sh), 348 (5.4). NMR ($CDCl_3$) δ: 3.87 (2H, d, J=4 Hz), 5.32 (1H, J=4 Hz), 6.6—8.25 (14H, m). *Anal.* Calcd. for $C_{21}H_{18}ON_2S$: C, 72.80; H, 5.24; N, 8.09; S, 9.26. Found: C, 72.89; H, 5.39; N, 8.10; S, 9.44.

6) With EtSH: The solution of **7** in *t*-BuOH was prepared from potassium (3.44 g, 0.088 mole), *t*-BuOH (300 ml) and **2a** (21.8 g, 0.08 mole). To the solution was added EtSH (9.92 g, 0.16 mole) and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was extracted with $CHCl_3$. The extract was concentrated. The residue was crystallized by trituration with iso-PrOH and the crystals were collected by filtration to give crude 3-ethylthio-4-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (**12**, 5.1 g), mp 180—184°. Recrystallization from EtOH–dioxane gave pure **12** as colorless leaflests (4.5 g, 18.8%), mp 192—193°. UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$): 230 (27.0), 261 (sh), 348 (4.3). NMR ($CDCl_3$) δ: 1.08 (3H, t, J=7 Hz), 2.56 (2H, q, J=7 Hz), 3.84 (1H, d, J=5 Hz), 3.86 (1H, d, J=3 Hz), 5.09 (1H, d.d, J=5 Hz, J=3 Hz), 4.40 (1H, br. s), 6.5—8.25 (9H, m). *Anal.* Calcd. for $C_{17}H_{18}ON_2S$: C, 68.42; H, 6.08; N, 9.39; S, 10.75. Found: C, 68.14; H, 6.13; N, 9.35; S, 10.62.

The mother liquor from the crystallization of crude **12** was concentrated under reduced pressure and the residue was crystallized by trituration with iso-Pr_2O. The crystals were collected by filtration and recrystallized from iso-PrOH–iso-Pr_2O to give pure 2-ethylthiomethyl-3-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (**13**) as colorless prisms (13.0 g, 54.2%), mp 98—100°. UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$): 227 (39.2), 250 (sh), 352 (3.7). NMR ($CDCl_3$) δ: 1.07 (3H, t, J=7 Hz), 2.39 (2H, q, J=7 Hz), 2.92 (1H, d, J=10 Hz), 2.95 (1H, d, J=6 Hz), 4.98 (1H, d.d, J=10 Hz, J=6 Hz), 5.40 (1H, br. s), 6.6—8.1 (9H, m). *Anal.* Calcd. for $C_{17}H_{18}ON_2S$: C, 68.42; H, 6.08; N, 9.39; S, 10.75. Found: C, 68.20; H, 6.13; N, 9.23; S, 10.50.

Reaction of Benzodiazepine (9) with EtOH——A solution of **9** (0.5 g) in EtOH (10 ml) was warmed at 60—70° for 30 min and the solution was concentrated to give a crystalline product. Recrystallization from EtOH gave a pure sample as colorless prisms, mp 163—165°. The IR spectrum of this compound was identical with that of **4a**.

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