[Chem. Pharm. Bull. 28(9)2720—2733(1980)]

Anticoccidials. IV.[1] A Convenient Synthesis of 2(1*H*)-Pyrazinone 4-Oxide Derivatives

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(Received April 25, 1980)

2(1*H*)-Pyrazinone 4-oxide (emimycin) and its 1- and 6-substituted derivatives were synthesized by the reaction of a variety of 2-(hydroxyamino)acetamides with glyoxals.

Keywords——N-benzylidenecarbamoylmethylamine N-oxide; 2-(hydroxyamino)-acetamide; pyrazine; 2(1*H*)-pyrazinone 4-oxide; emimycin; anticoccidial activity

As a continuation of previous work directed at the development of novel anticoccidial agents, we became interested in preparing 2(1*H*)-pyrazinone 4-oxide (**1**) (emimycin) and its derivatives. This paper describes a convenient and general method for the preparation of this class of compounds which involves the reaction of 2-(hydroxyamino)acetamides with glyoxals.

Synthesis

Treatment of 2-chloro- or 2-iodoacetamide with (*Z*)-benzaldehyde oxime (**4**)[3] provided N-benzylidenecarbamoylmethylamine N-oxide (**2**), which was then treated with hydroxylamine hydrochloride to afford 2-(hydroxyamino)acetamide hydrochloride (**3**) in good yield. Compound **3** was also obtained by hydrolysis with hydrochloric acid but was accompanied by an inseparable by-product. Condensation of **3** with glyoxal in the presence of sodium hydroxide gave **1**, which was identical with an authentic sample[4] (Chart 1).

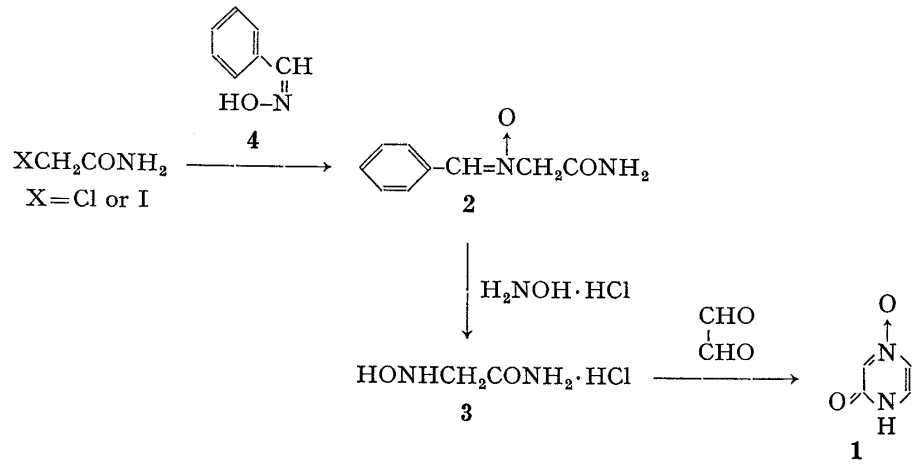

Chart 1

Compound **3** was found to react with a variety of substituted glyoxals, including methyl, hydroxymethyl, styryl and aryl derivatives, to give 6-substituted 2(1*H*)-pyrazinone 4-oxides.

1) Part III: K. Imai and T. Seo, *Eur. J. Med. Chem.*, **15**, 207 (1980).
2) Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*
3) *a*) T. Poloński and A. Chimiak, *J. Org. Chem.*, **41**, 2092 (1976); *b*) E. Buehler and G.B. Brown, *ibid.*, **32**, 265 (1967).
4) *a*) M. Bobek and A. Bloch, *J. Med. Chem.*, **15**, 164 (1972); *b*) P.T. Berkowitz, T.J. Bardos, and A. Bloch, *ibid.*, **16**, 183 (1973).

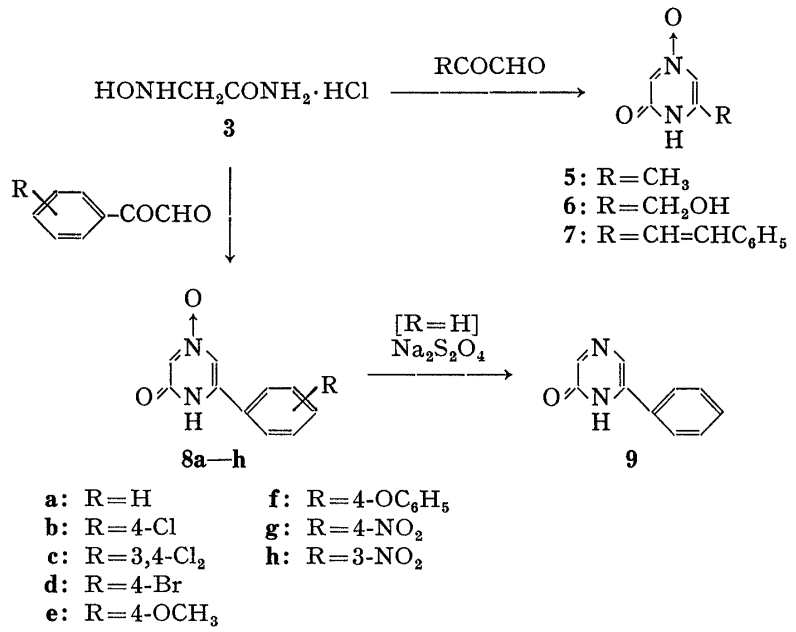

Chart 2

The compounds synthesized in this manner are summarized in Chart 2. In the proton magnetic resonance (PMR) spectra of the compounds (**5**, **6** and **8b**—**h**)[5] small spin couplings (J=1.5—2 Hz) between 3-H and 5-H were observed, in agreement with the assigned structures.[6] The structure of **8a** was confirmed by conversion to the known 6-phenyl-2(1*H*)-pyrazinone (**9**)[7] by reduction with sodium hydrosulfide. It is of interest to note that the formation of 6-aryl-2(1*H*)-pyrazinone 4-oxides (**8**) by the reaction of **3** with arylglyoxals is in contrast with the reaction of glycinamide with phenylglyoxal, which gave 5-phenyl-2(1*H*)-pyrazinone.[7,8]

A similar reaction of 2-(hydroxyamino)propionamide hydrochloride (**11**), prepared from N-benzylidene-(1-carbamoyl)-ethylamine N-oxide (**10**), with hydroxymethylglyoxal yielded 6-hydroxymethyl-3-methyl-2(1*H*)-pyrazinone 4-oxide (**12**), whose structure was confirmed by oxidation to 1,6-dihydro-5-methyl-6-oxo-2-pyrazinecarboxylic acid 4-oxide[9] (Chart 3).

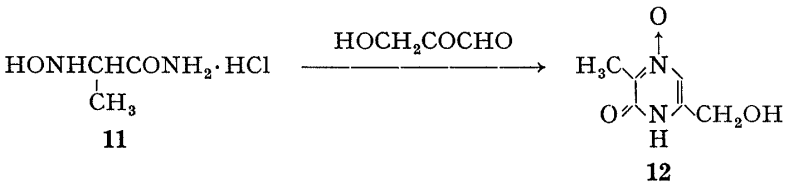

Chart 3

We have further extended this reaction to the synthesis of 1-alkyl and 1-aryl derivatives. This requires N-(alkyl or aryl)-2-(hydroxyamino)acetamides. The N-alkyl derivatives (**15**) were prepared by hydrolysis of N-benzylidenealkylcarbamoylmethylamine N-oxides (**14**), which in turn were obtained by the reaction of N-alkyl-2-chloroacetamides (**13**) and **4** (Chart 4). The N-aryl derivatives (**20**) were prepared in a similar way starting from N-aryl-2-iodoacetamides (**18**), as shown in Chart 5.

5) In the cases of **7** and **8a**, the couplings could not be seen because the pyrazinone ring protons were overlapped by other signals.
6) G.P. Syrova, Yu. N. Sheinker, I.S. Musatova, and A.S. Elina, *Chem. Heterocycl. Compd.*, **8**, 240 (1972).
7) *a*) P.J. Lont and H.C. Van Der Plas, *Rec. Trav. Chim. Pays-Bas*, **92**, 449 (1973); *b*) N. Sato, *J. Heterocycl. Chem.*, **15**, 665 (1978).
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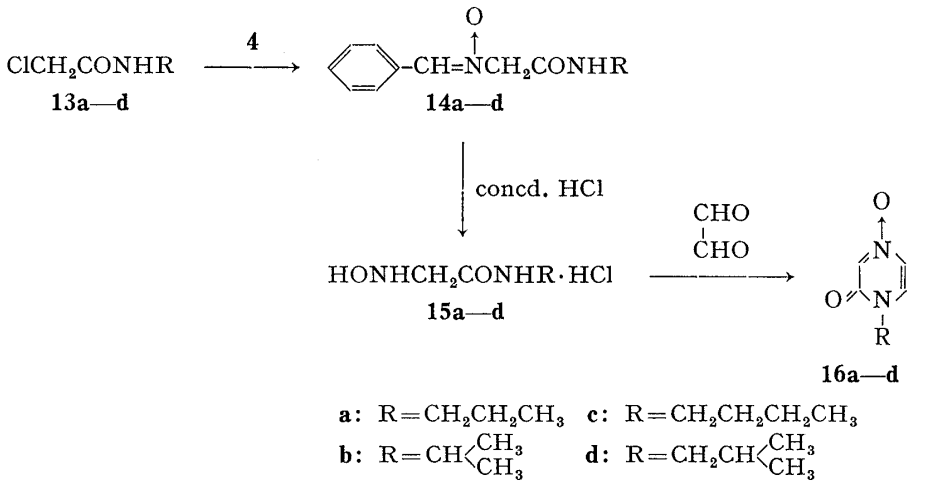
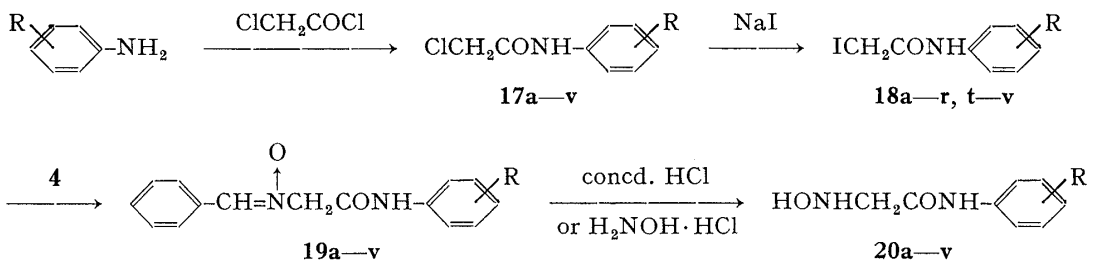
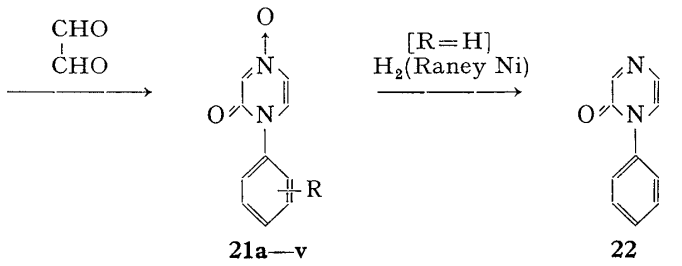


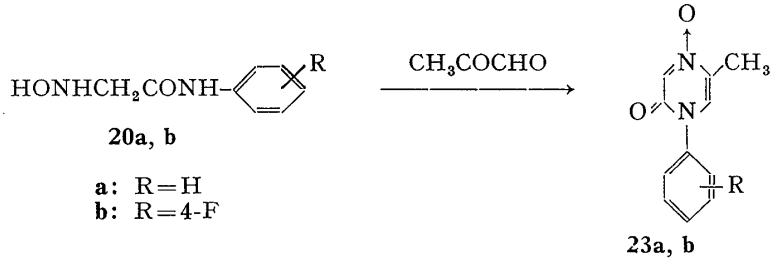
Chart 4





a: R=H
b: R=4-F
c: R=3-F
d: R=2-F
e: R=4-Cl
f: R=3-Cl
g: R=2-Cl
h: R=3,4-Cl_2
i: R=3,5-Cl_2
j: R=4-Br
k: R=4-CH_3
l: R=3-CH_3
m: R=2-CH_3
n: R=4-OCH_3
o: R=3-OCH_3
p: R=2-OCH_3
q: R=4-OC_6H_5
r: R=4-COC_6H_5
s: R=4-$N(CH_3)_2$
t: R=4-NO_2
u: R=3-NO_2
v: R=2-NO_2

Chart 5



a: R=H
b: R=4-F

Chart 6

Condensation of **15** and **20** with glyoxal or methylglyoxal gave the desired 1-alkyl (**16**) and 1-aryl derivatives (**21** and **23**), respectively (Charts 4—6). The structure of **21a** was confirmed by catalytic hydrogenation to 1-phenyl-2(1*H*)-pyrazinone (**22**), which was identical with the product obtained from glycinanilide and glyoxal.[10] The structure of **23** was deduced from the observation that the M-17 ion is more intense than the M-16 ion in the mass spectra (MS).[11]

This new method for the preparation of 2(1*H*)-pyrazinone 4-oxides has several advantages compared with previously known methods: (i) it does not require a peracid, (ii) it is suitable for large-scale production, and (iii) it is particularly useful for the preparation of the otherwise inaccessible 1-aryl derivatives.[10]

Anticoccidial Activity

Anticoccidial screening in chickens against *Eimeria tenella* was carried out in battery experiments as described in the preceding paper.[12] 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.[13]

Of the compounds tested (**1**, **5**—**9**, **12**, **16**, **21** and **23**), **1** exhibited potent activity. The biological results for **1** are shown in Table I.

Table I. Anticoccidial Activity of 2(1*H*)-Pyrazinone 4-Oxide (**1**)

Minimum effective concentration in feed (%)	Bloody droppings at day 5 after infection	Mortality	Average cecal lesion score	Relative weight gain (%)
0.05	—	0/78[a]	0.2	98.0
Infected unmedicated control	+++	15/39[b]	4.0	41.0
Uninfected unmedicated control	—	0/39[b]	0	100.0

a) 3 Birds×26 replicates.
b) 3 Birds×13 replicates.

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Hitachi 260-10 spectrophotometer, ultraviolet (UV) spectra with a Perkin-Elmer 450 spectrophotometer, and MS with a Hitachi RMU-6D mass spectrometer. 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. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Concentration operations were carried out under reduced pressure with a rotary evaporator.

Materials——Hydroxymethyl-,[14] styryl-,[15] 4-chlorophenyl-,[16] 3,4-dichlorophenyl-,[17] 4-bromophenyl-,[16]

10) M. Mano, T. Seo, T. Hattori, T. Kaneko, and K. Imai, *Chem. Pharm. Bull.*, **28**, 2734 (1980).
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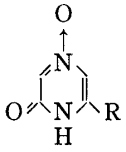
4-methoxyphenyl-,[18] 4-phenoxyphenyl-,[19] 4-nitrophenyl-[20] and 3-nitrophenylglyoxals,[20] N-propyl-,[21] N-isopropyl-,[22] N-butyl-[22] and N-isobutyl-2-chloroacetamides[23] were prepared by the reported procedures.

N-Benzylidenecarbamoylmethylamine N-Oxide (2)——Compound **4** (121 g, 1 mol) was dissolved with stirring in an ice-cooled solution of sodium (22.9 g, 950 mg-atom) in EtOH (2.5 l), and then 2-chloroacetamide (95 g, 1.01 mol) was added. The mixture was stirred at room temperature for 3 hr and cooled. The precipitate was collected by filtration, washed with cold EtOH and H_2O, and recrystallized from MeOH to give colorless crystals (83.5 g, 47%), mp 186—190°. *Anal.* Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.70; H, 5.65; N, 15.64.

2-(Hydroxyamino)acetamide Hydrochloride (3)——$H_2NOH \cdot HCl$ (2.08 g, 30 mmol) was dissolved in a solution of **2** (5.35 g, 30 mmol) in MeOH (150 ml) with heating. After stirring the mixture at room temperature for 1 hr, MeOH was removed and the residue was dissolved in AcOEt and H_2O. The aqueous layer was separated, washed with AcOEt and filtered. The filtrate was evaporated to dryness and the residue was recrystallized from aqueous EtOH to give colorless crystals (2.61 g, 69%), mp 135—138°. *Anal.* Calcd for $C_2H_6N_2O_2 \cdot HCl$: C, 18.98; H, 5.58; N, 22.14. Found: C, 19.09; H, 5.78; N, 22.07.

2(1*H*)-Pyrazinone 4-Oxide (1)——To a solution of **3** (5.6 g, 44 mmol) in MeOH (220 ml), 40% aqueous glyoxal (7.2 g, 50 mmol) was added at −40 to −30° with stirring. Next, 10 N NaOH (11 ml) was added dropwise at −40 to −30° over 20 min with stirring. After stirring at −30° for 1.5 hr, at −5 to 0° for 1 hr and at room temperature for 1 hr, the ice-cooled and stirred reaction mixture was treated with concentrated HCl (11 ml), followed by $NaHCO_3$ (8.8 g). The solvent was removed and the residue was dissolved in H_2O.

Table II. 6-Substituted 2(1*H*)-Pyrazinone 4-Oxides



Compound No.	R	Recrystn. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
5	CH_3	90% EtOH–ether	60	268—270[b] (dec.)	$C_5H_6N_2O_2$	47.62 (47.37	4.80 4.64	22.21 21.85)
6	CH_2OH	MeOH	18	225—230 (dec.)	$C_5H_6N_2O_3$	42.26 (42.23	4.26 4.25	19.71 19.64)
7	$CH{=}CHC_6H_5$	MeOH	7	210—213 (dec.)	$C_{12}H_{10}N_2O_2$	67.28 (67.12	4.71 4.43	13.08 12.86)

Compound No.	PMR[a]
5	[c] 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)
6	[d] 4.29 (2H, s, CH_2), 5.10—6.20 (1H, br, OH), 7.05 (1H, d, J=2 Hz, 3-H or 5-H), 7.39 (1H, d, J=2 Hz, 5-H or 3-H), 11.50—12.50 (1H, br, NH)
7	[c] 6.90 (1H, d, J=18 Hz, CH=CH), 7.3—7.7 (7H, m, 3-H, 5-H and Ar–H), 7.70 (1H, d, J=18 Hz, CH=CH)

a) Measured in dimethyl sulfoxide (DMSO)-d_6.
b) Lit.[4a] mp>250° (dec.).
c) Taken with a Varian XL-100-12 spectrometer.
d) Taken with a Varian EM-390 spectrometer.
e) Taken with a Varian T-60 spectrometer.

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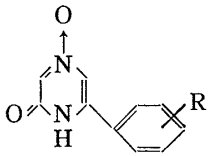
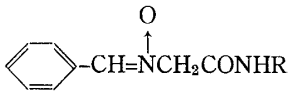
TABLE III. 6-Aryl-2(1*H*)-pyrazinone 4-Oxides



Compound No.	R	Recrystn. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	PMR[a]
8a	H	DMF[b]	50	270—273 (dec.)	$C_{10}H_8N_2O_2$	63.83 (63.77	4.29 4.08	14.89 14.79)	[c] 7.44—7.66 (4H, m, 3-H or 5-H and Ar–H), 7.74—8.00 (3H, m, 5-H or 3-H and Ar-H)
8b	4-Cl	EtOH	44	289—290	$C_{10}H_7ClN_2O_2$	53.95 (53.95	3.17 3.01	12.58 12.47)	7.56 (2H, d, J=9 Hz, Ar–H), 7.63 (1H, d, J=1.5 Hz, 3-H or 5-H), 7.94 (2H, d, J=9 Hz, Ar–H), 8.03 (1H, d, J=1.5 Hz, 5-H or 3-H)
8c	3,4-Cl_2	EtOH	40	284—285 (dec.)	$C_{10}H_6Cl_2N_2O_2$	46.72 (46.57	2.35 2.26	10.90 10.80)	7.58—8.18 (3H, m, Ar–H), 7.66 (1H, d, J=1.5 Hz, 3-H or 5-H), 8.21 (1H, d, J=1.5 Hz, 5-H or 3-H)
8d	4-Br	EtOH	36	301—302 (dec.)	$C_{10}H_7BrN_2O_2$	44.97 (44.82	2.64 2.50	10.49 10.39)	7.61 (1H, d, J=1.5 Hz, 3-H or 5-H), 7.64 (2H, d, J=9 Hz, Ar–H), 7.86 (2H, d, J=9 Hz, Ar–H), 8.01 (1H, d, J=1.5 Hz, 5-H or 3-H)
8e	4-OCH_3	EtOH	38	265—266	$C_{11}H_{10}N_2O_3$	60.55 (60.55	4.62 4.51	12.84 12.46)	3.83 (3H, s, OCH_3), 7.05 (2H, d, J=9 Hz, Ar–H), 7.51 (1H, d, J=1.5 Hz, 3-H or 5-H), 7.79 (1H, d, J=1.5 Hz, 5-H or 3-H), 7.84 (2H, d, J=9 Hz, Ar–H)
8f	4-OC_6H_5	EtOH	24	246—247 (dec.)	$C_{16}H_{12}N_2O_3$	68.57 (68.33	4.32 4.16	9.99 9.89)	6.95—7.64 (7H, m, Ar–H), 7.56 (1H, d, J=1.5 Hz, 3-H or 5-H), 7.88 (1H, d, J=1.5 Hz, 5-H or 3-H), 7.89 (2H, d, J=9 Hz, Ar–H)
8g	4-NO_2	DMF–H_2O	30	286—288 (dec.)	$C_{10}H_7N_3O_4$	51.51 (51.51	3.03 2.88	18.02 17.74)	*d*) 7.80 (1H, d, J=2 Hz, 3-H or 5-H), 8.15—8.50 (5H, m, 5-H or 3-H and Ar-H)
8h	3-NO_2	EtOH	41	251—252	$C_{10}H_7N_3O_4 \cdot 1/7C_2H_5OH$	51.53 (51.51	3.30 3.22	17.53 17.30)	7.65—7.98 (1H, m, Ar–H), 7.74 (1H, d, J=1.5 Hz, 3-H or 5-H), 8.20—8.50 (3H, m, 5-H or 3-H and Ar–H), 8.72—8.85 (1H, m, Ar–H)

a) Measured in DMSO-d_6 with a Varian A-60A spectrometer.
b) N,N-Dimethylformamide.
c) Taken with a Varian XL-100-12 spectrometer.
d) Taken with a Varian T-60 spectrometer.

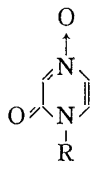
Table IV. N-Benzylidenealkylcarbamoylmethylamine N-Oxides[a]



Compound No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
14a	$CH_2CH_2CH_3$	56	152—153	$C_{12}H_{16}N_2O_2$	65.43 (65.25	7.32 7.19	12.72 12.82)
14b	$CH_2<^{CH_3}_{CH_3}$	57	201—202	$C_{12}H_{16}N_2O_2$	65.43 (65.21	7.32 7.27	12.72 12.75)
14c	$CH_2CH_2CH_2CH_3$	67	150—151	$C_{13}H_{18}N_2O_2$	66.64 (66.83	7.74 7.86	11.96 12.01)
14d	$CH_2CH<^{CH_3}_{CH_3}$	70	164—165	$C_{13}H_{18}N_2O_2$	66.64 (66.74	7.74 7.58	11.96 11.89)

a) Recrystallized from 50% EtOH.

Table V. 1-Alkyl-2(1*H*)-pyrazinone 4-Oxides



Compound No.	R	Recrystn. solvent	Yield[a] (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
16a	$CH_2CH_2CH_3$	—	27	Oil	—	—	—	—
16b	$CH<^{CH_3}_{CH_3}$	AcOEt–petroleum ether	13	133—135	$C_7H_{10}N_2O_2$	54.54 (54.54	6.54 6.59	18.17 18.04)
16c	$CH_2CH_2CH_2CH_3$	—	28	Oil	—	—	—	—
16d	$CH_2CH<^{CH_3}_{CH_3}$	—	29	Oil	—	—	—	—

Compound No.	PMR[b] Solvent	Chemical shift
16a	$CDCl_3$	1.00 (3H, t, J=7 Hz, CH_3), 1.50—2.17 (2H, m, $CH_2\underline{CH_2}CH_3$), 3.92 (2H, t, J=7 Hz, $\underline{CH_2}CH_2CH_3$), 7.14 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.39 (1H, d, J=6 Hz, 6-H), 7.59 (1H, d, J=2 Hz, 3-H)
16b	DMSO-d_6	1.31 (6H, d, J=7 Hz, 2×CH_3), 4.60—5.13 (1H, m, CH), 7.23 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.55 (1H, d, J=2 Hz, 3-H), 7.84 (1H, d, J=6 Hz, 6-H)
16c	$CDCl_3$	0.98 (3H, t, J=7 Hz, CH_3), 1.20—2.07 (4H, m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$), 3.92 (2H, t, J=7 Hz, $\underline{CH_2}CH_2CH_2CH_3$), 7.10 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.27 (1H, d, J=6 Hz, 6-H), 7.60 (1H, d, J=2 Hz, 3-H)
16d	$CDCl_3$	0.97 (6H, d, J=6 Hz, 2×CH_3), 1.82—2.53 (1H, m, CH), 3.75 (2H, d, J=7 Hz, CH_2), 7.12 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.35 (1H, d, J=6 Hz, 6-H), 7.59 (1H, d, J=2 Hz, 3-H)

a) Based on N-benzylidenealkylcarbamoylmethylamine N-oxide.
b) Taken with a Varian T-60 spectrometer.

The aqueous solution was adjusted to pH 1 with concentrated HCl and adsorbed on a column of activated charcoal (Shirasagi for chromatography, Takeda Chemical Industries, Ltd.) (50 g). The column was washed with H_2O and eluted with EtOH–H_2O–28% NH_4OH (25: 24: 1). The eluate (*ca.* 300 ml) was evaporated to dryness and the residue was recrystallized twice from 96% EtOH–ether (1: 1) with activated charcoal to give crystals (1.04 g, 21%), mp 245—250° (dec.) [lit.[4a] mp>250° (dec.)]. *Anal.* Calcd for $C_4H_4N_2O_2 \cdot 1/4H_2O$: C, 41.21; H, 3.89; N, 24.03. Found: C, 41.59; H, 3.53; N, 24.38. PMR (DMSO-d_6, HA-100): 7.12 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.49 (1H, d, J=2 Hz, 3-H), 7.51 (1H, d, J=6 Hz, 6-H).

6-Hydroxymethyl-2(1*H*)-pyrazinone 4-Oxide (6) (Table II)——Hydroxymethylglyoxal (352 mg, 4 mmol) was added to a solution of **3** (508 mg, 4 mmol) in MeOH (20 ml) at −40 to −30° with stirring, then 12.5 N NaOH (0.8 ml) was added dropwise at −40 to −30°. After stirring at −30° for 1.5 hr and at −5 to 0° for 2 hr, the ice-cooled and stirred reaction mixture was adjusted to pH 3 with concentrated HCl. The solvent was evaporated off and H_2O (5 ml) was added to the residue. After cooling, the precipitate was collected by filtration, washed with a small amount of cold H_2O and recrystallized with activated charcoal to give colorless needles (100 mg). UV $\lambda_{max}^{0.1NHCl}$ nm (ε): 220 (19300), 270 (8000), 330 (5800); $\lambda_{max}^{H_2O}$ nm (ε): 221.5 (18700), 270 (7500), 330 (5800); $\lambda_{max}^{0.1NNaOH}$ nm (ε): 230 (23800), 254 (7300), 330 (6500).

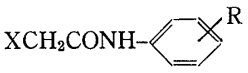
6-Phenyl-2(1*H*)-pyrazinone 4-Oxide (8a) (Table III)——A solution of **3** (6.325 g, 50 mmol) in MeOH (250 ml) was treated with phenylglyoxal hydrate (7.608 g, 50 mmol) and 12.5 N NaOH (10 ml) in the manner described for **6** (the reaction mixture was adjusted to pH 5) to give needles (4.7 g). UV $\lambda_{max}^{0.1NHCl}$ nm (ε): 244 (17900), 347.5 (8500); $\lambda_{max}^{H_2O}$ nm (ε): 243 (19100), 345 (10400); $\lambda_{max}^{0.1NNaOH}$ nm (ε): 242 (24900), 342.5 (10500).

6-Phenyl-2(1*H*)-pyrazinone (9)——$Na_2S_2O_4$ (2 g) was added to a suspension of **8a** (940 mg, 5 mmol) in EtOH (100 ml) and H_2O (50 ml), and the mixture was refluxed for 30 min, followed by addition of further $Na_2S_2O_4$ (500 mg) and refluxing for 30 min. The EtOH was then removed and the reaction mixture cooled. The precipitate was collected by filtration, washed with H_2O and recrystallized from EtOH to give crystals (510 mg, 59%), mp 238—241° (lit.[7a] mp 239—241°). *Anal.* Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.76; H, 4.61; N, 16.43. PMR (DMSO-d_6, T-60): 7.4—7.7 (3H, m, Ar–H), 7.9—8.0 (2H, m, Ar–H), 8.00 (1H, s, 3-H or 5-H), 8.27 (1H, s, 5-H or 3-H).

N-Benzylidene-(1-carbamoyl)-ethylamine N-Oxide (10)——2-Bromopropionamide[24] (7.61 g, 50 mmol) was treated in the manner described for **2**. The reaction mixture was concentrated and diluted with H_2O. After cooling, the precipitate was collected by filtration, washed with H_2O and recrystallized twice from AcOEt to give colorless needles (5.4 g, 56%), mp 173—174°. *Anal.* Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.32; H, 6.34; N, 14.33.

6-Hydroxymethyl-3-methyl-2(1*H*)-pyrazinone 4-Oxide (12)——Compound **10** (12.5 g, 65 mmol) was treated in the manner described for **3** to give **11** as a colorless liquid. Next, **11** was treated according to the procedure described for **6**. The reaction mixture was adjusted to pH 2 with concentrated HCl and cooled.

Table VI. Substituted 2-Chloro- and 2-Iodo-N-arylacetamides

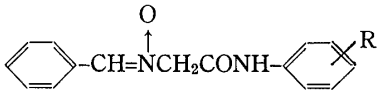


Compound No.	X	R	Recrystn. solvent	Yield (%)	mp (°C)
17c	Cl	3-F	AcOEt–petroleum ether	89	118—120
17d	Cl	2-F	AcOEt–petroleum ether	89	84— 86
17r	Cl	4-COC_6H_5	AcOEt–petroleum ether	96	123—124
18b	I	4-F	EtOH–H_2O	94	139—141
18c	I	3-F	EtOH–H_2O	97	113—115
18d	I	2-F	EtOH–H_2O	96	110—111
18g	I	2-Cl	EtOH–H_2O	95	117—119
18i	I	3,5-Cl_2	EtOH–H_2O	71	132—133
18k	I	4-CH_3	EtOH–H_2O	93	161—163
18l	I	3-CH_3	EtOH–H_2O	94	88— 89
18o	I	3-OCH_3	EtOH–H_2O	71	89— 90
18p	I	2-OCH_3	EtOH–H_2O	94	87— 89
18r	I	4-COC_6H_5	EtOH–H_2O	95	167—168
18t	I	4-NO_2	EtOH	68	210—212
18u	I	3-NO_2	EtOH–H_2O	96	134—136
18v	I	2-NO_2	EtOH–H_2O	80	91— 93

24) C.A. Bischoff, *Ber.*, **30**, 2310 (1897).

The precipitate was collected by filtration and washed with MeOH and cold H_2O (20 ml) to give a powder (7.55 g, 74%), mp 235—238° (dec.). For analysis, 300 mg of the powder was recrystallized from 90% EtOH to afford crystals (180 mg), mp 235—240° (dec.). *Anal.* Calcd for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.40; H, 5.11; N, 17.88. PMR (DMSO-d_6, T-60): 2.14 (3H, s, CH_3), 4.31 (2H, d, $J=4$ Hz, CH_2), 5.34—5.80 (1H, br, OH), 7.12 (1H, s, 5-H), 11.92—12.37 (1H, br, NH). UV $\lambda_{max}^{0.1NHCl}$ nm (ε): 221.5 (18000), 265 (6800), 317.5 (6600); $\lambda_{max}^{H_2O}$ nm (ε): 222 (18500), 265 (6700), 317.5 (6700); $\lambda_{max}^{0.1NNaOH}$ nm (ε): 226 (25700), 254 (shoulder) (5900), 325 (7600). MS *m/e* (relative intensity): 156 (M^+) (100), 140 (M^+-16) (24), 139 (M^+-17) (98), 111 (33), 110 (50).

TABLE VII. N-Benzylidenearylcarbamoylmethylamine N-Oxides



Compound No.	R	Recrystn. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
19a	H	EtOH	60	188—190	$C_{15}H_{14}N_2O_2$	70.85 (70.84	5.55 5.43	11.02 11.06)
19b	4-F	EtOH	55	174—176	$C_{15}H_{13}FN_2O_2$	66.17 (66.02	4.81 4.50	10.29 10.37)
19c	3-F	EtOH	47	191—193	$C_{15}H_{13}FN_2O_2$	66.17 (66.26	4.81 4.65	10.29 10.56)
19d	2-F	EtOH	51	179—181	$C_{15}H_{13}FN_2O_2$	66.17 (65.85	4.81 4.58	10.29 10.55)
19e	4-Cl	EtOH	37	198—200 (dec.)	$C_{15}H_{13}ClN_2O_2$	62.40 (62.53	4.54 4.27	9.70 9.76)
19f	3-Cl	EtOH	61	187—189	$C_{15}H_{13}ClN_2O_2$	62.40 (62.35	4.54 4.66	9.70 9.67)
19g	2-Cl	EtOH	43	163—165	$C_{15}H_{13}ClN_2O_2$	62.40 (62.49	4.54 4.56	9.70 9.69)
19h	3,4-Cl_2	MeOH	52	200—203 (dec.)	$C_{15}H_{12}Cl_2N_2O_2$	55.75 (55.81	3.74 3.53	8.67 8.73)
19i	3,5-Cl_2	MeOH	34	199—200	$C_{15}H_{12}Cl_2N_2O_2 \cdot 1/2H_2O$	54.24 (54.02	3.94 3.96	8.43 8.32)
19j	4-Br	EtOH	62	202—204 (dec.)	$C_{15}H_{13}BrN_2O_2$	54.07 (54.06	3.93 3.78	8.41 8.35)
19k	4-CH_3	EtOH	61	199—200	$C_{16}H_{16}N_2O_2$	71.62 (71.45	6.01 5.94	10.44 10.65)
19l	3-CH_3	EtOH	75	193—195	$C_{16}H_{16}N_2O_2$	71.62 (71.68	6.01 5.79	10.44 10.48)
19m	2-CH_3	EtOH	58	183—185	$C_{16}H_{16}N_2O_2$	71.62 (71.45	6.01 5.96	10.44 10.58)
19n	4-OCH_3	EtOH	69	179—181	$C_{16}H_{16}N_2O_3$	67.59 (67.72	5.67 5.60	9.85 10.12)
19o	3-OCH_3	EtOH	78	145—146	$C_{16}H_{16}N_2O_3$	67.59 (67.64	5.67 5.34	9.85 9.86)
19p	2-OCH_3	EtOH	66	167—169	$C_{16}H_{16}N_2O_3$	67.59 (67.76	5.67 5.41	9.85 9.96)
19q	4-OC_6H_5	EtOH	33	200—201	$C_{21}H_{18}N_2O_3$	72.82 (72.80	5.24 5.06	8.09 8.12)
19r	4-COC_6H_5	EtOH	14	194—195	$C_{22}H_{18}N_2O_3$	73.73 (74.16	5.06 4.81	7.82 8.01)
19s[a]	4-$N(CH_3)_2$	EtOH	34	204—205	$C_{17}H_{19}N_3O_2$	68.67 (68.48	6.44 6.38	14.13 14.40)
19t	4-NO_2	EtOH	37	213—215	$C_{15}H_{13}N_3O_4$	60.20 (60.26	4.38 4.51	14.04 13.97)
19u	3-NO_2	EtOH	57	201—202	$C_{15}H_{13}N_3O_4$	60.20 (60.09	4.38 4.27	14.04 14.18)
19v	2-NO_2	EtOH	48	153—154.5	$C_{15}H_{13}N_3O_4$	60.20 (60.19	4.38 4.15	10.04 14.07)

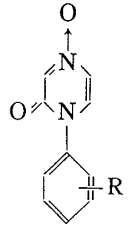
a) Prepared from 2-chloro-N-[(4-dimethylamino)phenyl]acetamide.

TABLE VIII. N-Aryl-2-(hydroxyamino)acetamides

Compound No.	R	Method	Reaction temperature (°C)	Reaction time (hr)	Recrystn. solvent[a]	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
20a	H	A	Room temperature	10	A	72	126—127	$C_8H_{10}N_2O_2$	57.82	6.07	16.86	57.95	5.92	16.52
20b	4-F	A	50	9.5	A	33	106—107	$C_8H_9FN_2O_2$	57.17	4.93	15.21	52.31	4.88	14.95
20c	3-F	A	50	9.5	A	40	122—123	$C_8H_9FN_2O_2$	52.17	4.93	15.21	52.38	4.84	14.91
20d	2-F	A	50	13	A	25	114—115	$C_8H_9FN_2O_2$	52.17	4.93	15.21	52.19	4.87	15.01
20e	4-Cl	A	50	22	A	22	143—145[b] (dec.)	$C_8H_9ClN_2O_2$	47.89	4.52	13.96	47.54	4.84	14.01
20f	3-Cl	B	50	30	A	13	118—119	$C_8H_9ClN_2O_2$	47.89	4.52	13.96	47.81	4.52	13.46
20g	2-Cl	A	80	8	A	57	106—108	$C_8H_9ClN_2O_2$	47.89	4.52	13.96	47.97	4.28	14.01
20h	3,4-Cl_2	A	50	3	A	47	121—122	$C_8H_8Cl_2N_2O_2$	40.88	3.43	11.92	41.29	3.35	11.99
20i[c]	3,5-Cl_2	C	Room temperature	3	B	58	—	$C_8H_8Cl_2N_2O_2 \cdot HCl \cdot 1/2(H_2NOH \cdot HCl)$	31.37	3.62	11.43	31.25	3.48	11.83
20j	4-Br	A	50	15	A	22	140—142 (dec.)	$C_8H_9BrN_2O_2$	39.21	3.70	11.43	39.33	3.78	11.53
20k	4-CH_3	A	50	18	A	16	141—143	$C_9H_{12}N_2O_2$	59.99	6.71	15.54	59.65	6.73	14.92
20l	3-CH_3	A	50	13	A	26	110—111	$C_9H_{12}N_2O_2$	59.99	6.71	15.54	60.29	6.78	14.87
20m	2-CH_3	B	50	18	A	23	125—126	$C_9H_{12}N_2O_2$	59.99	6.71	15.54	59.77	6.74	15.24
20n	4-OCH_3	A	50	18	A	21	140—141[d]	$C_9H_{12}N_2O_3$	55.09	6.16	14.28	55.31	6.16	13.74
20o	3-OCH_3	B	Room temperature	6	A	19	82— 84	$C_9H_{12}N_2O_3$	55.09	6.16	14.28	54.95	6.06	14.02
20p	2-OCH_3	B	50	18	A	14	89— 91	$C_9H_{12}N_2O_3$	55.09	6.16	14.28	54.68	6.06	14.12
20q[e,f]	4-OC_6H_5	A	50	2.5	B	37	129—130	—	—	—	—	—	—	—
20r[f]	4-COC_6H_5	A	50	10	A	28	149—150	—	—	—	—	—	—	—
20s	4-$N(CH_3)_2$	A	50	0.5	A	70	154—155	$C_{10}H_{15}N_3O_2$	57.40	7.23	20.08	57.79	7.28	19.41
20t	4-NO_2	A	50	2	C	44	171—174 (dec.)	$C_8H_9N_3O_4$	45.50	4.30	19.90	45.41	4.26	20.07
20u[f]	3-NO_2	A	50	1	D	43	104—105	—	—	—	—	—	—	—
20v	2-NO_2	A	50	1	C	75	136—138	$C_8H_9N_3O_4$	45.50	4.30	19.90	45.35	4.16	19.84

a) A: AcOEt–petroleum ether, B: EtOH–ether, C: EtOH, D: $CHCl_3$–MeOH.
b) S.C. Bell, R.J. McCaully, and S.J. Childress, *J. Org. Chem.*, **33**, 216 (1968), reported mp 144—146°.
c) Obtained as a mixture of the hydrochloride and hydroxylamine hydrochloride.
d) S.C. Bell, R.J. McCaully, and S.J. Childress, *J. Heterocycl. Chem.*, **4**, 647 (1967), reported mp 137—138°.
e) Isolated as the hydrochloride.
f) A trace amount of impurity was detected by TLC.

TABLE IX. 1-Aryl-2(1*H*)-pyrazinone 4-Oxides



Compound No.	R	Method	Recrystn. solvent[a]	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	PMR[b]
21a	H	A	A	53	206—208 (dec.)	$C_{10}H_8N_2O_2$	63.83 (64.00	4.29 4.11	14.89 15.02)	[c] 7.21 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.42 (5H, s, Ar–H), 7.64 (1H, d, J=2 Hz, 3-H), 7.78 (1H, d, J=6 Hz, 6-H)
21b	4-F	A	A	31	225—227 (dec.)	$C_{10}H_7FN_2O_2$	58.26 (58.20	3.42 3.35	13.59 13.33)	[d] 7.23—7.73 (5H, m, 5-H and Ar–H), 7.78 (1H, d, J=2 Hz, 3-H) ,7.92 (1H, d, J=6 Hz, 6-H)
21c	3-F	A	A	44	235—238 (dec.)	$C_{10}H_7FN_2O_2$	58.26 (58.03	3.42 3.27	13.59 13.32)	[d] 7.17—7.75 (5H, m, 5-H and Ar–H), 7.73 (1H, d, J=2 Hz, 3-H), 7.85 (1H, d, J=6 Hz, 6-H)
21d	2-F	A	A	45	223—226 (dec.)	$C_{10}H_7FN_2O_2$	58.26 (57.84	3.42 3.32	13.59 13.57)	[d] 7.20—7.78 (5H, m, 5-H and Ar–H), 7.80 (1H, d, J=2 Hz, 3-H), 7.93 (1H, d, J=6 Hz, 6-H)
21e	4-Cl	B	C	47	197—198 (dec.)	$C_{10}H_7ClN_2O_2$	53.95 (53.82	3.17 3.11	12.58 12.66)	[c] 7.24 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.39—7.59 (4H, m, Ar–H), 7.64 (1H, d, J=2 Hz, 3-H), 7.79 (1H, d, J=6 Hz, 6-H)
21f	3-Cl	A	C	42	227—229 (dec.)	$C_{10}H_7ClN_2O_2$	53.95 (54.11	3.17 3.06	12.58 12.54)	[d] 7.67 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.50—7.70 (4H, m, Ar–H), 7.80 (1H, d, J=2 Hz, 3-H), 7.93 (1H, d, J=6 Hz, 6-H)
21g	2-Cl	B	B	43	160—162	$C_{10}H_7ClN_2O_2$	53.95 (53.72	3.17 3.30	12.58 12.61)	[d] 7.29 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.43—7.67 (4H, m, Ar–H), 7.73 (1H, d, J=2 Hz, 3-H), 7.78 (1H, d, J=6 Hz, 6-H)
21h	3,4-Cl_2	A	A	31	245—246	$C_{10}H_6Cl_2N_2O_2$	46.72 (46.77	2.35 2.28	10.90 11.08)	
21i	3,5-Cl_2	A	D	5	210—211	$C_{10}H_6Cl_2N_2O_2$	46.72 (46.89	2.35 2.30	10.90 10.78)	[e] 7.27 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.55—7.75 (3H, m, Ar–H), 7.69 (1H, d, J=2 Hz, 3-H), 7.87 (1H, d, J=6 Hz, 6-H)
21j	4-Br	B	B	61	199—201	$C_{10}H_7BrN_2O_2$	44.97 (45.08	2.64 2.41	10.49 10.27)	[d] 7.31 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.44 (2H, d, J=9 Hz, Ar–H), 7.73 (1H, d, J=2Hz, 3-H), 7.77 (2H, d, J=9 Hz, Ar–H), 7.87 (1H, d, J=6 Hz, 6-H)

Compound No.	R	Method	Recrystn. solvent[a]	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	PMR[b]
21k	4-CH_3	B	B	64	173—175	$C_{11}H_{10}N_2O_2$	65.34 (65.13	4.98 4.87	13.85 13.85)	[d] 2.35 (3H, s, CH_3), 7.25 (1H, dd, J=2Hz, 6Hz, 5-H), 7.28 (4H, s, Ar-H), 7.65 (1H, d, J=2 Hz, 3-H), 7.70 (1H, d, J=6 Hz, 6-H)
21l	3-CH_3	B	B	57	155—157	$C_{11}H_{10}N_2O_2$	65.34 (64.94	4.98 4.93	13.85 13.91)	[d] 2.37 (3H, s, CH_3), 7.27—7.53 (5H, m, 5-H and Ar-H), 7.70 (1H, d, J=2 Hz, 3-H), 7.82 (1H, d, J=6 Hz, 6-H)
21m	2-CH_3	B	B	72	145—147	$C_{11}H_{10}N_2O_2$	65.34 (64.95	4.98 4.82	13.85 13.81)	[d] 2.12 (3H, s, CH_3), 7.23—7.53 (5H, m, 5-H and Ar-H), 7.75 (1H, d, J=2Hz, 3-H), 7.77 (1H, d, J=6 Hz, 6-H)
21n	4-OCH_3	B	B	72	175—178	$C_{11}H_{10}N_2O_3$	60.55 (60.43	4.62 4.52	12.84 12.66)	[d] 3.79 (3H, s, OCH_3), 7.00 (2H, d, J=9 Hz, Ar-H), 7.23 (1H, dd, J=2 Hz, 6Hz, 5-H), 7.34 (2H, d, J=9 Hz, Ar-H), 7.63 (1H, d, J=2 Hz, 3-H), 7.77 (1H, d, J=6 Hz, 6-H)
21o	3-OCH_3	B	B	41	202—203	$C_{11}H_{10}N_2O_3$	60.55 (60.54	4.62 4.59	12.84 12.97)	[d] 3.79 (3H, s, OCH_3), 6.92—7.63 (5H, m, 5-H and Ar-H), 7.70 (1H, d, J=1 Hz, 3-H), 7.82 (1H, d, J=6 Hz, 6-H)
21p	2-OCH_3	B	B	53	153—155	$C_{11}H_{10}N_2O_3$	60.55 (60.50	4.62 4.55	12.84 12·61)	[d] 3.62 (3H, s, OCH_3), 7.07—7.60 (5H, m, 5-H and Ar-H), 7.65—7.82 (2H, m, 3-H and 6-H)
21q	4-OC_6H_5	B	D	51	191—192	$C_{16}H_{12}N_2O_3$	68.57 (68.61	4.32 4.29	9.99 9.90)	[f] 6.96—7.62 (10H, m, 5-H and Ar-H), 7.70 (1H, d, J=2 Hz, 3-H), 7.83 (1H, d, J=6 Hz, 6-H)
21r	4-COC_6H_5	B	D	28	222—223	$C_{17}H_{12}N_2O_3$	69.86 (69.59	4.14 4.06	9.58 9.11)	[f] 7.33 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.45—7.90 (10H, m, 3-H and Ar-H), 7.93 (1H, d, J=6 Hz, 6-H)
21s	4-$N(CH_3)_2$	A	A	39	234—235 (dec.)	$C_{12}H_{13}N_3O_2$	62.33 (61.92	5.67 5.67	18.17 17.57)	[f] 2.96 (6H, s, 2×CH_3), 6.75 (2H, d, J=9 Hz, Ar-H), 7.19 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.21 (2H, d, J=9 Hz, Ar-H), 7.59 (1H, d, J=2 Hz, 3-H), 7.71 (1H, d, J=6 Hz, 6-H)
21t	4-NO_2	B	A	10	194—197 (dec.)	$C_{10}H_7N_3O_4$	51.51 (51.42	3.03 3.08	18.02 17.99)	[f] 7.33 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.73 (1H, d, J=2 Hz, 3-H), 7.78 (2H, d, J=9 Hz, Ar-H), 7.91 (1H, d, J=6 Hz, 6-H), 8.35 (2H, d, J=9 Hz, Ar-H)
21u	3-NO_2	B	A	15	206—209 (dec.)	$C_{10}H_7N_3O_4$	51.51 (51.41	3.03 2.95	18.02 17.98)	[f] 7.33 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.65—8.50 (6H, m, 3-H, 6-H and Ar-H)
21v	2-NO_2	B	A	10	201—203 (dec.)	$C_{10}H_7N_3O_4$	51.51 (51.32	3.03 3.19	18.02 17.42)	[f] 7.42 (1H, dd, J=2 Hz, 6 Hz, 5-H), 7.60—8.31 (6H, m, 3-H, 6-H and Ar-H)

a) A: EtOH, B: AcOEt–petroleum ether, C: MeOH, D: AcOEt.
b) Measured in DMSO-d_6.
c) Taken with a Varian HA-100 spectrometer.
d) Taken with a Varian T-60 spectrometer.
e) Taken with a Varian EM-390 spectrometer.
f) Taken with a Varian A-60A spectrometer.

N-Benzylideneisopropylcarbamoylmethylamine N-Oxide (14b) (Table IV)——Compound **14b** (1.205 g) was prepared from **13b** (1.39 g, 10.2 mmol) in the manner described for **2**.

1-Isopropyl-2(1*H*)-pyrazinone 4-Oxide (16b) (Table V)——A mixture of **14b** (20 g, 91 mmol) and concentrated HCl (200 ml) was stirred at 50° for 8 hr and concentrated. The residue was diluted with H_2O. The solution was washed with benzene and filtered. The filtrate was evaporated to dryness and the residue was recrystallized from MeOH–ether (1: 1) to give **15b** (11.6 g) as colorless needles, which gave two spots on thin layer chromatography (TLC) (silica gel). A solution of **15b** (12.3 g, 72.8 mmol) in MeOH (250 ml) was treated with 40% aqueous glyoxal (16.5 g, 109 mmol) and 10 N NaOH (18.1 ml) according to the procedure described for **1**. The ice-cooled and stirred reaction mixture was treated with concentrated HCl (18.2 ml), followed by $NaHCO_3$ (14.6 g). The solvent was removed and the residue was extracted with hot $CHCl_3$ (500 ml × 4). The extract was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (Merck) (50 g) with $CHCl_3$ as the eluent, and recrystallization gave colorless needles (1.89 g).

2-Chloro- and 2-Iodo-N-arylacetamides (17 and 18)——Compounds **17** and **18** were prepared by the method of Adams and Deebel.[25] New compounds are listed in Table VI.

N-Benzylidene-(4-methylphenyl)-carbamoylmethylamine N-Oxide (19k) (Table VII)——Compound **19k** (19.8 g) was prepared from **18k** (33 g, 120 mmol) in the manner described for **2**.

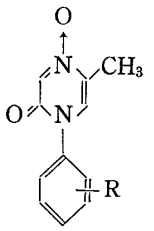
2-Hydroxyamino-N-(4-methylphenyl)acetamide (20k) (Table VIII)——(Method A) A mixture of **19k** (19.1 g, 71.4 mmol) and concentrated HCl–MeOH (1: 1) (1.2 l) was stirred and concentrated. The residue was diluted with H_2O and the solution was washed with benzene. The aqueous layer was made alkaline with Na_2CO_3 and extracted with AcOEt (300 ml × 3). The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized to give needles (2.08 g).

2-Hydroxyamino-N-(2-methylphenyl)acetamide (20m) (Table VIII)——(Method B) Compound **19m** (17.5 g, 65.4 mmol) was treated in the manner described for **20k**. After removal of AcOEt, the residue was chromatographed on silica gel (100 g) with $CHCl_3$–MeOH (9: 1) as the eluent, and recrystallization gave colorless needles (2.69 g).

2-Hydroxyamino-N-(3,5-dichlorophenyl)acetamide Hydrochloride (20i) (Table VIII)——(Method C) A solution of **19i** (9.45 g, 29.2 mmol) in MeOH (1 l) was treated with $H_2NOH \cdot HCl$ (2.05 g, 29.5 mmol) in the manner described for **3**. After removal of MeOH, the residue was triturated with ether. The precipitate was collected by filtration and recrystallized to give colorless needles (5.15 g).

1-Phenyl-2(1*H*)-pyrazinone 4-Oxide (21a) (Table IX)——(Method A) Compound **20a** (3.32 g, 20 mmol) was treated in the manner described for **1**. After removal of the solvent, the residue was extracted with

Table X. 1-Aryl-5-methyl-2(1*H*)-pyrazinone 4-Oxides[a]



Compound No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	PMR[b]
23a	H	9	183—184	$C_{11}H_{10}N_2O_2$	65.34 (65.27	4.98 4.87	13.85 13.81)	[c] 2.11 (3H, s, CH_3), 7.48 (5H, s, Ar–H), 7.73 (1H, s, 3-H or 6-H), 7.89 (1H, s, 6-H or 3-H)
23b	4-F	5	188—189	$C_{11}H_9FN_2O_2$	60.00 (60.20	4.12 4.09	12.72 12.65)	[d] 2.12 (3H, s, CH_3), 7.12—7.73 (4H, m, Ar–H), 7.74 (1H, s, 3-H or 6-H), 7.93 (1H, s, 6-H or 3-H)

a) Recrystallized from EtOH.
b) Measured in DMSO-d_6.
c) Taken with a Varian EM-390 spectrometer.
d) Taken with a Varian T-60 spectrometer.

25) J.S. Adams, Jr. and G.F. Deebel, *J. Chem. Eng. Data*, **12**, 619 (1967).

$CHCl_3$. The extract was dried over $MgSO_4$ and concentrated. The residue was recrystallized with activated charcoal to give needles (1.985 g). UV $\lambda_{max}^{0.1NHCl}$ nm (ε): 223 (24400), 280 (11200), 332.5 (5400); $\lambda_{max}^{H_2O}$ nm (ε): 223 (24500), 280 (11000), 335 (5400); $\lambda_{max}^{0.1NNaOH}$ nm (ε): 282 (8300), 330 (5300).

1-(4-Methylphenyl)-2(1*H*)-pyrazinone 4-Oxide (21k) (Table IX)——(Method B) Compound **20k** (1.44 g, 8 mmol) was treated in the manner described for **21a**. Crude products were chromatographed on silica gel (50 g) with $CHCl_3$ as the eluent, and recrystallization gave needles (1.036 g).

1-Phenyl-2(1*H*)-pyrazinone (22)——A mixture of **21a** (188 mg, 1 mmol) and Raney Ni (0.2 ml) in MeOH (15 ml) was hydrogenated at room temperature for 3 hr. The catalyst was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel (10 g) with $CHCl_3$ as the eluent, and recrystallization from AcOEt–petroleum ether gave a colorless powder (60 mg, 35%), mp 140—142°. IR ν_{max}^{KBr} cm^{-1}: 1650 ($c=0$).

5-Methyl-1-phenyl-2(1*H*)-pyrazinone 4-Oxide (23a) (Table X)——Compound **23a** (207 mg) was prepared from **20a** (1.88 g, 11.3 mmol) and 40% aqueous methylglyoxal (3.17 g, 17 mmol) in the manner described for **21k**. MS *m/e* (relative intensity): 202 (M^+) (41), 186 (M^+-16) (24), 185 (M^+-17) (63), 157 (76), 130 (61), 104 (27), 77 (100).

Acknowledgement The authors are grateful to Drs. S. Yamatodani and T. Kanzaki for their encouragement throughout this work. Thanks are also due to Mr. T. Yamazaki and Mr. T. Matsuno for testing anticoccidial activity.