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Anticoccidials. V.[1] Synthesis and Anticoccidial Activity of 2(1*H*)-Pyrazinone 4-Oxide Derivatives

Mitsuhiko Mano, Takuji Seo,[2a] Toshinori Hattori, Tatsuhiko Kaneko,[2b] and Kin-ichi Imai[2a]

Animal Health Products Division[2a] and Central Research Division,[2b] Takeda Chemical Industries, Ltd.

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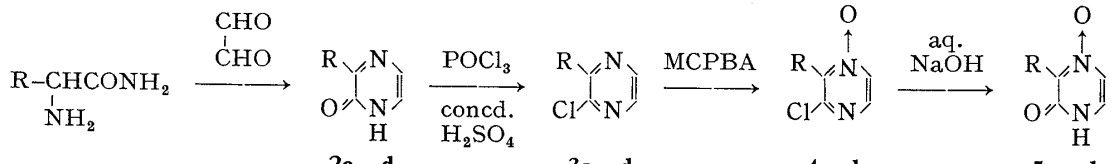
A series of 1-, 3-, 5- and 6-substituted 2(1*H*)-pyrazinone 4-oxides were synthesized and tested for anticoccidial activity. Of the compounds tested, 1-(β-D-ribofuranosyl)-(**22**), 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-(**21**) and 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2(1*H*)-pyrazinone 4-oxides (**24**) showed high activity.

Keywords——pyrazine; 2(1*H*)-pyrazinone; 2(1*H*)-pyrazinone 4-oxide; 1-(β-D-ribofuranosyl)-2(1*H*)-pyrazinone 4-oxide; anticoccidial activity

In the preceding paper, we reported that 2(1*H*)-pyrazinone 4-oxide (**1**) (emimycin) had potent anticoccidial activity.[1] This finding encouraged us to undertake a more extensive investigation of related 2(1*H*)-pyrazinone 4-oxide derivatives. This paper describes the synthesis and anticoccidial activity of this class of compounds.

Synthesis

The synthesis of 3-substituted 2(1*H*)-pyrazinone 4-oxides (**5a—d**) is outlined in Chart 1. The 3-alkyl-2(1*H*)-pyrazinones (**2a—d**) were prepared by condensation of the appropriate α-amino acid amides with glyoxal.[3] These were converted to the 2-chloropyrazines (**3a—d**) by treatment with phosphoryl chloride containing sulfuric acid,[3] and these compounds were then oxidized with *m*-chloroperbenzoic acid (MCPBA) in 1,2-dichloroethane to give the corresponding 4-oxides (**4a—d**) (**4a** and **4b** were not isolated).[4] Heating **4a—d** with aqueous sodium hydroxide gave the desired **5a—d**.



a: R=CH(CH$_3$)$_2$ **c**: R=CH$_2$CH(CH$_3$)$_2$

b: R=CH(CH$_3$)CH$_2$CH$_3$ **d**: R=CH$_2$C$_6$H$_5$

Chart 1

5-Aryl-2(1*H*)-pyrazinone 4-oxides (**11a—e**) were synthesized by a similar sequence of reactions. Thus, condensation of glycinamide hydrochloride (**6**) and arylglyoxals gave 5-aryl-

1) Part IV: M. Mano, T. Seo, and K. Imai, *Chem. Pharm. Bull.*, **28**, 2720 (1980).
2) Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*
3) G. Karmas and P.E. Spoerri, *J. Am. Chem. Soc.*, **74**, 1580 (1952).
4) *a*) C.E. Mixan and R.G. Pews, *J. Org. Chem.*, **42**, 1869 (1977); *b*) N. Sato, *ibid.*, **43**, 3367 (1978).

2(1*H*)-pyrazinones (**7a**—**e**)[5] which were converted to the corresponding 2-chloropyrazines (**8a**—**e**) by heating with a mixture of phosphoryl chloride and N,N-dimethylformamide (DMF). Oxidation of **8b**, **e** with MCPBA gave mixtures of the corresponding 4-oxides (**9b**, **e**) and 1-oxides (**10b**, **e**),[4b] which were separated by column chromatography on silica gel. Alkaline hydrolysis of **9b**, **e** and **10b**, **e** gave 2(1*H*)-pyrazinone 4-oxides (**11b**, **e**) and 1-hydroxy-2(1*H*)-pyrazinones (**12b**, **e**), respectively. A similar oxidation of **8a**, **c**, **d** with MCPBA gave inseparable mixtures of the 4-oxides and 1-oxides, which were directly hydrolyzed and then separated by fractional recrystallization to provide **11a**, **c**, **d** and **12a**, **c**, **d** (Chart 2). The structures of **11** and **12** could be readily differentiated by means of the ferric chloride test.[6]

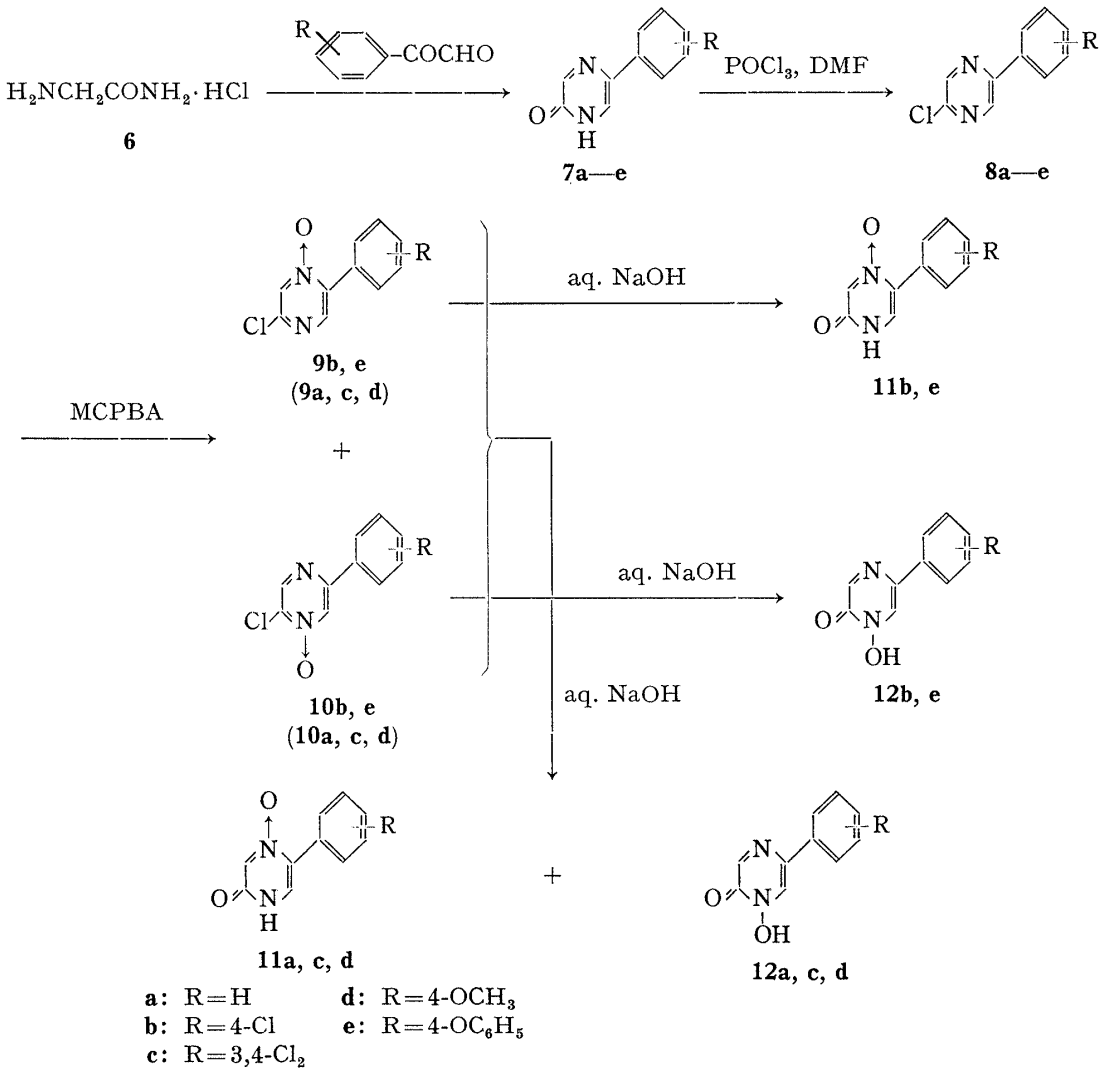


Chart 2

6-Methyl- (**15a**) and 5,6-dimethyl-2(1*H*)-pyrazinone 4-oxides (**15b**) were prepared from the corresponding 2-chloropyrazines (**13a**, **b**) as shown in Chart 3.

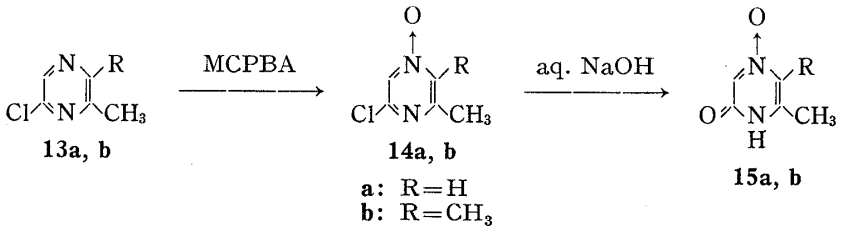
1-Alkyl-2(1*H*)-pyrazinone 4-oxides (**16a**—**s** and **17a**—**w**) were prepared by alkylation of **1** using dimethyl sulfate or alkyl halides in the presence of sodium hydride in DMF or sodium

5) *a*) S. Sugiura, S. Inoue, Y. Kishi, and T. Goto, *Yakugaku Zasshi*, **89**, 1646 (1969); *b*) P.J. Lont and H.C. Van Der Plas, *Rec. Trav. Chim. Pay-Bas*, **92**, 449 (1973); *c*) N. Sato, *J. Heterocycl. Chem.*, **15**, 665 (1978).

6) G. Dunn, J.A. Elvidge, G.T. Newbold, D.W.C. Ramsay, F.S. Spring, and W. Sweeny, *J. Chem. Soc.*, **1949**, 2707.

methoxide in methanol. In some cases, O-alkylation products (**18d, k—m**) were isolated as by-products (Charts 4 and 5).

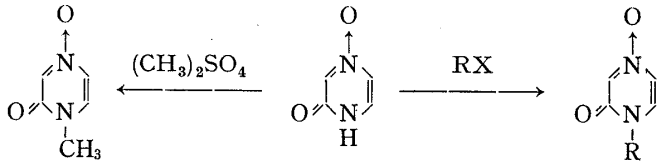
To extend our studies of 2(1*H*)-pyrazinone 4-oxides we also prepared 1-D-ribofuranosyl and 1-tetrahydrofuryl derivatives. 1-(β-D-Ribofuranosyl)-2(1*H*)-pyrazinone 4-oxide (**22**) was first synthesized by Bobek and Bloch in 10% overall yield by the reaction of 2-trimethylsilyloxypyrazine 4-oxide (**19**) with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose in the presence of titanium tetrachloride, followed by deacetylation.[7] We were able to obtain **22** in 36% overall yield by a slight modification of this procedure: treatment of **19** with 1-O-acetyl-2,3,5-tri-O-



13a, b **14a, b** **15a, b**

a: R=H
b: R=CH_3

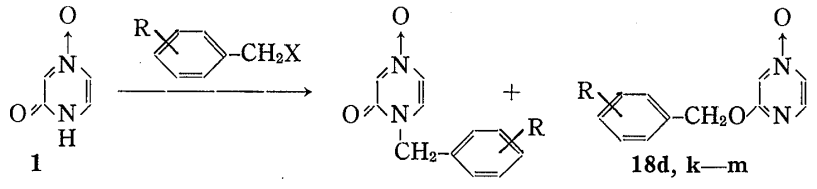
Chart 3



16a **1** **16b—s**

b: R=$CH_2CH{=}C(CH_3)_2$
c: R=$CH_2CH{=}CHC_6H_5$
d: R=CH_2CN
e: R=$CH_2CH_2CH_2CN$
f: R=$CH_2CH(O)CH_2$
g: R=CH_2CH_2OH
h: R=$CH_2CH(OH)CH_2OH$
i: R=CH_2COCH_3
j: R=$CH_2COC_6H_5$
k: R=$CH_2COC_6H_4$-4-Cl
l: R=$CH_2CONHC_6H_4$-4-Cl
m: R=$COOC_2H_5$
n: R=CH_2COOCH_3
o: R=$CH_2CH_2COOC_2H_5$
p: R=CH_2-(4-pyridyl)
q: R=CH_2-(2-furyl)
r: R=$CH(CH_3)C_6H_5$
s: R=$CH(C_6H_5)_2$
X=Cl or Br

Chart 4



1 **17a—w** **18d, k—m**

a: R=H
b: R=4-CH_3
c: R=2,4,6-$(CH_3)_3$
d: R=4-F
e: R=4-Cl
f: R=3-Cl
g: R=2-Cl
h: R=2,4-Cl_2
i: R=2,6-Cl_2
j: R=3,4-Cl_2
k: R=3,5-Cl_2
l: R=2-Cl-6-F
m: R=4-OCH_3
n: R=3-OCH_3
o: R=2-OCH_3
p: R=4-$N(CH_3)_2$
q: R=4-NO_2
r: R=3-NO_2
s: R=2-NO_2
t: R=4-CN
u: R=3-CN
v: R=2-CN
w: R=4-$CONH_2$
X=Cl or Br

Chart 5

7) M. Bobek and A. Bloch, *J. Med. Chem.*, **15**, 164 (1972).

benzoyl-β-D-ribofuranose (**20**) in the presence of stannic chloride gave 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2(1*H*)-pyrazinone 4-oxide (**21**), which was treated with methanolic ammonia to give **22**. Alternatively, transribosylation from N^4-acetyl-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)cytosine (**23**) to **19**, using the procedure of Azuma and Isono,[8] followed by treatment with sodium methoxide also gave **22**, but in only 3% overall yield. In addition, the proton magnetic resonance (PMR) spectrum of this product exhibited two doublets for 1′-H at 6.06 ppm (90%) and 6.33 ppm (10%). Since 1′-H of a β-anomer generally appears at higher field than that of an α-anomer,[9] this product must be a mixture of β- and α-anomers in a ratio of 9 : 1. In contrast, the product obtained from **21** showed only one doublet for 1′-H at 6.06 ppm, indicating that this is the β-anomer. 1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-2(1*H*)-pyrazinone 4-oxide (**24**) was also obtained by acetylation of **22** with acetic anhydride in pyridine. 1-(2-Tetrahydrofuryl)-2(1*H*)-pyrazinone 4-oxide (**26**) was obtained by reacting **19** with 2-*tert*-butoxytetrahydrofuran (**25**)[10] in the presence of stannic chloride in acetonitrile at room temperature (Chart 6).

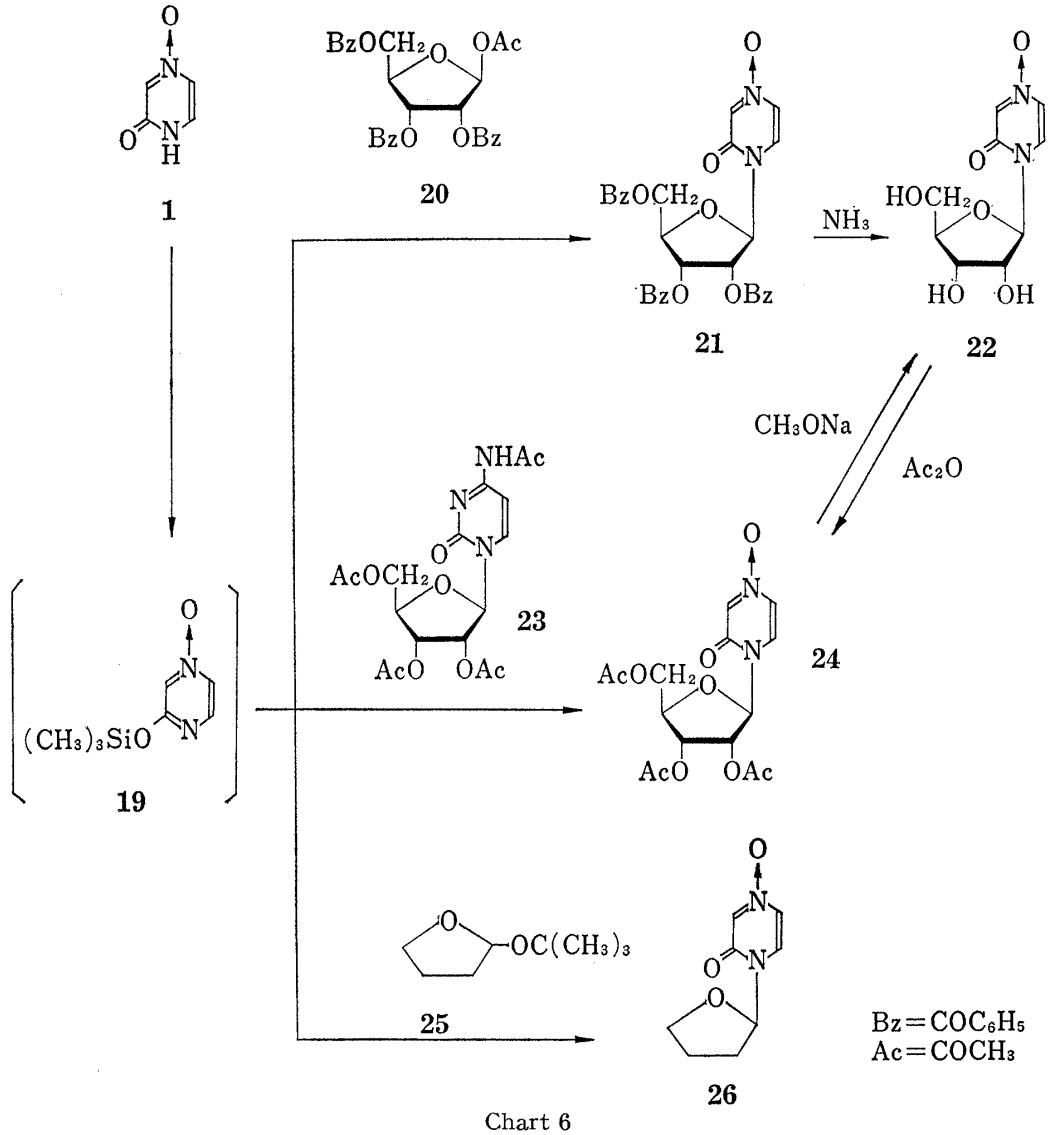
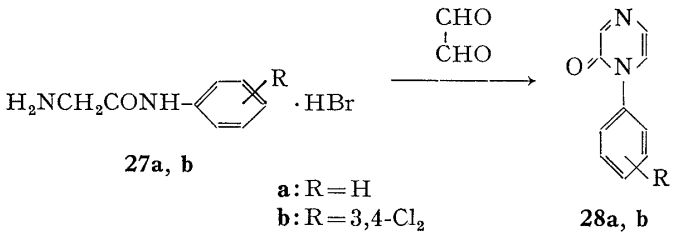


Chart 6

8) T. Azuma and K. Isono, *Chem. Pharm. Bull.*, **25**, 3347 (1977).
9) T. Nishimura and B. Shimizu, *Chem. Pharm. Bull.*, **13**, 803 (1965).
10) T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, O. Kusama, K. Kawasaki, and H. Sugi, *J. Heterocycl. Chem.*, **14**, 473 (1977).



27a, b

a: R=H
b: R=3,4-Cl_2

28a, b

Chart 7

Finally, in order to synthesize 1-aryl-2(1*H*)-pyrazinone 4-oxides, 1-aryl-2(1*H*)-pyrazinones (**28a, b**) were prepared by reaction of the corresponding glycinanilide hydrobromides (**27a, b**) with glyoxal in the presence of sodium hydroxide. However, an attempt to oxidize **28a, b** with MCPBA in 1,2-dichloroethane failed to give the 4-oxides (Chart 7).

Anticoccidial Activity

Anticoccidial screening in chickens against *Eimeria tenella* was carried out in battery experiments as described in the preceding paper,[11] except that each experiment was done in three replicates. Indicators of efficacy included measurements of bloody droppings, mortality, cecal lesions and relative weight gain. Bloody droppings per bird were graded as follows: −(normal), +(mild), ++(moderate), +++(severe). The cecal lesions were scored by the procedure of Johnson and Reid.[12]

Of the compounds tested (**2**—**5**, **7**—**18**, **21**, **22**, **24**, **26** and **28**), **21**, **22** and **24** exhibited marked activity. Complete protection was obtained with **22** at a dose level as low as 0.0016%. The biological results for these compounds are shown in Table I.

Table I. Anticoccidial Activity

Compound No.	Minium effective concentration in feed (%)	Bloody droppings (day after infection) 4	5	6	7	Mortality	Average cecal lesion score	Relative weight gain (%)
21	0.00625	−	−	−	−	0/9	0	105.1
22	0.0016	−	−	−	−	0/9	0	106.1
24	0.00312	−	−	−	−	0/9	0	107.0
Infected unmedicated control		+++	+++	+++	+++	3/9	4.0	40.6
Uninfected unmedicated control		−	−	−	−	0/9	0	100.0

Experimental

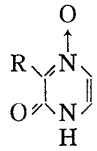
Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Boiling points are also uncorrected. Infrared (IR) spectra were recorded with a Hitachi 260-10 spectrophotometer, ultraviolet (UV) spectra with a Perkin-Elmer 450 spectrophotometer, and mass spectra (MS) with a Hitachi RMU-6D mass spectrometer. Optical rotation was measured with a Perkin-Elmer 141 polarimeter. PMR spectra were taken with a Varian T-60, A-60A, EM-390, HA-100 or XL-100-12 spectrometer and chemical shifts are expressed in ppm (δ) using tetramethylsilane as an internal standard. When D_2O was used as a solvent, sodium 2,2-dimethyl-2-silapentane-5-sulfonate was used as an internal standard. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Concentration operations were carried out under reduced pressure with a rotary evaporator.

11) M. Mano, T. Seo, T. Matsuno, and K. Imai, *Chem. Pharm. Bull.*, **24**, 2871 (1976).
12) J. Johnson and W.M. Reid, *Experimental Parasitol.*, **28**, 30 (1970).

Materials——3-Isobutyl-2(1*H*)-pyrazinone (**2c**),[13] 2-chloro-3-isopropyl- (**3a**),[3] 3-benzyl-2-chloro- (**3d**),[14] 2-chloro-5-phenyl- (**8a**),[5a,b] 2-chloro-5-(4-chlorophenyl)- (**8b**),[15] 2-chloro-6-methyl- (**13a**)[16] and 2-chloro-5,6-dimethylpyrazines (**13b**),[3] 4-chloro-,[17] 3,4-dichloro-,[18] 4-methoxy-[19] and 4-phenoxyphenylglyoxals[20] and glycinanilide hydrobromide (**27a**)[21] were prepared by the reported procedures.

3-*sec*-Butyl-2(1*H*)-pyrazinone (2b)——Compound **2b** was obtained as an oil by application of the procedure of Karmas and Spoerri.[3] PMR (CCl_4, T-60): 0.6—2.1 (8H, m, CH_3 and CH_2CH_3), 3.0—3.6 (1H, m, CH), 7.09 (1H, d, J=4 Hz, 5-H or 6-H), 7.37 (1H, d, J=4 Hz, 6-H or 5-H), 12.9 (1H, br s, NH).

Table II. 3-Substituted 2(1*H*)-Pyrazinone 4-Oxides



Compound No.	R	Recrystn. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
5a	$CH(CH_3)_2$	AcOEt–petroleum ether	45	148—150	$C_7H_{10}N_2O_2$	54.54 (54.52	6.54 6.57	18.17 18.09)
5b	$CH(CH_3)CH_2CH_3$	AcOEt–petroleum ether	18	121—124	$C_8H_{12}N_2O_2$	57.13 (57.07	7.19 7.21	16.65 16.44)
5c	$CH_2CH(CH_3)_2$	AcOEt	39	204—207	$C_8H_{12}N_2O_2 \cdot 1/2H_2O$	54.22 (54.12	7.39 6.89	15.81 16.18)
5d	$CH_2C_6H_5$	EtOH	38	231—234 (dec.)	$C_{11}H_{10}N_2O_2$	65.34 (65.57	4.98 4.75	13.85 13.57)

Compound No.	PMR[a] Solvent	Chemical shift
5a	$CDCl_3$	1.34 (6H, d, J=8 Hz, 2×CH_3), 3.6—4.0 (1H, m, CH), 7.06 (1H, d, J=6 Hz, 5-H or 6-H), 7.16 (1H, d, J=6 Hz, 6-H or 5-H)
5b	$CDCl_3$	0.88 (3H, t, J=8 Hz, $CH_2\underline{CH_3}$), 1.30 (3H, d, J=7 Hz, CH_3), 1.6—2.2 (2H, m, $\underline{CH_2}CH_3$), 3.4—3.9 (1H, m, CH), 7.08 (1H, d, J=5 Hz, 5-H or 6-H), 7.18 (1H, d, J=5 Hz, 6-H or 5-H)
5c	DMSO[b]-d_6	0.87 (6H, d, J=7Hz, 2×CH_3), 1.9—2.4 (1H, m, CH), 2.60 (2H, d, J=8 Hz, CH_2), 7.08 (1H, d, J=6 Hz, 5-H or 6-H), 7.35 (1H, d, J=6 Hz, 6-H or 5-H)
5d	DMSO-d_6	4.00 (2H, s, CH_2), 7.12 (1H, d, J=6 Hz, 5-H or 6-H), 6.9—7.5 (5H, m, Ar–H), 7.39 (1H, d, J=6 Hz, 6-H or 5-H), 11.9—12.4 (1H, br, NH)

a) Taken with a Varian HA-100 spectrometer.
b) Dimethyl sulfoxide.

13) R.M. Seifert, R.G. Buttery, D.G. Guadagni, D.R. Black, and J.G. Harris, *J. Agr. Food Chem.*, **18**, 246 (1970).
14) C.E.M. Ferber, H.E. Nursten, and M.R. Sheen, *Chem. Ind.* (London), **1975**, 746.
15) McNeil Laboratories, Inc., U.S. Patent 3761477 (1973).
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17) N. Kornblum, J.W. Powers, G.J. Anderson, W.J. Jones, H.O. Larson, O. Levand, and W.M. Weaver, *J. Am. Chem. Soc.*, **79**, 6562 (1957).
18) F. Kröhnke and E. Börner, *Ber.*, **69**, 2006 (1936).
19) H.-D. Becker and G.A. Russell, *J. Org. Chem.*, **28**, 1895 (1963).
20) G. Cavallini, *J. Med. Chem.*, **7**, 255 (1964).
21) M. Bergmann and H. F.-Conrat, *J. Biol. Chem.*, **124**, 1 (1938).

3-*sec*-Butyl-2-chloro- (3b) and 2-Chloro-3-isobutylpyrazine (3c)——Compounds **3b, c** were prepared according to the procedure of Karmas and Spoerri.[3] **3b**; yield 78%, bp 100—101° (18 mmHg). **3c**; yield 65%, bp 105—106° (20 mmHg).

2-Chloro-3-isobutylpyrazine 4-Oxide (4c)——A solution of **3c** (2.4 g, 14.2 mmol) and MCPBA (2.9 g, 16.9 mmol) in 1,2-dichloroethane (40 ml) was stirred at 65° for 15 hr. After cooling, the solution was successively washed with saturated $NaHCO_3$ (30 ml), 5% $Na_2S_2O_4$ (30 ml) and saturated $NaHCO_3$ (30 ml), then dried over $MgSO_4$, and concentrated. The residue was recrystallized from ligroin to give needles (1.5 g, 57%), mp 46—47°. *Anal.* Calcd for $C_8H_{11}ClN_2O$: C, 51.48; H, 5.94; N, 15.01. Found: C, 51.90; H, 5.87; N, 15.07. PMR ($CDCl_3$, T-60): 0.99 (6H, d, $J=6$ Hz, $2\times CH_3$), 2.0—2.7 (1H, m, CH), 2.99 (2H, d, $J=8$ Hz, CH_2), 8.12 (2H, s, 5-H and 6-H).

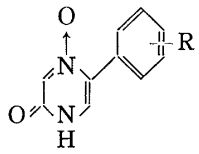
3-Benzyl-2-chloropyrazine 4-Oxide (4d)——Compound **4d** (6.23 g, 75%) was obtained from **3d** (3.97 g) in the manner described for **4c**, mp 117—118.5° (benzene–ligroin). *Anal.* Calcd for $C_{11}H_9ClN_2O$: C, 59.88; H, 4.11; N, 12.70. Found: C, 59.63; H, 3.85; N, 12.50. PMR ($CDCl_3$, T-60): 4.30 (2H, s, CH_2), 6.9—7.5 (5H, m, Ar–H), 7.95 (2H, s, 5-H and 6-H).

Compounds **4a** and **4b** were also prepared in the same manner and used for the next reaction without purification.

3-Isobutyl-2(1*H*)-pyrazinone 4-Oxide (5c) (Table II)——A mixture of **4c** (1.87 g, 10 mmol) and aqueous NaOH (NaOH 800 mg, H_2O 4 ml) was refluxed for 2 hr, diluted with H_2O, and passed through an Amberlite IR-120B (H^+) column (40 ml). After washing the column with H_2O, the effluent and the washings were combined (300 ml) and evaporated to dryness. The residue was recrystallized to give colorless needles (697 mg).

5-(3,4-Dichlorophenyl)- (7c), 5-(4-Methoxyphenyl)- (7d) and 5-(4-Phenoxyphenyl)-2(1*H*)-pyrazinone (7e)——Compounds **7c—e** were prepared according to the procedure of Sugiura *et al.*[5a] or Lont and Plas.[5b]

TABLE III. 5-Aryl-2(1*H*)-pyrazinone 4-Oxides[a]



Compound No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
11b	4-Cl	71	266—268 (dec.)	$C_{10}H_7ClN_2O_2$	53.95 (53.86	3.17 3.06	12.58 12.37)
11e	4-OC_6H_5	63	247—248 (dec.)	$C_{16}H_{12}N_2O_3$	68.57 (68.14	4.32 4.14	9.99 9.77)
11a	H	7[c]	245—248 (dec.)	$C_{10}H_8N_2O_2$	63.83 (63.48	4.29 4.15	14.89 14.63)
11c	3,4-Cl_2	11[c]	274—275 (dec.)	$C_{10}H_6Cl_2N_2O_2$	46.72 (46.91	2.35 2.30	10.90 10.76)
11d	4-OCH_3	21[c]	263—264 (dec.)	$C_{11}H_{10}N_2O_3$	60.55 (60.16	4.62 4.42	12.84 12.67)

Compound No.	PMR[b]
11b	7.41 (2H, d, $J=9$ Hz, Ar–H), 7.61 (2H, d, $J=9$ Hz, Ar–H), 7.66 (1H, s, 3-H or 6-H), 7.79 (1H, s, 6-H or 3-H)
11e	6.85—7.60 (7H, m, Ar–H), 7.55 (2H, d, $J=9$ Hz, Ar–H), 7.64 (1H, s, 3-H or 6-H), 7.72 (1H, s, 6-H or 3-H)
11a	7.30—7.55 (5H, m, Ar–H), 7.65 (1H, s, 3-H or 6-H), 7.68 (1H, s, 6-H or 3-H)
11c	7.55—7.95 (5H, m, 3-H, 6-H and Ar–H)
11d	3.80 (3H, s, OCH_3), 6.96 (2H, d, $J=9$ Hz, Ar–H), 7.49 (2H, d, $J=9$ Hz, Ar–H), 7.64 (1H, s, 3-H or 6H), 7.67 (1H, s, 6-H or 3-H)

a) Recrystallized from EtOH.
b) Measured in DMSO-d_6 with a Varian A-60A spectrometer.
c) Based on 2-chloro-5-arylpyrazine.

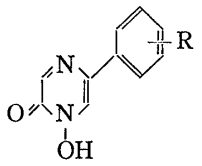
7c; yield 61%, mp 197—198° (AcOEt). *Anal.* Calcd for $C_{10}H_6Cl_2N_2O$: C, 49.82; H, 2.51; N, 11.62. Found: C, 49.60; H, 2.30; N, 11.59. **7d**; yield 60%, mp 187—188° (AcOEt). *Anal.* Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.58; H, 4.94; N, 13.68. **7e**; yield 52%, mp 202—203° (AcOEt). *Anal.* Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.37; H, 4.32; N, 10.56.

2-Chloro-5-(3,4-dichlorophenyl)pyrazine (8c)——A mixture of **7c** (13.7 g, 57 mmol), phosphoryl chloride (39 ml) and DMF (8 drops) was refluxed for 1.5 hr. After cooling, the solution was poured into ice-H_2O and extracted with ether (300, 200, 100 ml). The combined ether extract was washed with 10% NaOH (200, 100 ml) and H_2O (100 ml), dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (Merck) (100 g) with $CHCl_3$ as the eluent. The eluate was evaporated to dryness and the residue was recrystallized from MeOH to give needles (3.85 g, 26%), mp 121—122°. *Anal.* Calcd for $C_{10}H_5Cl_3N_2$: C, 46.28; H, 1.94; N, 10.79. Found: C, 46.12; H, 1.81; N, 10.59.

5-(4-Methoxyphenyl)- (8d) and 5-(4-Phenoxyphenyl)-2-chloropyrazine (8e)——Compounds **8d, e** were prepared in the manner described for **8c**. **8d**; yield 31%, mp 117—118° (MeOH). *Anal.* Calcd for $C_{11}H_9ClN_2O$: C, 59.88; H, 4.11; N, 12.70. Found: C, 59.97; H, 3.91; N, 12.58. **8e**; yield 40%, mp 95—96° (MeOH). *Anal.* Calcd for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; N, 9.91. Found: C, 68.09; H, 3.65; N, 9.73.

5-(3,4-Dichlorophenyl)-2(1*H*)-pyrazinone 4-Oxide (11c) and 5-(3,4-Dichlorophenyl)-1-hydroxy-2(1*H*)-pyrazinone (12c) (Tables III and IV)——A solution of **8c** (3.5 g, 13.5 mmol) and MCPBA (2.55 g, 14.7 mmol) in 1,2-dichloroethane (60 ml) was stirred at 70° for 10 hr. Additional MCPBA (1.2 g, 7 mmol) was added and the mixture was stirred at 70° for 11.5 hr. Further MCPBA (800 mg, 4.6 mmol) was then added and the

Table IV. 1-Hydroxy-5-aryl-2(1*H*)-pyrazinones[a]

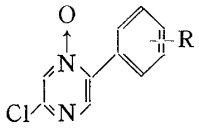


Compound No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
12b	4-Cl	62	171—173	$C_{10}H_7ClN_2O_2$	53.95 (53.60	3.17 2.92	12.58 12.39)
12e	4-OC_6H_5	58	185—187	$C_{16}H_{12}N_2O_3$	68.57 (68.21	4.32 4.21	9.99 9.86)
12a	H	7[c]	182—185[d]	$C_{10}H_8N_2O_2$	63.83 (63.71	4.29 4.17	14.89 14.65)
12c	3,4-Cl_2	9[c]	201—203	$C_{10}H_6Cl_2N_2O_2$	46.72 (46.69	2.35 2.38	10.90 10.39)
12d	4-OCH_3	14[c]	187—188	$C_{11}H_{10}N_2O_3$	60.55 (60.02	4.62 4.46	12.84 12.55)

Compound No.	PMR[b]
12b	7.42 (2H, d, J=9 Hz, Ar–H), 7.90 (2H, d, J=9 Hz, Ar–H), 8.19 (1H, s, 3-H or 6-H), 8.61 (1H, s, 6-H or 3-H)
12e	6.85—7.6 (7H, m, Ar–H), 7.88 (2H, d, J=9 Hz, Ar–H), 8.19 (1H, s, 3-H or 6-H), 8.52 (1H, s, 6-H or 3-H)
12a	7.2—7.6 (3H, m, Ar–H), 7.7—8.0 (2H, m, Ar–H), 8.22 (1H, s, 3-H or 6-H), 8.56 (1H, s, 6-H or 3-H)
12c	7.62 (1H, d, J=9 Hz, Ar–H), 7.90 (1H, dd, J=2 Hz, 9 Hz, Ar–H), 8.13 (1H, d, J=2 Hz, Ar–H), 8.21 (1H, s, 3-H or 6-H), 8.75 (1H, s, 6-H or 3-H)
12d	3.80 (3H, s, OCH_3), 6.97 (2H, d, J=9 Hz, Ar–H), 7.81 (2H, d, J=9 Hz, Ar–H), 8.19 (1H, s, 3-H or 6-H), 8.46 (1H, s, 6-H or 3-H)

a) Recrystallized from $CHCl_3$–petroleum ether.
b) Measured in DMSO-d_6 with a Varian A-60A spectrometer.
c) Based on 2-chloro-5-arylpyrazine.
d) Lit.[6] mp 194—196° (dec.).

Table V. 2-Chloro-5-arylpyrazine 4-Oxides[a)]

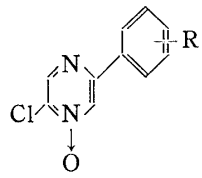


Compound No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
9b	4-Cl	16	215—216	$C_{10}H_6Cl_2N_2O$	49.82 (50.00	2.51 2.45	11.62 11.49)
9e	4-OC_6H_5	24	147—148	$C_{16}H_{11}ClN_2O_2$	64.33 (63.98	3.71 3.61	9.38 9.29)

Compound No.	PMR[b)]
9b	7.55 (2H, d, J=9 Hz, Ar–H), 7.85 (2H, d, J=9 Hz, Ar–H), 8.63 (1H, s, 3-H or 6-H), 8.73 (1H, s, 6-H or 3-H)
9e	7.09 (2H, d, J=9 Hz, Ar–H), 7.0—7.65 (5H, m, Ar–H), 7.86 (2H, d, J=9 Hz, Ar–H), 8.61 (1H, s, 3-H or 6-H), 8.71 (1H, s, 6-H or 3-H)

a) Recrystallized from MeOH.
b) Measured in DMSO-d_6 with a Varian A-60A spectrometer.

Table VI. 2-Chloro-5-arylpyrazine 1-Oxides[a)]



Compound No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
10b	4-Cl	8	204—205	$C_{10}H_6Cl_2N_2O$	49.82 (50.12	2.51 2.18	11.62 11.49)
10e	4-OC_6H_5	16	136—137	$C_{16}H_{11}ClN_2O_2$	64.33 (63.84	3.71 3.48	9.38 9.20)

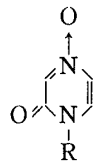
Compound No.	PMR[b)]
10b	7.53 (2H, d, J=9 Hz, Ar–H), 8.10 (2H, d, J=9 Hz, Ar–H), 8.88 (1H, s, 3-H or 6-H), 9.18 (1H, s, 6-H or 3-H)
10e	7.08 (2H, d, J=9 Hz, Ar–H), 7.0—7.65 (5H, m, Ar–H), 8.11 (2H, d, J=9 Hz, Ar–H), 8.87 (1H, s, 3-H or 6-H), 9.12 (1H, s, 6-H or 3-H)

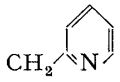
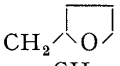
a) Recrystallized from MeOH.
b) Measured in DMSO-d_6 with a Varian A-60A spectrometer.

mixture was stirred at 70° for 31.5 hr. After work-up as described for **4c**, the residue was purified by column chromatography on silica gel (50 g) with $CHCl_3$ as the eluent, and recrystallization from MeOH gave a mixture of **9c** and **10c** as colorless needles (942 mg). PMR (DMSO-d_6, A-60A): 7.65—8.40 (6H, m, Ar–H), 8.68 (1H, s, 3-H or 6-H of **9c**), 8.77 (1H, s, 6-H or 3-H of **9c**), 8.90 (1H, s, 3-H or 6-H of **10c**), 9.26 (1H, s, 6-H or 3-H of **10c**).

The mixture of **9c** and **10c** (750 mg) was directly hydrolyzed by heating with a solution of NaOH (327 mg, 8.2 mmol) in H_2O (20 ml) and dioxane (20 ml) at 70° for 3 hr. After removal of dioxane, the aqueous solution

TABLE VII. 1-Alkyl-2(1*H*)-pyrazinone 4-Oxides



Compound No.	R	Recrystn.[a] solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1} (C=O)
16a	CH_3	A	20	182—183[b]	$C_5H_6N_2O_2$	47.62 (47.32	4.80 4.68	22.21 22.19)	1655
16b	$CH_2CH{=}C(CH_3)_2$	B	28	56— 60	$C_9H_{12}N_2O_2$	59.99 (59.58	6.71 6.73	15.54 15.30)	1655
16c	$CH_2CH{=}CHC_6H_5$	C	45	131—132	$C_{13}H_{12}N_2O_2$	68.41 (67.93	5.30 5.27	12.27 12.07)	1665
16d	CH_2CN	—[c]	9	135—139	$C_6H_5N_3O_2$	47.69 (47.34	3.33 3.25	27.80 27.87)	1670
16e	$CH_2CH_2CH_2CN$	D	34	125—128	$C_8H_9N_3O_2$	53.63 (53.33	5.06 5.08	23.45 23.47)	1660
16f	$CH_2CH(O)CH_2$	B	7	105	$C_7H_8N_2O_3$	50.00 (49.97	4.80 4.70	16.66 16.66)	1660
16g	CH_2CH_2OH	—[c]	15	100—106	$C_6H_8N_2O_3 \cdot 1/4H_2O$	44.86 (44.92	5.33 5.15	17.44 17.27)	1660
16h	$CH_2CH(OH)CH_2OH$	—	16	Oil	—	—	—	—	1660[d]
16i	CH_2COCH_3	E	43	143	$C_7H_8N_2O_3 \cdot 3/4H_2O$	46.28 (45.98	5.27 5.03	15.42 15.33)	1660
16j	$CH_2COC_6H_5$	C	27	151	$C_{12}H_{10}N_2O_3$	62.61 (62.33	4.38 4.20	12.17 11.80)	1665
16k	$CH_2COC_6H_4$-4-Cl	F	43	215	$C_{12}H_9ClN_2O_3$	54.46 (54.36	3.43 3.44	10.58 10.94)	1660
16l	$CH_2CONHC_6H_4$-4-Cl	F	23	267 (dec.)	$C_{12}H_{10}ClN_3O_3$	51.53 (51.37	3.60 3.74	15.02 15.09)	1660
16m	$COOC_2H_5$	B	11	107—110	$C_7H_8N_2O_4$	45.66 (45.65	4.38 4.36	15.21 15.23)	1680
16n	CH_2COOCH_3	B	56	145—148	$C_7H_8N_2O_4$	45.66 (45.37	4.38 4.35	15.21 15.30)	1670
16o	$CH_2CH_2COOC_2H_5$	—	18	Oil	—	—	—	—	1660[d]
16p		D	23	119	$C_{10}H_9N_3O_2$	59.11 (59.05	4.46 4.25	20.68 20.81)	1660
16q		D	11	108—109	$C_9H_{12}N_2O_3$	55.09 (54.93	6.16 6.11	14.28 14.02)	1665
16r	$CH(CH_3)C_6H_5$	G	18	106—107	$C_{12}H_{12}N_2O_2$	66.65 (66.52	5.59 5.64	12.95 12.79)	1665
16s	$CH(C_6H_5)_2$	G	4	161—163	$C_{17}H_{14}N_2O_2$	73.37 (73.16	5.07 5.09	10.07 9.97)	1660

a) A: $CHCl_3$–petroleum ether; B: CH_2Cl_2–ether; C: CH_2Cl_2; D: AcOEt–MeOH; E: EtOH; F: DMF; G: AcOEt–petroleum ether.
b) Lit.[7] mp 190—191°.
c) Not recrystallized.
d) Neat.

was diluted with H_2O and adjusted to pH 1 with 20% HCl. The precipitate was collected by filtration and recrystallized to give **11c** (298 mg) as needles. The mother liquor was evaporated to dryness and the residue was recrystallized twice to give **12c** (253 mg) as needles.

2-Chloro-5-(4-phenoxyphenyl)pyrazine 4-Oxide (9e) and 1-Oxide (10e) (Tables V and VI)——Compound **8e** (3.9 g, 13.8 mmol) was oxidized in the manner described for **11c**. Crude products were chromatographed on silica gel (50 g) with $CHCl_3$ as the eluent to give **9e** (980 mg) as needles and **10e** (647 mg) as needles.

5-(4-Phenoxyphenyl)-2(1*H*)-pyrazinone 4-Oxide (11e) (Table III)——Using a procedure similar to that described for **11c**, **9e** (750 mg, 2.5 mmol) was treated with a solution of NaOH (300 mg, 7.5 mmol) in H_2O (15 ml) and dioxane (15 ml) to give needles (440 mg).

1-Hydroxy-5-(4-phenoxyphenyl)-2(1*H*)-pyrazinone (12e) (Table IV)——Compound **12e** (262 mg) was prepared from **10e** (480 mg, 1.6 mmol) in the manner described for **11e**.

2-Chloro-6-methylpyrazine 4-Oxide (14a)——Compound **14a** (300 mg, 42%) was obtained from **13a** (643 mg) in the manner described for **4c**, mp 109—110° (AcOEt-petroleum ether) (lit.[22] mp 109—110°). PMR ($CDCl_3$, XL-100-12): 2.51 (3H, s, CH_3), 7.93 (1H, br s, 3-H or 5-H), 8.02 (1H, br s, 5-H or 3-H); in a spin decoupling experiment, irradiation at 2.51 ppm changed the signals at 7.93 and 8.02 ppm to doublets (J= 1.5 Hz).

2-Chloro-5,6-dimethylpyrazine 4-Oxide (14b)——Compound **14b** (1.2 g, 52%) was obtained from **13b** (2.06 g) in the manner described for **4c**, mp 53—54.5° (ligroin). *Anal.* Calcd for $C_6H_7ClN_2O$: C, 45.44; H, 4.45; N, 17.66. Found: C, 45.24; H, 4.51; N, 18.01.

6-Methyl-2(1*H*)-pyrazinone 4-Oxide (15a)——Compound **15a** (170 mg, 67%) was obtained from **14a** (288 mg) in the manner described for **5c**, mp 250—253° (dec.) [90% EtOH–ether (1: 1)] [lit.[7] mp>250° (dec.)]. PMR (DMSO-d_6, XL-100-12): 2.14 (3H, s, CH_3), 7.05—7.17 (1H, m, 3-H or 5-H), 7.38 (1H, d, J= 2 Hz, 5-H or 3-H); in a spin decoupling experiment, irradiation at 2.14 ppm collapsed the signal at 7.05—7.17 ppm to a doublet (J=2 Hz).

5,6-Dimethyl-2(1*H*)-pyrazinone 4-Oxide (15b)——Compound **15b** (282 mg, 40%) was obtained from **14b** (795 mg) in the manner described for **5c**, mp 236—239° (dec.) [90% EtOH–ether (1: 1)]. *Anal.* Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.26; H, 5.77; N, 20.00.

1-Methyl-2(1*H*)-pyrazinone 4-Oxide (16a) (Table VII)——An ice-cooled and stirred suspension of **1** (560 mg, 5 mmol) in DMF (7 ml) was treated with 50% NaH–mineral oil (240 mg, 5 mmol) and the mixture was stirred for 1 hr. Dimethyl sulfate (630 mg, 5 mmol) was then added and the mixture was allowed to stand overnight at room temperature. The solvent was removed and the residue was extracted with hot $CHCl_3$. After removal of $CHCl_3$, the residue was chromatographed on silica gel (20 g) with $CHCl_3$ as the eluent. The eluate was evaporated to dryness and the residue was recrystallized to give needles (124 mg).

Compounds **16b—s** were prepared similarly.

1-(α-Methylbenzyl)-2(1*H*)-pyrazinone 4-Oxide (16r)——UV $\lambda_{max}^{0.1NHCl}$ nm (ε): 222.5 (25000), 275 (9600), 330 (5100); $\lambda_{max}^{H_2O}$ nm (ε): 222.5 (24800), 275 (9600), 332.5 (5100); $\lambda_{max}^{0.1NNaOH}$ nm (ε): 222.5 (25300), 276 (9600), 332.5 (5100).

1-(4-Fluorobenzyl)-2(1*H*)-pyrazinone 4-Oxide (17d) and 2-(4-Fluorobenzyloxy)pyrazine 4-Oxide (18d) (Tables VIII and IX)——(Method A) A solution of **1** (785 mg, 7 mmol) in DMF (35 ml) was treated with 50% NaH–mineral oil (336 mg, 7 mmol) in the manner described for **16a**. After addition of 4-fluorobenzyl chloride (1.01 g, 7 mmol), the mixture was stirred at 80° for 2 hr and evaporated to dryness. The residue was dissolved in $CHCl_3$ and the $CHCl_3$ solution was washed with H_2O, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (50 g) with $CHCl_3$ as the eluent to give **18d** (145 mg) and **17d** (668 mg).

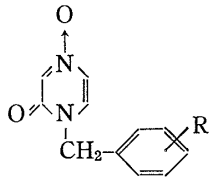
1-Benzyl-2(1*H*)-pyrazinone 4-Oxide (17a) (Table VIII)——(Method B) Compound **1** (560 mg, 5 mmol) was treated with benzyl chloride (0.57 ml, 5 mmol) in the manner described for **17d**. The crude products were chromatographed on silica gel (20 g) with $CHCl_3$ as the eluent. The eluate was evaporated to dryness and the residue was recrystallized to give needles (336 mg). UV $\lambda_{max}^{0.1NHCl}$ nm (ε): 222 (24900), 275 (9700), 330 (5000); $\lambda_{max}^{H_2O}$ nm (ε): 222 (24400), 275 (9700), 330 (5000); $\lambda_{max}^{0.1NNaOH}$ nm (ε): 222.5 (26100), 275 (9800), 330 (5100).

1-(4-Nitrobenzyl)-2(1*H*)-pyrazinone 4-Oxide (17q) (Table VIII)——(Method C) Using a procedure similar to that described for **17a**, **17q** (948 mg) was prepared from **1** (785 mg, 7 mmol) without purification by column chromatography.

1-(4-Methylbenzyl)-2(1*H*)-pyrazinone 4-Oxide (17b) (Table VIII)——(Method D) Compound **1** (560 mg, 5 mmol) was added to a solution of sodium (115 mg, 5 mg-atom) in anhydrous MeOH (20 ml), and the mixture was refluxed for 30 min. 4-Methylbenzyl chloride (774 mg, 5.5 mmol) was then added and the mixture was refluxed for 5 hr. After cooling, MeOH was removed and the residue was dissolved in $CHCl_3$ and H_2O. The $CHCl_3$ layer was separated, washed with H_2O, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (15 g) with $CHCl_3$ as the eluent. The eluate was evaporated to dryness and the residue was recrystallized to give needles (320 mg).

22) B. Klein, N.E. Hetman, and M.E. O'Donnel, *J. Org. Chem.*, **28**, 1682 (1963).

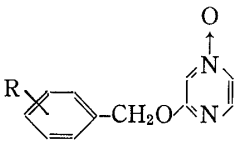
TABLE VIII. 1-Benzyl-2(1*H*)-pyrazinone 4-Oxides



Compound No.	R	Method	Recrystn. solvent[a]	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N	IR ν_{max}^{KBr} cm^{-1} (C=O)	PMR[b] Solvent	Chemical shift CH_2 (s)
17a	H	B	A	33	93— 95	$C_{11}H_{10}N_2O_2$	65.34	4.98	13.85	65.13	4.89	13.82	1660	$CDCl_3$	5.02
17b	4-CH_3	D	A	30	129—131	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.95	66.78	5.34	12.92	1660	$CDCl_3$	5.02
17c	2,4,6-$(CH_3)_3$	B	B	53	173—174	$C_{14}H_{16}N_2O_2$	68.83	6.60	11.47	68.94	6.58	11.26	1655	$CDCl_3$	5.05
17d	4-F	A	B	43	115—116	$C_{11}H_9FN_2O_2$	60.00	4.12	12.72	60.17	4.07	12.68	1655	$CDCl_3$	5.05
17e	4-Cl	B	B	50	128—129	$C_{11}H_9ClN_2O_2$	55.83	3.83	11.84	55.93	3.71	11.81	1665	$CDCl_3$	5.04
17f	3-Cl	D	B	37	70— 71	$C_{11}H_9ClN_2O_2$	55.83	3.83	11.84	55.74	3.70	11.86	1660	$CDCl_3$	5.03
17g	2-Cl	B	B	50	128—130	$C_{11}H_9ClN_2O_2$	55.83	3.83	11.84	56.07	3.66	11.86	1665	$CDCl_3$	5.19
17h	2,4-Cl_2	B	B	53	142—143	$C_{11}H_8Cl_2N_2O_2$	48.73	2.97	10.33	48.92	2.86	10.44	1660	$CDCl_3$	5.17
17i	2,6-Cl_2	C	C	56	179—180	$C_{11}H_8Cl_2N_2O_2$	48.73	2.97	10.33	49.08	2.86	10.15	1660	$CDCl_3$	5.42[c]
17j	3,4-Cl_2	D	D	28	166—168	$C_{11}H_8Cl_2N_2O_2$	48.73	2.97	10.33	48.67	2.98	10.16	1655	$CDCl_3$	5.07
17k	3,5-Cl_2	A	B	42	195—196	$C_{11}H_8Cl_2N_2O_2$	48.73	2.97	10.33	48.67	2.90	10.36	1650	DMSO-d_6	5.07
17l	2-Cl-6-F	A	B	46	160—161	$C_{11}H_8ClFN_2O_2$	51.88	3.17	11.00	51.89	3.05	11.00	1655	$CDCl_3$	5.20[d]
17m	4-OCH_3	A	B	46	114—115	$C_{12}H_{12}N_2O_3$	62.06	5.21	12.06	62.15	5.24	12.04	1660	$CDCl_3$	4.99
17n	3-OCH_3	B	B	54	84—85	$C_{12}H_{12}N_2O_3$	62.06	5.21	12.06	61.97	5.07	12.03	1660	$CDCl_3$	5.02
17o	2-OCH_3	B	B	61	126—127	$C_{12}H_{12}N_2O_3$	62.06	5.21	12.06	62.00	5.09	12.00	1650	$CDCl_3$	5.03
17p	4-$N(CH_3)_2$	B[e]	B	25	163—164	$C_{13}H_{15}N_3O_2$	63.66	6.16	17.13	63.69	6.00	16.85	1650	DMSO-d_6	4.92
17q	4-NO_2	C	E	55	199—200	$C_{11}H_9N_3O_4$	53.45	3.67	17.00	53.32	3.61	17.00	1650	DMSO-d_6	5.23
17r	3-NO_2	C	E	52	145—146	$C_{11}H_9N_3O_4$	53.45	3.67	17.00	53.40	3.66	17.09	1650	DMSO-d_6	5.25
17s	2-NO_2	C	E	54	195—196	$C_{11}H_9N_3O_4$	53.45	3.67	17.00	53.37	3.67	17.06	1650	DMSO-d_6	5.42
17t	4-CN	C	E	38	196—197	$C_{12}H_9N_3O_2$	63.43	3.99	18.49	63.12	4.03	18.22	1650	DMSO-d_6	5.22
17u	3-CN	C	E	35	178—179	$C_{12}H_9N_3O_2$	63.43	3.99	18.49	63.33	3.94	18.28	1655	DMSO-d_6	5.16
17v	2-CN	C	E	38	161—162	$C_{12}H_9N_3O_2$	63.43	3.99	18.49	63.49	3.93	18.27	1660	DMSO-d_6	5.25
17w	4-$CONH_2$	C	E	28	198—199	$C_{12}H_{11}N_3O_3 \cdot 1/4C_2H_5OH$	58.47	4.91	16.37	58.10	4.66	16.68	1650	DMSO-d_6	5.17

a) A: $CHCl_3$–petroleum ether; B: AcOEt–petroleum ether; C: benzene; D: MeOH–H_2O; E: EtOH.
b) Taken with a Varian T-60 spectrometer.
c) Taken with a Varian HA-100 spectrometer.
d) Taken with a Varian EM-390 spectrometer.
e) 4-Dimethylaminobenzyl chloride hydrochloride[f] was used.
f) M. Wakselman and M. Domé, *Bull. Soc. Chim. Fr.*, **1975**, 571.

Table IX. 2-Benzyloxypyrazine 4-Oxides



Compound No.	R	Recrystn. solvent	Yield (%)	mp (°C)	PMR[a] CH_2(s)
18d	4-F	Ether–petroleum ether	9	93— 95	5.35
18k	3,5-Cl_2	AcOEt–petroleum ether	10	144—145	5.41[b]
18l	2-Cl-6-F	Ether–petroleum ether	8	93— 94	5.53
18m	4-OCH_3	Ether–petroleum ether	7	87— 89	5.30

a) Measured in $CDCl_3$ with a Varian EM-390 spectrometer.
b) Taken with a Varian T-60 spectrometer.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-2(1*H*)-pyrazinone 4-Oxide (21)——A mixture of **1** (5.6 g, 50 mmol), hexamethyldisilazane (50 ml) and chlorotrimethylsilane (2.5 ml) was heated at 90—95° with stirring until a clear solution was obtained (7.5 hr). The solution was cooled, diluted with anhydrous toluene (250 ml) and concentrated. The remaining residue was coevaporated once more with anhydrous toluene (250 ml) to give **19** as crystals, which were dissolved in dichloromethane (500 ml). To this solution, **20** (25.15 g, 50 mmol) and $SnCl_4$ (5 ml) were added. The mixture was then stirred at room temperature for 1.5 hr. After standing overnight, the solution was poured into saturated $NaHCO_3$ (1.8 l) with vigorous stirring. The mixture was filtered using Hyflo Super-Cel as a filter aid, and was subsequently washed with $CHCl_3$. The organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (200 g) with $CHCl_3$ as the eluent. The eluate was concentrated and the residue was recrystallized from toluene to give colorless needles (11.75 g, 42%), mp 136—137°. *Anal.* Calcd for $C_{30}H_{24}N_2O_9$: C, 64.75; H, 4.35; N, 5.03. Found: C, 64.80; H, 4.33; N, 4.75. PMR ($CDCl_3$, EM-390): 4.61—4.92 (3H, m, 4′-H and 5′,5′-H), 5.69—5.93 (2H, m, 2′-H and 3′-H), 6.43 (1H, d, J=4 Hz, 1′-H), 6.84 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.20—7.67 (12H, m, 3-H, 6-H and Ar-H), 7.87—8.13 (5H, m, Ar-H). IR ν_{max}^{KBr} cm^{-1}: 1720, 1665, 1620.

1-(β-D-Ribofuranosyl)-2(1*H*)-pyrazinone 4-Oxide (22)——i) An ice-cooled solution of **21** (37.6 g, 68 mmol) in methanolic ammonia (2.1 l) was stirred for 7 hr, concentrated and diluted with H_2O. The aqueous solution was washed with benzene and evaporated to dryness. The residue was dissolved in MeOH and treated with activated charcoal. After removal of MeOH, the residue was triturated with acetone to give colorless crystals (14.09 g, 85%). For analysis, a 300 mg portion of these crystals was recrystallized from 96% EtOH to give **22** as colorless prisms (150 mg), mp 129—131° [lit.[7] mp 196—197° (dec.)]. *Anal.* Calcd for $C_9H_{12}N_2O_6$: C, 44.27; H, 4.95; N, 11.47. Found: C, 44.29; H, 4.91; N, 11.50. PMR (D_2O, EM-390): 3.73—4.08 (2H, m, 5′,5′-H), 4.13—4.48 (3H, m, 2′-H, 3′-H and 4′-H), 6.06 (1H, d, J=2 Hz, 1′-H), 7.47 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.87 (1H, d, J=2 Hz, 3-H), 8.20 (1H, d, J=6 Hz, 6-H). IR ν_{max}^{KBr} cm^{-1}: 1640, 1605. MS *m/e*: 244 (M^+), 228 (M^+-16), 171, 152, 133, 113.

ii) Compound **19** prepared from **1** (3.36 g, 30 mmol) was dissolved in 1,2-dichloroethane (70 ml) and acetonitrile (80 ml), then **23** (8.24 g, 20 mmol) and $SnCl_4$ (4 ml) were added. After refluxing for 24 hr with stirring, the solution was treated according to the procedure described for **21**. Elution with $CHCl_3$–MeOH (9: 1) afforded **24** (1.28 g) as a yellow oil, which was dissolved in MeOH (100 ml). Next, 28% MeONa–MeOH (2 ml) was added dropwise at room temperature with stirring until the pH reached 9. After stirring for 30 min, the solution was adjusted to pH 5 with MeOH-washed Amberlite IR-120 B(H^+) resin. The resin was filtered and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel (40 g), eluting with $CHCl_3$–MeOH (19: 1) followed by $CHCl_3$–MeOH (9: 1). The fraction eluted with the latter solvent was concentrated and the residue was reprecipitated from MeOH–ether to give an anomeric mixture of **22** (150 mg, 3%) as a colorless powder. PMR (D_2O, EM-390): 3.68—4.10 (2H, m, 5′,5′-H), 4.13—4.50 (3H, m, 2′-H, 3′-H and 4′-H), 6.06 (1H, d, J=2 Hz, 1′-H), 7.46 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.86 (1H, d, J=2 Hz, 3-H), 8.19 (1H, d, J=6 Hz, 6-H), 6.33 (d, J=4 Hz, 1′-H of the α-anomer).

1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-2(1*H*)-pyrazinone 4-Oxide (24)——A mixture of **22** (732 mg, 3 mmol) and acetic anhydride (1.23 ml, 11.3 mmol) in pyridine (7.5 ml) was stirred at room temperature for 3 hr and then allowed to stand overnight. The solution was evaporated to dryness and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with saturated $NaHCO_3$ and H_2O, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (50 g) with $CHCl_3$ as the eluent. The eluate was concentrated to give an oil (915 mg, 83%). PMR ($CDCl_3$, T-60): 2.10 (6H, s, $2\times COCH_3$), 2.12 (3H, s, $COCH_3$), 4.44 (3H, br s, 4′-H and 5′,5′-H), 5.23—5.53 (2H, m, 2′-H and 3′-H), 6.13 (1H, d, J=4 Hz, 1′-H), 7.08 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.50 (1H, d, J=2 Hz, 3-H), 7.52 (1H, d, J=6 Hz, 6-H).

1-(2-Tetrahydrofuryl)-2(1*H*)-pyrazinone 4-Oxide (26)——Compound **25**[23] (6.9 g, 48 mmol) and $SnCl_4$ (4 ml) were added to a solution of **19** [prepared from **1** (4.48 g, 40 mmol)] in acetonitrile (400 ml). The solution was stirred at room temperature for 1 hr and treated according to the procedure described for **21**. Column chromatography on silica gel (100 g) with AcOEt as the eluent afforded two fractions. After removal of the solvent from the latter fraction, purification of the residue by column chromatography on silica gel (40 g) with $CHCl_3$ followed by recrystallization from AcOEt–petroleum ether gave **26** (315 mg, 4%) as colorless needles, mp 127—128°. *Anal.* Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.71; H, 5.47; N, 15.33. PMR ($CDCl_3$, EM-390): 1.63—2.77 (4H, m, 3′,3′-H and 4′,4′-H), 3.83—4.40 (2H, m, 5′,5′-H), 6.02 (1H, dd, J=2 Hz, 5 Hz, 2′-H), 7.05 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.37 (1H, d, J=6 Hz, 6-H), 7.48 (1H, d, J=2 Hz, 3-H). IR ν_{max}^{KBr} cm^{-1}: 1660, 1600. UV $\lambda_{max}^{0.1NHCl}$ nm (ε): 220.5 (21900); 272 (9100), 330 (4800); $\lambda_{max}^{H_2O}$ nm (ε): 221.5 (22600), 272 (9200), 330 (5000); $\lambda_{max}^{0.1NNaOH}$ nm (ε): 220.5 (24600), 272 (9300), 327.5 (5200). $[\alpha]_D^{23}$ 0° (c=1, MeOH).

2-Benzyloxycarbonylamino-3′,4′-dichloroacetanilide (29)——$SOCl_2$ (0.73 ml, 10 mmol) was added dropwise to DMF (1 ml) at −20 to −10° with stirring. The mixture was stirred at the same temperature for 10 min and at room temperature for 30 min, and was then evaporated to dryness. A solution of benzyloxycarbonylglycine (2.09 g, 10 mmol) in DMF (3 ml) was added to the residue at −20 to −10° with stirring. After stirring at −20 to −10° for 10 min, the resulting solution was added dropwise to an ice-cooled, stirred solution of 3,4-dichloroaniline (1.62 g, 10 mmol) and pyridine (1.6 ml, 20 mmol) in DMF (2 ml). The mixture was stirred for 1 hr and diluted with H_2O (100 ml). The precipitate was collected by filtration, washed with H_2O and recrystallized from MeOH to give colorless needles (2.55 g, 72%), mp 161—162°. *Anal.* Calcd for $C_{16}H_{14}Cl_2N_2O_3$: C, 54.41; H, 4.00; N, 7.93. Found: C, 54.61; H, 3.90; N, 7.94.

2-Amino-3′,4′-dichloroacetanilide Hydrobromide (27b)——A mixture of **29** (23 g, 65 mmol) and 30% HBr–AcOH (80 ml) was stirred at room temperature for 2 hr, diluted with ether (500 ml) and cooled. The precipitate was collected by filtration, washed with ether and recrystallized from EtOH–ether to give colorless needles (18.77 g, 96%), mp 217—218°. *Anal.* Calcd for $C_8H_8N_2O \cdot HBr$: C, 32.03; H, 3.02; N, 9.34. Found: C, 32.18; H, 2.99; N, 9.53.

1-(3,4-Dichlorophenyl)-2(1*H*)-pyrazinone (28b)——A stirred solution of **27b** (17.25 g, 57.5 mmol) in MeOH (125 ml) was treated with 40% aqueous glyoxal (10.35 g, 71.5 mmol) at −40°, then aqueous NaOH (NaOH 5.75 g, H_2O 11.5 ml) was added dropwise at −40 to −30° with stirring. After stirring at −30° for 1.5 hr and at −5 to 0° for 3 hr, the ice-cooled and stirred reaction mixture was treated with concentrated HCl (14.4 ml), followed by $NaHCO_3$ (11.5 g). The solvent was removed and the residue was dissolved in $CHCl_3$ and H_2O. The $CHCl_3$ layer was separated, washed with H_2O, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (100 g) with $CHCl_3$ as the eluent. The eluate was evaporated to dryness and the residue was recrystallized from EtOH to give needles (2.05 g, 15%), mp 205—206°. *Anal.* Calcd for $C_{10}H_6Cl_2N_2O$: C, 49.82; H, 2.51; N, 11.62. Found: C, 50.09; H, 2.27; N, 11.74. PMR (DMSO-d_6, HA-100): 7.36 (1H, d, J=4 Hz, 5-H), 7.50 (1H, dd, J=2 Hz, 9 Hz, Ar–H), 7.63 (1H, dd, J=1.5 Hz, 4 Hz, 6-H), 7.78 (1H, d, J=9 Hz, Ar–H), 7.86 (1H, d, J=2 Hz, Ar–H), 8.09 (1H, d, J=1.5 Hz, 3-H). IR ν_{max}^{KBr} cm^{-1}: 1650.

1-Phenyl-2(1*H*)-pyrazinone (28a)——Compound **28a** (310 mg, 36%) was obtained from **27a** (1.15 g) in the manner described for **28b**, mp 140—141° ($CHCl_3$–petroleum ether). *Anal.* Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.68; H, 4.63; N, 15.99. PMR (DMSO-d_6, HA-100): 7.14 (1H, d, J=4 Hz, 5-H), 7.40—7.54 (5H, m, Ar–H), 7.60 (1H, dd, J=1.5 Hz, 4 Hz, 6-H), 8.07 (1H, d, J=1.5 Hz, 3-H). IR ν_{max}^{KBr} cm^{-1}: 1650.

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23) *tert*-Butoxytetrahydrofuran was kindly provided by Grelan Pharmaceutical Co., Ltd.