Studies on Pyrazines. I. The Syntheses of 2,3-Dihydroxypyrazines and Their Derivatives

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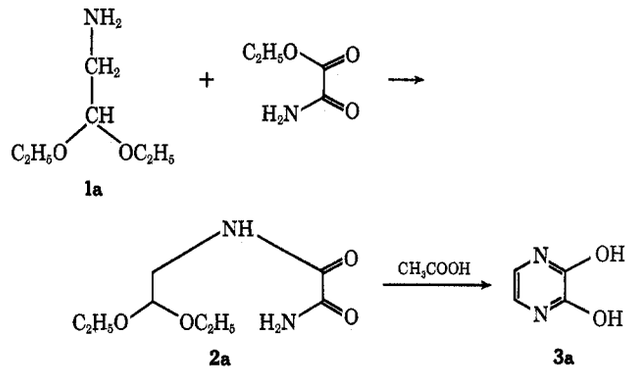
Received July 8, 1971

This report describes a new method for the preparations of 2,3-dihydroxypyrazines **3** containing (**a**) H, H, (**b**) H, CH_3, (**c**) CH_3, CH_3, (**d**) H, C_6H_5, (**e**) CH_3, C_6H_5 and (**f**) C_6H_5, C_6H_5 at 5,6 positions. As starting materials, five amino ketals **1b–f** were prepared by two steps from phthalimido ketones **4b–f**. Amino ketals **1a**, **1b**, and **1d** (R_1 = H) were readily condensed with ethyl oxamate to provide oxamoyl amino ketals **2** in good yields, although condensations of amino ketals **1c**, **1e**, and **1f**, which were sterically crowded with methyl or phenyl groups, with ethyl oxamate required drastic conditions. The subsequent cyclizations of oxamoyl amino ketals **2a**, **2b**, and **2c** in acetic acid proceeded in excellent yields to 2,3-dihydroxypyrazines **3a**, **3b**, and **3c**, respectively. While a steric hindrance due to the substituents was recognized, cyclizations of **2d**, **2e**, and **2f** (R_2 = C_6H_5) in acetic acid in the presence of *p*-toluenesulfonic acid provided the corresponding 2,3-dihydroxypyrazines in 50–60% yields. The structures of these 2,3-dihydroxypyrazines were established by conversion to 2,3-dichloropyrazines **9a–f** and subsequently 2,3-diaminopyrazines **10b**, **10d**, and **10e**.

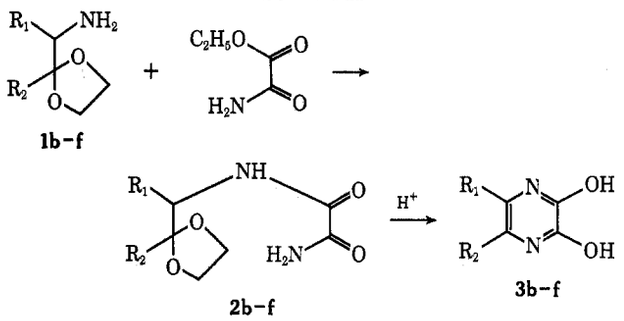
In 1947, McDonald and Ellingson[1] reported first that 2,3-di(N^4-acetylsulfamido)pyrazine was hydrolyzed with hydrochloric acid to provide 2,3-dihydroxypyrazine. Subsequently, various methods for the preparation of 2,3-dihydroxypyrazine and its 5,6-dimethyl and 5,6-diphenyl derivatives were reported, most of which were derived *via* hydrolysis of the corresponding amino-,[2,3] halo-,[4,5] or nitropyrazine[6,7] derivatives. In 1962, the authors reported briefly a new method for the synthesis of 2,3-dihydroxypyrazine,[8,9] which involves cyclization of oxamoyl amino acetal, obtained from ethyl oxamate and amino acetal, in acetic acid as a condensing agent (Scheme I).

SCHEME I



The present paper reports this method and its successful application to syntheses of 2,3-dihydroxypyrazine with methyl or/and phenyl groups at 5 and 6 positions. This sequence is outlined in Scheme II. This method would be applicable to the preparations of 2,3-dihydroxypyrazines substituted by other alkyl or aryl groups.

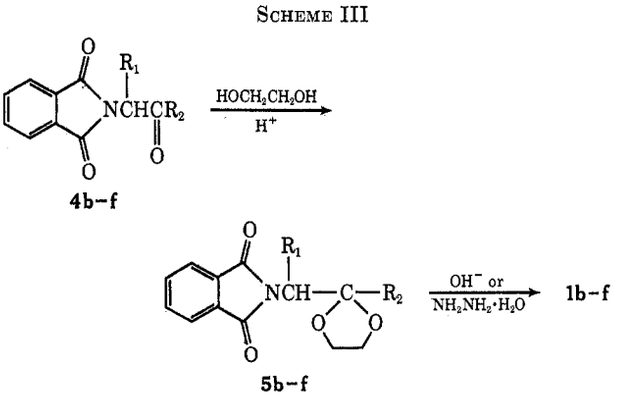
SCHEME II



	R_1	R_2
a	H	H
b	H	CH_3
c	CH_3	CH_3
d	H	C_6H_5
e	CH_3	C_6H_5
f	C_6H_5	C_6H_5

Preparation of Amino Ketals 1b–f.—The key step of this synthetic method is the preparation of amino ketals **1b–f** because α-amino ketones are readily self-condensed.[10] Our starting materials, amino ketals, were prepared by the method shown in Scheme III.

SCHEME III



Phthalimido ketones **4b–d**[11] and **4e**[12] were transformed into their ketals **5** by treatment with ethylene

(1) F. G. McDonald and R. C. Ellingson, *J. Amer. Chem. Soc.*, **69**, 1034 (1947).
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(3) L. Bernardi, G. Palamidessi, A. Leone, and G. Larini, *Gazz. Chim. Ital.*, **91**, 1431 (1961).
(4) G. Karmas and P. E. Spoerri, *J. Amer. Chem. Soc.*, **78**, 4071 (1956).
(5) G. Karmas and P. E. Spoerri, *ibid.*, **79**, 680 (1957).
(6) G. Karmas and P. E. Spoerri, *ibid.*, **75**, 5517 (1953).
(7) J. D. Ratajczyk and J. A. Carbon, *J. Org. Chem.*, **27**, 2644 (1962).
(8) J. Adachi and K. Kishimoto, reported to the 15th Annual Meeting of Chemical Society of Japan, Tokyo, April 1962.
(9) The analogous method for the preparation of 2,3-dihydroxypyrazine was also reported: G. Palamidessi and M. Bonanomi, *Farmaco, Ed. Sci.*, **21**, 799 (1966); *Chem. Abstr.*, **66**, 37884 (1967).
(10) I. J. Krems and P. E. Spoerri, *Chem. Rev.*, **40**, 290 (1947).
(11) J. C. Sheehan and W. A. Bolhofer, *J. Amer. Chem. Soc.*, **72**, 2786 (1950).
(12) Shu-Sing Cheng, S. Jonsson, and F. T. Semeniuk, *J. Pharm. Sci.*, **51**, 108 (1962).

glycol in the presence of *p*-toluenesulfonic acid in refluxing benzene with azeotropic removal of the water formed (see Table III). Ketalization of **4f** in refluxing benzene was not successful, because of the steric hindrance due to its two bulky phenyl groups. However, in refluxing toluene the conversion proceeded successfully to give **5f** in about 60% yield.

On hydrolysis of phthalimido ketals to amino ketals **1**, a steric effect due to the substituents of **5** on the ease of the hydrolysis emerged (see Table IV). Thus, **5b–d** (R_1 = H or CH_3) could be easily hydrolyzed by treatment with 30% aqueous sodium hydroxide. Whereas hydrolysis of **5e** (R_1 = CH_3; R_2 = C_6H_5) required drastic conditions (45% aqueous sodium hydroxide), **5e** and **5f** were readily converted to **1** in excellent yields by use of hydrazine hydrate in the place of an aqueous sodium hydroxide.

Preparation of 2,3-Dihydroxypyrazines 3 from Amino Ketals 1.—For the first step, amino ketals **1a**, **1b**, and **1d** (R_1 = H), excepting **1c** and **1e** (R_1 = CH_3), were easily condensed with ethyl oxamate in refluxing ethanol to give the corresponding oxamoyl amino ketals **2** (see Table I). In the condensation of **1e** with ethyl oxamate, a large amount of insoluble salt **6** was produced in the refluxing reaction mixture. When isobutyl alcohol was used as a condensing solvent, a slight amount of oxamide was formed but **2c** was obtained in good yield, which was contaminated with **7c**. The structures of **6** and **7** were confirmed by elemental and spectral analyses. In refluxing isoamyl alcohol as a condensing agent, the yield of **7c** was increased. Under the same conditions, **2e** was prepared in 61% yield and formation of the insoluble by-products (**6**, **7e**, and oxamide) was reduced. These experimental results suggest that the steric hindrance to this series of condensations is influenced by both R_1 and R_2 substituents of the amino ketals, and therefore it is especially difficult to condense **1f** with ethyl oxamate. Actually, the condensation product obtained in refluxing isoamyl alcohol was a mixture of **2f**, **7f**, and the salt or/and oxamide. An improvement in the yield of **2f** was was achieved by fusing **1f** with ethyl oxamate for shorter time to reduce formation of **7f**. The results in a series of these condensations are satisfactorily interpretable by considering their steric hindrances.

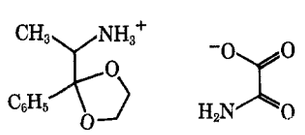
Cyclization of oxamoyl amino ketals **2a–c** (R_2 = H or CH_3) in refluxing glacial acetic acid provided 2,3-dihydroxypyrazines **3a–c** in excellent yields (see Table II). In contrast, **2d–f** (R_2 = C_6H_5) were unreactive under the same conditions. Some experiments under various acidities afforded following results. The reaction of **2d** with refluxing 0.01 *N* hydrochloric acid proceeded quantitatively to ketone **8d**, and that of **2e** with refluxing 0.1 *N* hydrochloric acid provided 2,3-dihydroxypyrazine **3e**. With trifluoroacetic acid, **2d** and **2f** afforded ketones **8d** and **8f**, respectively, but **2e** gave only **3e**. Consequently, cyclization to 2,3-dihydroxypyrazines **3d–f** was successful only by treating the oxamoyl amino ketals in refluxing glacial acetic acid or propionic acid in the presence of *p*-toluenesulfonic acid. In those cyclizations, a steric influence of substituent R_1 was unrecognized, and the yields were in a range of 50–60%.

Chlorination and Amination of 2,3-Dihydroxypyrazines. –The 2,3-dihydroxypyrazines were treated with excess phosphoryl chloride to provide the corresponding 2,3-dichloropyrazines **9** in 70–90% yields.

TABLE I
CONDENSATION OF AMINO KETALS 1 WITH ETHYL OXAMATE

Amino ketal	Condensing solvent	Reaction time, hr	Yield of 2, %	Other products (%)
1a	C_2H_5OH	6	91.5	
1b	C_2H_5OH	6	73.7	
1c	C_2H_5OH	4.5	20.6	
1c	C_2H_5OH	24	54.3	Salt[a]
1c	*i*-C_4H_9OH	29	61.5	7c (1.0)
1c	*i*-$C_5H_{11}OH$	120	40.3	7c (49.7)
1d	C_2H_5OH	7	67.0	
1e	C_2H_5OH	7	28.4	6 (20.3)
1e	*i*-$C_5H_{11}OH$	148	61.1	6 (2.4), 7e (3.7)
1f	*i*-$C_5H_{11}OH$	120	39.4[b]	
1f		1.5	54.1	

[a] The structure has not been determined. [b] Melting point is in the range of 175–195° because of contamination with minor components.



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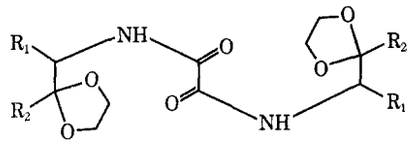

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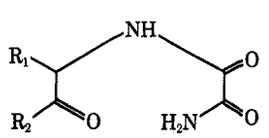
TABLE II
CYCLIZATION OF OXAMOYL AMINO KETALS 2

Oxamoyl amino ketal	Solvent	Reaction time, hr	Product	Yield, %
2a	CH_3COOH	6	3a	98.5
2b	CH_3COOH	93	3b	84.8
2c	CH_3COOH	116	3c	93.7
2d	0.01N HCl	3	8d[a]	100
2d	CF_3COOH[c]	24	8d[a]	83.2
2d	TsOH[b]–CH_3COOH	93	3d	50.5
2d	TsOH[b]–C_2H_5COOH	120	3d	61.3
2e	0.1 *N* HCl	17	3e	50.4
2e	CF_3COOH[c]	28	3e	43.2
2e	TsOH[b]–CH_3COOH	107	3e	53.6
2f	CF_3COOH[d]	21	8f	100
2f	TsOH[b]–CH_3COOH	120	3f	52.7

[a] This compound was converted to **3d** in 21% yield by treatment with CH_3COOH in the presence of TsOH. [b] TsOH–CH_3COOH or C_2H_5COOH (1 g/50 ml). [c] At room temperature. [d] At reflux.



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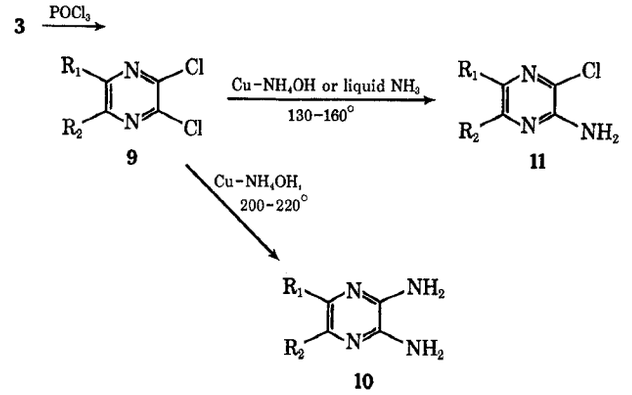
Some procedures for amination of 2,3-dichloro- and 2-halo-3-aminopyrazines have been reported,[13-17] which consist of heating in a sealed vessel with ammonium hydroxide in the presence of activated copper powder for about 24 hr or longer at 120–140° to give 2,3-diaminopyrazines. By this procedure, 2,3-dichloropyrazines **9a** and **9b** were converted not to diaminopyrazines **10** but to chloroaminopyrazines **11** in



60–70% yields.[18] Diaminopyrazines **10b**, **10d**, and **10e** were prepared only at elevated temperature, 200–220°, in 28–66% yields.

Experimental Section

Melting points were determined in capillary and are corrected. Boiling points are uncorrected. Infrared spectra were recorded on Hitachi Model EPI-G$_3$ grating spectrometer. Ultraviolet spectra (95% C_2H_5OH) were recorded on JASCO Model ORD/UV-5 spectrometer. Nmr spectra were recorded on JEOL Model JNM-C-60HL or JNM-PS-100 instruments with tetramethylsilane as an internal standard.

A. Reaction of α-Halo Ketone and Potassium Phthalimide. 2-(*N*-Phthalimido)-1,2-diphenylacetaldehyde (4f).—Potassium phthalimide (63.0 g, 0.34 mol) was added in small portions to a stirred solution of 2-chloro-1,2-diphenylacetaldehyde (75.7 g, 0.33 mol) in 500 ml of dimethylformamide, and the suspension was refluxed for 41 hr. The reaction mixture was allowed to stand at room temperature, poured into 1000 ml of water, and extracted with 200 ml of chloroform. After further extraction with a 100-ml portion of chloroform, the combined chloroform extracts were washed with 3% aqueous sodium hydroxide and a large amount of water, dried over magnesium sulfate, and evaporated. The crystalline residue was washed with ether to afford 45.7 g (43.9%), mp 155–158°, of **4f**. Recrystallization from ethanol gave colorless crystals, mp 158–159°.

Anal. Calcd for $C_{22}H_{15}NO_3$: C, 77.40; H, 4.43; N, 4.10. Found: C, 77.47; H, 4.59; N, 4.23.

B. General Procedure for Ketalization of Phthalimido Ketones 4.—An apparatus for this procedure consists of a 300–500-ml three-necked round-bottomed flask (A) fitted on a mantle heater and a magnetic stirrer, a condenser (B), and a water removable separator (C) with a U-tube (D) packed anhydrous calcium chloride. An azeotropic mixture was condensed in B to drop into C and returned into A through D.

A solution of phthalimido ketone **4** (0.20 mol) and ethylene glycol (50 ml) in 100–200 ml of benzene or toluene in the presence of *p*-toluenesulfonic acid (2.0 g) was refluxed with stirring for about 50 hr, and additional ethylene glycol (50 ml) was added to it and then refluxed again for the total time indicated in Table III. The reaction mixture was cooled to room temperature, the benzene layer was separated, and the ethylene glycol layer was extracted with two or three 100-ml portions of benzene or ether. The combined benzene and/or ether extracts were washed with 5% aqueous sodium hydroxide and then with water, dried over magnesium sulfate, and evaporated to afford phthalimido ketal **5**, which was purified by recrystallization from ethanol or by distillation.

TABLE III

KETALIZATION OF PHTHALIMIDO KETONES 4[a]

Phthalimido ketone	Reaction time, hr[b]	Yield of 5, %	Mp, °C
4b	100	80.2	93–95[c]
4c	136	89.0	60–62[d]
4d	95	94.7	145[c]
4e	137	93.8	131[c]
4f	100	59.1	172–173[c]

[a] Satisfactory analytical data (±0.37% for C, H, and N) were reported for all compounds: Ed. [b] Reactions of **4b–e** were carried out in benzene; toluene was used for **4f**. [c] Recrystallized from ethanol. [d] Distilled [bath temperature 250° (3 mm)].

C. General Procedure for Hydrolysis of Phthalimido Ketals 5.—A solution of **5** (0.60 mol) in 500 ml of 15% aqueous sodium hydroxide was refluxed with stirring and sodium hydroxide (75 g) was added in one or several portions to it. Sodium phthalate precipitated on standing at room temperature and was redissolved by addition of water and the resulting solution was extracted with ether mechanically or on a continuous liquid extractor. The ether extracts were dried over sodium or potassium hydroxide pellets, filtered, and evaporated. The residue was distilled affording **1** as a colorless oil.

The method of using hydrazine hydrate was as follows. A solution of **5** (0.20 mol) in 100 ml (2.0 mol) of 80% hydrazine hydrate was refluxed. The reaction mixture was allowed to stand

TABLE IV

HYDROLYSIS OF PHTHALIMIDO KETAL 5[a]

Phthalimido ketal	Hydrolytic reagent	Reaction time, hr	Yield of 1, %
5b	30% NaOH	65	88.3
5c	30% NaOH	90	77.2
5c	80% $NH_2NH_2 \cdot H_2O$	46	86.6
5d	30% NaOH	90	87.0
5e	30% NaOH	120	30.4
5e	45% NaOH[a]	149	81.3
5e	80% $NH_2NH_2 \cdot H_2O$	24	86.5
5f	80% $NH_2NH_2 \cdot H_2O$	48	97.4

[a] Ethylene glycol–water–sodium hydroxide (50:15:12) at 150°.

TABLE V

PHYSICAL PROPERTIES OF AMINO KETALS 1[a]

Amino ketal	Bp, °C (mm)	$n^{25}D$	Nmr,[b] τ
1b	73 (31)	1.4420	8.81 (s, 3 H), 8.55 (s, 2 H, NH_2), 7.49 (s, 2 H), 6.19 (s, 4 H)
1c	86 (50)	1.4420	8.92 (d, 3 H, 7.1 Hz), 8.75 (s, 3 H), 8.64 (s, 2 H), 7.11 (q, 1 H, 7.0 Hz), 6.04 (s, 4 H)
1d	156 (30)	1.5311	8.60 (s, 2 H, CH_2), 7.08 (s, 2 H), 6.6–5.7 (br, 4 H), 2.8–2.3 (m, 5 H)
1e	110–111 (4)	1.5240	9.06 (d, 3 H, 7.5 Hz), 8.49 (s, 2 H), 6.87 (q, 1 H, 7.3 Hz), 5.95–5.8 (m, 4 H), 2.8–2.3 (m, 5 H)
1f	250[c] (2)	1.5720	8.22 (s, 2 H), 6,4–6.0 (m, 4 H), 5.80 (s, 1 H), 2.81 (s, 5 H), 2.75 (s, 5 H)

[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all compounds in the table: Ed. [b] Nmr spectra, excepting of **1b**, were determined in $CDCl_3$; that of **1b** was measured in DMSO-d_6. [c] Bath temperature. Mp 20–22°.

(13) R. C. Ellingson and R. L. Henry, *J. Amer. Chem. Soc.*, **70**, 1257 (1948).
(14) E. Schipper and A. R. Day, *ibid.*, **74**, 350 (1952)
(15) F. L. Muehlmann and A. R. Day, *ibid.*, **78**, 242 (1956).
(16) R. H. Martin and Z. Tarasiejska, *Bull. Soc. Chim. Belg.*, **66**, 136 (1957); *Chem. Abstr.*, **51**, 10533 (1957).
(17) F. Armarego, *J. Chem. Soc.*, 4304 (1963).
(18) In the absence of activated copper powder, **11b** was obtained in 77% yield (see Experimental Section).

TABLE VI
PHYSICAL PROPERTIES OF CONDENSATION PRODUCTS 2 AND 7[a]

Material	Mp,[b] °C	Ir (KBr), cm^{-1}	
		ν_{NH}	Amide I
2a	140–141[c]	3400, 3310, 3270	1655
2b	121	3400, 3350, 3200	1678
2c[d]	113	3370, 3310, 3200	1658
7c[e]	151–152	3310	1653
2d	124–125	3375, 3320, 3200	1655
2e[f]	164–165	3380, 3350, 3250	1675
7e[g]	211–213	3350	1678
2f	203–204	3400, 3340, 3210	1668
7f	227–229	3370	1668

[a] Satisfactory analytical values (±0.3% for C, H, and N) were reported for all compounds in the table: Ed. [b] Recrystallized from ethanol. [c] Lit.[9] mp 146°. [d] Nmr (CDCl$_3$) τ 8.78 (d, 3, J = 7.4 Hz, CH_3CH), 8.68 (s, 3, CH_3), 6.01 (s, 4, OCH_2CH_2O), 5.83 (d of q, 1, J = 10.0 and 7.4 Hz, CH_3CHNH), 3.29 and 2.40 (each s, 1 + 1, $H_2NC{=}O$), 2.43 (br d, 1, J = 10.0 Hz, $CHNHC{=}O$). [e] Nmr (CDCl$_3$) τ 8.78 (d, 6, J = 7.4 Hz, $2CH_3CH$), 8.68 (s, 6, $2CH_3$), 6.00 (s, 8, $2OCH_2CH_2O$), 5.84 (d of q, 2, J = 10.0 and 7.4 Hz, $2CH_3CHNH$), 2.48 (br d, 2, J = 10.0 Hz, $2CHNHC{=}O$). [f] Nmr (CDCl$_3$) τ 8.91 (d, 3, J = 7.5 Hz, CH_3CH), 6.4–5.8 (m, 4, OCH_2CH_2O), 5.60 (d of q, J = 10.0 and 7.5 Hz, CH_3CHNH), 3.83 (s, 1, one proton of $NH_2C{=}O$), 2.9–2.3 (m, 1 + 1 + 5, $CHNHC{=}O$, one proton of $H_2NC{=}O$, and C_6H_5). [g] Nmr (CDCl$_3$) τ 8.93 (d, 6, J = 7.5 Hz, $2CH_3$), 6.4–5.8 (m, 8, $2OCH_2CH_2O$), 5.62 (d, of q, 2, J = 10.0, and 7.5 Hz, $2CH_3CHNH$), 2.9–2.3 (m, 2 + 10, $2CHNHC{=}O$ and $2C_6H_5$).

pressure giving the second crop. The combined products were recrystallized from ethanol to afford **2**.

Compound **7c** was obtained by recrystallization of the second crop from ethanol. Compound **7e** was isolated by extraction of the insoluble material in refluxing isoamyl alcohol with hot chloroform. The undissolved material in hot chloroform was recrystallized from water giving **6**: mp 237–238°; ir (KBr) 3380, 1693, 1635 ($H_2NCOCO_2^-$), 3190, 1600, and 1310 cm^{-1} (NH_3^+).

Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 54.86; H, 6.56; N, 9.67.

Compound **7f** was obtained by five recrystallizations of condensation product in isoamyl alcohol from ethanol (Table VI).

E. General Procedure for Cyclization of Oxamoyl Amino Ketals 2.—A solution of **2** (0.10 mol) in 50–100 ml of a hydrolytic solvent was refluxed for the time indicated in Table II under nitrogen. The reaction mixture was allowed to stand at room temperature, the precipitate was collected, and mother liquor was evaporated to dryness under reduced pressure. The residue was washed with a small amount of water, triturated with hot chloroform, filtered, and recrystallized to give **3** or **8**. The physical properties of these compounds are summarized in Table VII.

F. General Procedure for Chlorination of 2,3-Dihydroxypyrazines 3.—A solution of **3** (20 mmol) in 30–50 ml of phosphoryl chloride was heated at 130–180° for the time indicated in Table VIII. The cooled solution was poured into ice–water and extracted with three to five 100-ml portions of ether or chloroform. The combined organic extracts were washed, dried over magnesium sulfate, and evaporated to afford 2,3-dichloropyrazine **9**.

G. General Procedure for Amination of 2,3-Dichloropyrazines 9.—A mixture of **9** (2.0 mmol) and ammonium hydroxide (25 ml) or liquid ammonia (40 ml) in the presence of activated

TABLE VII
PHYSICAL PROPERTIES OF CYCLIZATION PRODUCTS 3 AND 8[a]

Material	Mp, °C (lit.)	Uv max (ϵ)	Nmr (DMSO-d_6), τ			
			CH_3	Ring proton	C_6H_5	OH
3a	>360[b] (>350[1])	234 (5,180), 380 (4,860)				
3b	301–303 dec[c]	234 (6,770), 315 (6,470)	8.10 s	3.98 s		−1.08 s
3c	>360[b] (>340[4])	232 (7,240), 324 (6,850)	8.12 s			−1.09 s
3d	288–290 dec[d]	276 (7,240), 323 (7,240)		3.36 s	2.78–2.32 m	−1.52 s
3e	327–328 dec[e]	270 (5,520), 324 (6,960)	8.10 s		2.62 s	−2.11 s
3f	338–339[f] (335–340[6]) (340–342[7])	298 (10,500)			2.81 m	−1.44 s
8d[g]	202–203[e]					
8f[h]	200–201[d]					

[a] Satisfactory analytical values (±0.3% for C, H, and N) were reported for all compounds in the table: Ed. [b] Recrystallized from water, [c] methanol, [d] aqueous acetic acid (1:1 v/v), and [e] ethanol, respectively. [f] Recrystallized from acetic acid and water. The infrared spectrum of this compound was identical with that of an authentic sample.[8] [g] Ir (KBr) 1694, [h] 1691 cm^{-1}.

at room temperature, 30% aqueous sodium hydroxide or water was added to it to redissolve the resulting diketophthazine, and the oily layer was separated. The aqueous layer was extracted in several times with ether. The combined organic portions were worked up in the predescribed manner to give **1**. The results and physical properties of **1** are summarized in Tables IV and V.

D. Condensation of Amino Ketals 1 with Ethyl Oxamate.—The general procedure is as follows. A solution of amino ketal **1** (0.10 mol) and ethyl oxamate (0.11 mol) in 100 ml of a solvent was refluxed for the time indicated in Table I. When an insoluble material was formed, it was removed hot by filtration. If ethanol was not used as the solvent, the following pretreatment was carried out: the reaction mixture was evaporated to dryness under reduced pressure and the residue was redissolved in ethanol with heating.

After cooling to 0°, the precipitate was collected by filtration. Into the mother liquor was passed ammonia gas to remove unreacted ethyl oxamate as oxamide, and the resulting solution was boiled and an undissolved matter (oxamide) was removed hot by filtration. The solution was evaporated to dryness under reduced

copper powder (and potassium bromide) was heated in a sealed tube or a stainless steel autoclave (see Table IX). The reaction mixture was allowed to stand at room temperature, and the precipitate was collected, washed with a small amount of water, dried, and recrystallized giving amino product **10** or **11**.

Registry No.—**1b**, 3289-19-8; **1c**, 32493-50-8; **1d**, 32493-51-9; **1e**, 32493-52-0; **1f**, 32493-53-1; **2a**, 923-97-7; **2b**, 32493-55-3; **2c**, 32493-56-4; **2d**, 32493-57-5; **2e**, 32493-58-6; **2f**, 32493-59-7; **3a**, 931-18-0; **3b**, 32493-61-1; **3c**, 32493-62-2; **3d**, 32493-63-3; **3e**, 32493-64-4; **3f**, 32493-65-5; **4f**, 32493-66-6; **5b**, 1775-18-4; **5c**, 32493-67-7; **5d**, 32493-68-8; **5e**, 32493-69-9; **5f**, 32493-70-2; **6**, 32493-71-3; **7c**, 32493-72-4; **7e**, 32493-73-5; **7f**, 32493-74-6; **8d**, 32493-75-7; **8f**, 32493-76-8; **9a**, 4858-85-9; **9b**, 32493-78-0; **9c**, 32493-79-1; **9d**, 32493-80-4; **9e**, 32493-81-5; **10b**, 32493-82-6; **10d**, 32493-83-7; **10e**, 32493-84-8.

TABLE VIII

CHLORINATION OF 2,3-DIHYDROXYPYRAZINES 3[a]

2,3-Dihydroxypyrazine	Reaction time, hr	Yield of 9, %	Mp, °C (lit.)
3a	33	63.5	22–25 (22–24)[b]
3b	28	86.1	12[c]
3c	43	70.9	79–80[d] (80–81[4])
3d	90	77.1	106–107[e] (102)[f]
3e	96	79.8	69–70[g]
3f	48	69.9	182[h] (182–183[4])

[a] Satisfactory analytical values (±0.3% for C, H, N, and Cl) were reported for all compounds in the table: Ed. [b] American Cyanamide Co., British Patent 612,385 (1948); *Chem. Abstr.*, 44, 1537 (1950). [c] Bp 100–101° (20 mm); n^{25}D 1.5498. [d] Recrystallized from hexane and [e] ethanol. [f] S. T. Minovici and V. Th. Bente, *Bull. Sect. Sci. Acad. Roumaine*, 4, 185 (1915); *Chem. Abstr.*, 10, 606 (1916). [g] Recrystallized from petroleum ether (bp 30–50°). [h] Recrystallized from acetone.

TABLE IX

AMINATION OF 2,3-DICHLOROPYRAZINES 9[a]

Starting material	Conditions: Temp, °C	Conditions: Time, hr	Product	Yield, %	Mp, °C
9a	130–140[b]	50	11a	61	167[f]
9b	150–160[c]	70	11b	77	113[g]
9b	200–220[d]	60	10b	66	178[h]
9d	200–210[e]	85	10d	59	173[i]
9e	200–220[e]	72	10e	28	167–168[i]

[a] Satisfactory analytical values (±0.3% for C, H, and N) were reported for all compounds in the table: Ed. [b] Amination were carried out with activated copper powder in liquid ammonia, [c] ammonium hydroxide (*d* 0.880), [d] activated copper powder in ammonium hydroxide (*d* 0.880), and [e] activated copper powder and potassium bromide in ammonium hydroxide (*d* 0.880), respectively. [f] Recrystallized from water (lit.[15] mp 169°). The melting point of a mixture with an authentic sample[15] undepressed and ir spectra were identical. The authors are grateful to Mr. T. Kohagizawa for the synthesis of an authentic sample. [g] Recrystallized from ethanol. Mp 113°: G. Palamidassi, *Farmaco, Ed. Sci.*, 18, 557 (1963); *Chem. Abstr.*, 59, 13975 (1963). [h] Recrystallized from ethyl acetate and [i] benzene, respectively.

Acknowledgment.—The authors wish to thank Mr. K. Kishimoto, Mr. K. Kaneko, Mr. M. Ichinose, Mr. K. Ikeda, and Mr. Y. Nagatsu for their experimental assistances and Mr. A. Ito for nmr measurement. The authors are also grateful to Dr. T. Nakagawa for his helpful suggestions.

Derivatives of Thiacyclobutene (Thiete). V.[1] Molecular Reorganization in the Reaction of Thiete Sulfone and Tetraphenylcyclopentadienone[2-4]

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Thiete sulfone (**1**) and tetracyclone react in refluxing *m*-xylene to yield 1,2,6,7-tetraphenylcycloheptatriene (65%, **2**) and a bicyclic ketone (15%), 1,5,6,7-tetraphenylbicyclo[3.2.1]octa-2,6-dien-8-one (**3**). When 1,2,3,4-tetraphenylcyclopentadiene and thiete sulfone are refluxed in *m*-xylene, a 77% yield of the Diels–Alder adduct is obtained in addition to 1,5,6,7-tetraphenylbicyclo[3.2.1]octa-2,6-diene (13%). Thiete sulfone and phencyclone give a 69% yield of a cycloheptatriene (**4**) but no carbonyl compound. An alternate structure (**6**) for ketone **3** was abandoned on the basis of physical data and the conversion of the ketone to 1,5,6,7-tetraphenylbicyclo-[3.2.1]octene-6 (**8**). In dioxane a low (8%) yield of the Diels–Alder adduct **9** of thiete sulfone and tetracyclone is obtained. Decomposition of this adduct in refluxing *m*-xylene gives only cycloheptatriene **2**. A pathway for formation of bicyclic ketone **3** through the intermediacy of vinyl carbene (or some species which resembles it) derived from thiete sulfone is discussed. Reaction of a vinyl carbenoid species, obtained by the Simmons–Smith procedure from 3,3-dichloro-1-propene, with tetracyclone gives a 4% yield of bicyclic ketone **3**.

α,β-Unsaturated sulfones usually react normally as dienophiles in the Diels–Alder cycloaddition reaction[5] and a number of additions to thiete sulfone (thiacyclobutene 1,1-dioxide) (**1**) proceed normally.[6] A logical route to thiete sulfones containing a fused benzene ring involves the Diels–Alder addition of tetracyclone (tetraphenylcyclopentadienone) to thiete sulfone followed by loss of carbon monoxide and two hydrogens. In fact, a number of tetraphenylbenzene derivatives are obtained from Diels–Alder adducts of tetracyclone.[7] We have found that butadiene, furan, and 2,5-dimethylfuran, in addition to the dienes reported earlier,[6a] add normally to thiete sulfone. This report is about an anomalous reaction of thiete sulfone with tetracyclone.

Product Identification. A Cycloheptatriene and a Bicyclic Ketone.—When thiete sulfone and tetracyclone were refluxed in *m*-xylene (139°) until the color of tetracyclone was discharged (*ca.* 85 hr), two gases identified as sulfur dioxide and carbon monoxide were produced. The major organic products were two solids of empirical formulas $C_{31}H_{24}$ (65% yield) and

(1) Paper IV: D. C. Dittmer, R. S. Henion, and N. Takashina, *J. Org. Chem.*, **34**, 1310 (1969).

(2) This research was supported in part by National Science Foundation Grants GP 726, 5513 and 8086, and by National Institutes of Health Grant CA 08250, for which the authors are grateful.

(3) A preliminary report on some of this work has been given: D. C. Dittmer and J. M. Balquist, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstract K 37. The structure of compound **3** was given incorrectly at that time.

(4) Taken in part from the Ph.D. thesis of J. M. Balquist, Syracuse University, 1966.

(5) For example, see K. Alder, H. F. Rickert, and E. Windemuth, *Ber.*, **71**, 2451 (1938); H. R. Snyder, H. V. Anderson, and D. P. Hallada, *J. Amer. Chem. Soc.*, **73**, 3258 (1951); H. R. Snyder and D. P. Hallada, *ibid.*, **74**, 5595 (1952).

(6) (a) D. C. Dittmer and M. E. Christy, *ibid.*, **84**, 399 (1962); D. C. Dittmer and N. Takashina, *Tetrahedron Lett.*, 3809 (1964); L. A. Paquette, *J. Org. Chem.*, **30**, 629 (1965); L. A. Paquette and T. R. Phillips, *ibid.*, **30**, 3883 (1965). (b) Cycloaddition of diazoalkanes to thiete sulfone also occurs normally although certain adducts lose sulfur dioxide at 150°: D. C. Dittmer and R. Glassman, *ibid.*, **35**, 999 (1970).

(7) See the review by M. A. Ogliaruso, M. G. Romanelli, and E. I. Becker, *Chem. Rev.*, **65**, 261 (1965).