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Reaction of Salicylamine with α-Dicarbonyl Compounds. II. Formation of 2,2′-Bibenz-1,3-oxazines

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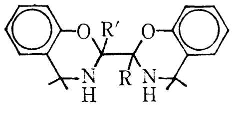
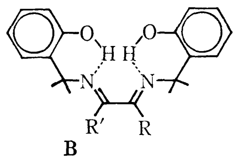
The compounds of a new type, 2,2′-bibenz-1,3-oxazine and its derivatives have been synthesized by the reactions of salicylamines with glyoxal or α-diketones in methanol at a temperature lower than 20°C. The oxazine structures were confirmed by infrared spectroscopy in solid state and by NMR spectroscopy in CCl_4, $CDCl_3$ and chlorobenzene. An oxazine-Schiff base equilibrium was observed in pyridine and in hot chlorobenzene by NMR spectra. It was found that hydrolytic decomposition of 2,2′-dimethyl-2,2′-bibenzoxazine leads to the formation of salicylidenesalicylamine through transamination. The mechanisms were investigated spectrophotometrically.

It has been reported in a previous paper[1] that the reaction of *o*-hydroxybenzylamine (salicylamine) with α-diketones, α-ketoaldehydes, and with α-keto acid ester in hot methanol gave rise to the formation of salicylidenesalicylamine in all cases. It was further found that the reactions proceeded with transamination followed by *trans*-Schiffization between salicylamine and the dicarbonyl compounds, where the former was converted into salicylaldehyde through corresponding Schiff base of the latter, and the Schiff bases were subjected to an exchange reaction at the amine moiety with unreacted salicylamine to yield salicylidenesalicylamine.

Since the initial subject of our investigation had been to obtain condensation products of salicylamine with α-dicarbonyl compounds, for which a bibenzoxazine A or a Schiff base B structure was proposed, the reactions were further examined under different conditions.


A


B

The possibility of forming A or B type compound is suggested from the fact that primary γ-amino alcohols condense with aldehydes or ketones to yield either oxazines or open-chain Schiff base or a tautomeric mixture of them.[2] In our previous experiments, it was found that the reactions did not terminate at the first condensation stage owing to the subsequent reactions. Therefore, it was considered that the reactions at a low temperature might be favorable for the prevent ion of subsequent reactions. Thus, two moles of salicylamine were allowed to react with α-dicarbonyl compounds at a temperature lower than 20°C in methanol, and the condensation products were obtained as expected in fairly good yields. The compounds isolated in this way are listed in Table 1.

McDonagh and Smith[3] have extensively studied a ring-chain tautomerism between oxazines and Schiff bases by means of infrared and NMR spectroscopy for the condensation products of salicylamine with aromatic or aliphatic aldehydes and ketones, and concluded that the products from aliphatic aldehydes and ketones were oxazines in the solid state exhibiting NH absorptions in infrared spectra, and even in solution they existed exclusively as oxazines, because the NMR peaks of the ring methylene protons appeared around at $6.0\,\tau$ as an AB pattern with a coupling constant of 17 Hz, and those of imino protons appeared around at $7\,\tau$ as weak several peaks.

In the present case, infrared and NMR spectroscopy were also employed for the structure determination.

The infrared spectrum of III in solid state (KBr disk) is shown as an example in Fig. 1. In the high frequency region, there is a sharp absorption at $3340\ cm^{-1}$ and this could be due to an OH or NH group. From the shape of the band it is more

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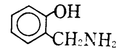
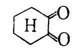
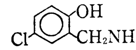
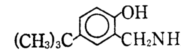
[1] H. Kanatomi and I. Murase, This Bulletin, **42**, 1329 (1969).

[2] a) A. C. Cope and E. M. Hancock, *J. Amer. Chem. Soc.*, **64**, 1503 (1942). b) E. D. Bergmann, E. Zimkin and S. Pinchas, *Rec. Trav. Chim. Pays-Bas* **71**, 168 (1952). c) E. D. Bergmann, E. Gil-Av and S. Pinchas, *J. Amer. Chem. Soc.*, **76**, 358 (1953). d) E. D. Bergmann, *Chem. Rev.*, **53**, 309 (1953). e) E. D. Bergmann and A. Kaluszyner, *Rec. Trav. Chim. Pays-Bas* **78**, 315 (1959). f) F. W. Holly and A. C. Cope, *J. Amer. Chem. Soc.*, **66**, 1875 (1944).

[3] A. F. McDonagh and H. E. Smith, *J. Org. Chem.*, **33**, 1(1968).

Table 1. Condensation products of salicylamines with α-dicarbonyl compounds

Compound No.	Reactants		Formula	Mp, °C	Recryst. solvent	Yield %
	Salicylamine	α-Dicarbonyl				
I		CHO-CHO	$C_{16}H_{16}N_2O_2$	139—140	—	80
II	〃	CHO-COCH$_3$	$C_{17}H_{18}N_2O_2$	155—157	acetone	85
III	〃	$CH_3COCOCH_3$	$C_{18}H_{20}N_2O_2$	99—100	petrol. benzine	85
IV	〃		$C_{20}H_{22}N_2O_2$	130—133.5	*n*-hexane	85
V		〃	$C_{20}H_{20}N_2O_2Cl_2$	142—144	CCl_4-methanol	25
VI		〃	$C_{28}H_{38}N_2O_2$	134—136	petrol. ether	75
VII	〃	$CH_3COCOCH_3$	$C_{26}H_{36}N_2O_2$	149—152	petrol. benzine	85

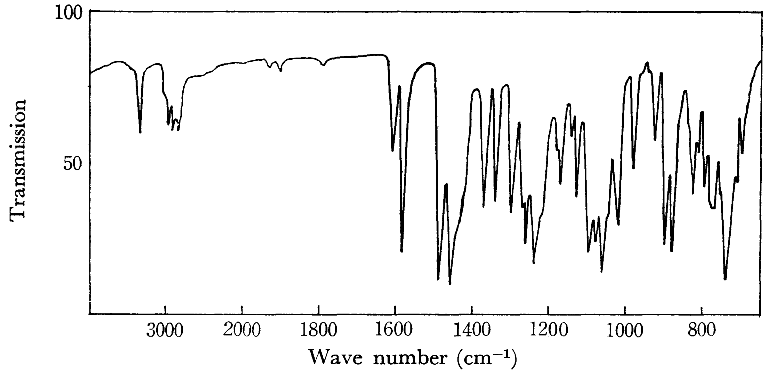
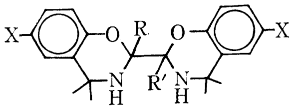


Fig. 1. IR spectrum of III (KBr).

Table 2. Analytical data and NH stretching vibrations of 2,2′-bibenzoxazine



Compound No.	R	R′	X	Formula	Found, %			Calcd, %			NH Frequency (cm^{-1})
					C	H	N	C	H	N	
I	H	H	H	$C_{16}H_{16}N_2O_2$	71.39	5.75	10.10	71.62	5.98	10.42	3245
II	CH_3	H	H	$C_{17}H_{18}N_2O_2$	72.50	6.40	9.84	72.33	6.42	9.93	3330
III	CH_3	CH_3	H	$C_{18}H_{20}N_2O_2$	72.71	6.76	9.39	72.94	6.76	9.45	3340
IV	spilocyclohexyl		H	$C_{20}H_{22}N_2O_2$	74.53	6.92	8.69	74.50	6.87	8.68	3320, 3350
V	spilocyclohexyl		Cl	$C_{20}H_{20}N_2O_2Cl_2$	61.30	5.17	7.03	61.38	5.15	7.15	3360
VI	spilocyclohexyl		$(CH_3)_3C$	$C_{28}H_{38}N_2O_2$	77.52	8.83	6.30	77.37	8.82	6.44	3370
VII	CH_3	CH_3	$(CH_3)_3C$	$C_{26}H_{36}N_2O_2$	76.43	8.88	6.69	76.43	8.88	6.85	3340

likely due to NH, hydrogen bonded in the crystals. In the double bond region, one can find no absorptions around 1620—1650 cm^{-1} which are in general due to a C=N group of a Schiff base.

From these evidences, the oxazine structure A could be assigned to this compound. Other compounds showed infrared absorption patterns similar to III, exhibiting sharp NH absorptions and no C=N absorptions. The NH frequency of each compound is listed in Table 2 together with analytical data.

It is therefore concluded from the infrared diagnosis that the condensation products of salicylamine with α-dicarbonyl compounds have the bibenzoxazine structure of the type A in solid state.

The NMR spectra of III in various solvents are

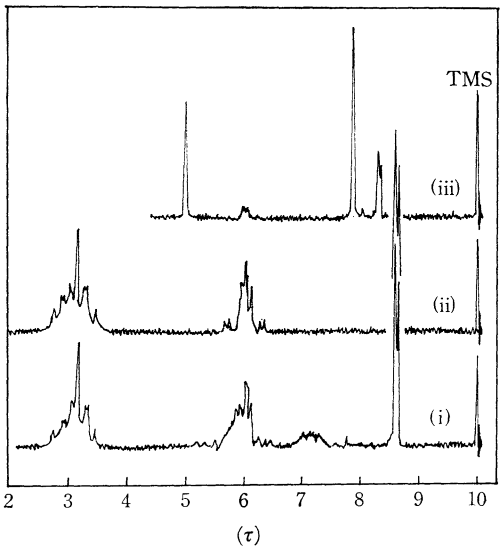
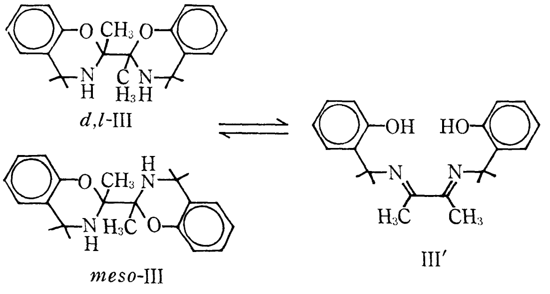


Fig. 2. NMR spectra of III, in CCl_4 (i), in CCl_4+D_2O (ii), in pyridine (iii).

shown in Fig. 2. In CCl_4, a broad signal centred at 7.2 τ and several complex peaks around 6 τ might be due to the imino and the methylene protons of the oxazine rings corresponding to A structure. On deuteration, the coupling of the methylene protons with the imino protons was excluded and the methylene proton resonance appeared as seven peaks as seen in Fig. 2, (ii).

Assuming that III is a mixture of stereo-isomers of bibenzoxazine for which a *d,l-* and a *meso*-configuration is possible, the NMR spectra will exhibit two kinds of patterns corresponding to each isomer, since the magnetic environment of protons especially in the oxazine rings will be different from each other and this will cause a different chemical shift. It is likely that the seven peaks are an overlapping of the two kinds of AB patterns corresponding to the methylene protons of each isomer. The coupling constants are both 17 Hz and the calculated chemical shifts are 5.97 τ, 6.18 τ and 5.80 τ, 6.04 τ respectively. The spliting of the methyl proton resonance at 8.50 τ and 8.45 τ might also be due to the configurational difference of *d,l-* and the *meso*-isomer.



In pyridine, two singlet peaks appeared at 7.75 τ and at 5.02 τ in addition to the bibenzoxazine proton signals as seen in Fig. 2, (iii). These new peaks suggest the formation of another species in the solution. The isomeric Schiff base (III′) is proposed, in which the methyl and the methylene proton peaks appear in a field lower than that of oxazine, because these protons are less shielded. The higher one (7.75 τ) can therefore be assigned to the methyl and the lower one (5.02 τ) to the methylene protons of the Schiff base (III′). Thus, it is seen that the compound exists as an equilibrium mixture of the oxazine (III) and the Schiff base (III′) in pyridine, and the ratio calculated from the intensities of each methyl proton peak will be about 1 : 4.

In chlorobenzene, III exists as a mixture of two isomeric bibenzoxazines at 40°C as seen in Fig. 3, (ii). At 120°C, an equilibrium of oxazine-Schiff

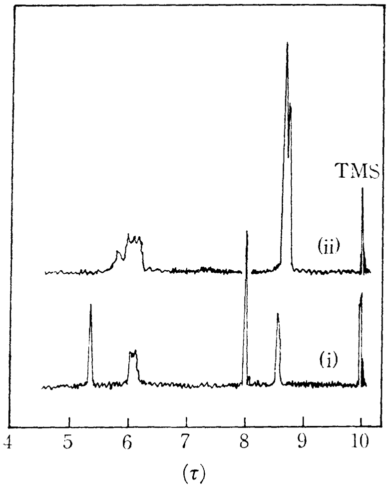


Fig. 3. NMR spectra of III in chlorobenzene, at 120°C (i), at 40°C (ii).

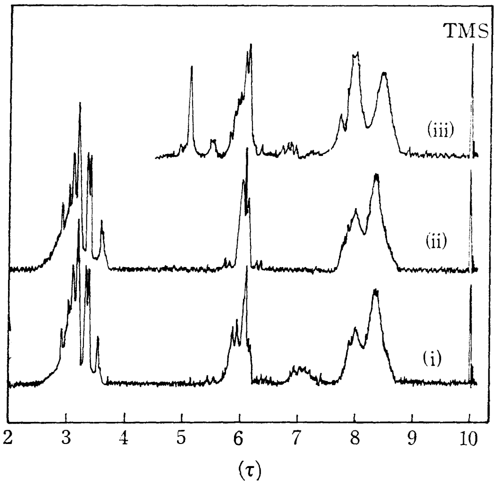
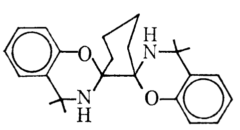


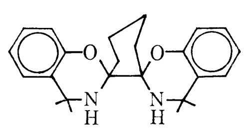
Fig. 4. NMR spectra of IV, in CCl_4 (i), in CCl_4+D_2O (ii), in pyridine (iii).

base was observed (i). Proton signals of oxazine rings decreased in intensity and new singlet peaks appeared at 8.05 τ and at 5.30 τ which due to the methyl and the methylene protons of the isomeric Schiff base, respectively. On cooling, these peaks disappeared and the spectrum gave rise to the original pattern. It is interesting to note that an oxazine-Schiff base equilibrium exists even in such a solvent less polar than pyridine.

For compound IV, the oxazine structure in CCl_4 was confirmed. In Fig. 4, (i), several peaks around 8 τ and weak multiplet centred at 7.2 τ are due to the eight protons of the cyclohexane ring and the imino protons respectively. The resonance of the ring methylene protons appeared on deuteration as partially overlapped two AB quartets centred at 6.11 τ and 6.05 τ with coupling constants of both 17 Hz. Each corresponds to those of the *d,l*- and the *meso*-isomer, and the calculated chemical shifts are 6.01 τ, 6.21 τ and 5.95 τ, 6.15 τ, respectively.



d,l-IV



meso-IV

In pyridine, a new singlet appeared at 5.07 τ in addition to similar peaks to those observed in CCl_4. This peak can be assigned to the methylene protons of the isomeric Schiff base for the same reason as the case of III and an equilibrium between the oxazine is evidenced in the solution. The ratio of the oxazine-Schiff base is approximately 2 : 1 from the intensities of the corresponding methylene peaks. In chlorobenzene, similar oxazine-Schiff base equilibrium was observed at elevated temperature (120°C), exhibiting a new singlet peak at 5.53 τ which is due to the methylene protons of the Schiff base.

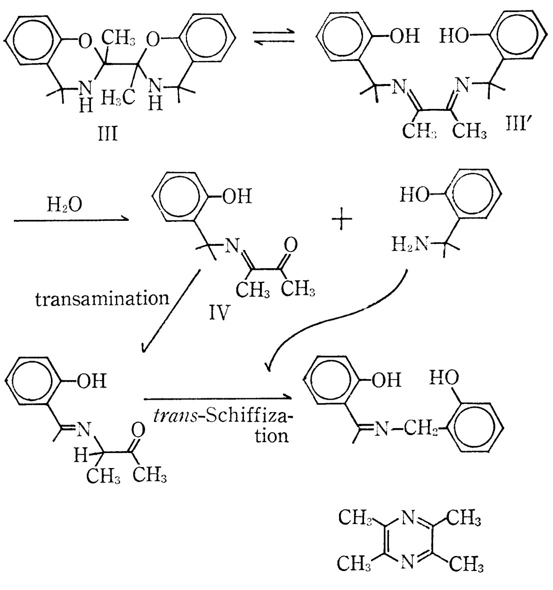
For compound I, well defined NMR spectra in various solvents could not be observed because of low solubility and of instability in solutions. The integrated spectrum in $CDCl_3$, however, shows an AB like pattern centred at 5.86 τ with a coupling constant of about 17 Hz corresponding to four protons of the methylene groups of the oxazine rings. The methine protons attached to the asymmetric carbon atoms are observed as two peaks at 4.91 τ and 4.97 τ. This suggests that I is also a mixture of the *d,l*- and *meso*-2,2′-bibenzoxazine for the same reason as given above.

Although the NMR spectrum was not measured for other compounds listed in Table 1, the oxazine structure can be confirmed by the similarity of their ultraviolet absorption spectra to those investigated above.

Higher homologues of α-diketone such as acetylpropionyl, dipropionyl, and acetylisobutylyl have beeen examined with salicylamine in the same manner as described above. However, the reactions failed to yield the corresponding oxazines, and salicylidenesalicylamine was obtained. It is clear that the transamination took place predominantly even at low temperatures in these cases. 5-Chlorosalicylamine did not react with α-diketones other than 1,2-cyclohexanedione. However, 5-*t*-butyl-derivative reacted with diacetyl and 1,2-cyclohexanedione to afford the corresponding oxazines. Slightly high acidity of the phenol group or low basicity of the amino group by chloro-substitution may reduce the reactivity. It is seen from these experiments that the formation of bibenzoxazines is limited when salicylamines having appropriate basicities react with α-dicarbonyl compounds which exhibit no steric hindrance.

Although bibenzoxazines have been isolated in well defined crystals, they are never stable in hot solutions, therefore, recrystallization seriously reduced the yield. In the case of III, salicylidenesalicylamine and tetramethylpyrazine were isolated from the 95% methanol solution on prolonged heating. It was found also that such decomposition scarcely occurred in absolute methanol with recovery of III. Assuming the presence of the oxazine-Schiff base equilibrium in methanol as well as in pyridine, the decomposition mechanism is given as shown in Scheme I, where the Schiff base (III′) is subjected to hydrolysis to give the ketimine (IV) and salicylamine. The ketimine (IV) undergoes transamination, and then *trans*-Schiffization between the salicylamine and affords salicylidenesalicylamine. The reaction mechanisms of the latter half have already been discussed.[1]

A problem which arises from the above evidence



Scheme I

is that the formation of salicylidenesalicylamine may always proceed through the oxazine formation even at elevated temperatures. To elucidate this, the rate of formation of salicylidenesalicylamine from III was measured spectrophotometrically and compared with that from the mixture of salicylamine and diacetyl. For this purpose, the increasing rate of absorbance at 400 mμ was measured, since only salicylidenesalicylamine among the reactants and the products has strong absorption in this region as seen in Fig. 5 and the absorbance is proportional to the concentration of this compound.

In Fig. 6, it is seen that the rate of formation of salicylidenesalicylamine from III in 95% methanol is greater than that in absolute methanol. This clearly indicates that hydrolysis takes part in the reaction as proposed in Scheme I. Further, the rate of formation from the mixture of salicylamine and diacetyl is much greater at the initial period of the reaction than that of hydrolytic decomposition of III. It is therefore obvious that the reaction of salicylamine and diacetyl to form salicylidenesalicylamine at elevated temperature (over 20°C) does not proceed through the initial formation of bibenzoxazine (III), but the Schiff base (III′) is the first product which undergoes further reactions. It should be noted that the formation of bibenzoxazines will take another route and it is only possible in cold.

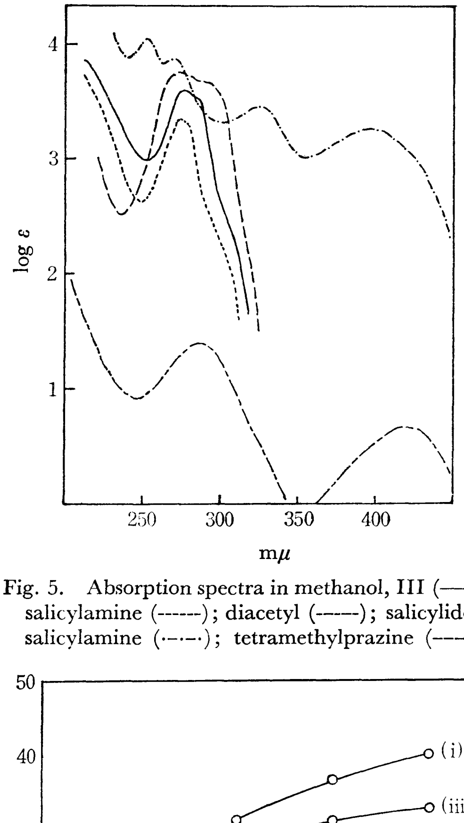


Fig. 5. Absorption spectra in methanol, III (——); salicylamine (------); diacetyl (-----); salicylidenesalicylamine (·—·—·); tetramethylprazine (-----).

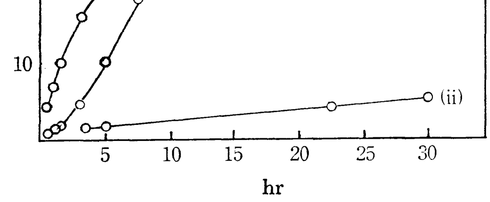


Fig. 6. Rate of formation of salicylidenesalicylamine (25°), (i) from III in methanol (*ca.* 95%), (ii) from III in absolute methanol, (iii) from salicylamine (2 mol)+diacetyl (1 mol) in absolute methanol.

Experimental

Salicylamine. Concerning the preparation of this compound, reduction of salicylaldoxime with sodium amalgam,[4] with aluminum amalgam[5] or catalytic reduction of salicylaldazine with Pd-BaSO$_4$ as a catalyst[6] have been reported. It was found, however, that catalytic reduction of salicylaldoxime by Pd-charcoal in acidic solution best proceeds conveniently in higher yield.

To a solution of salicylaldoxime (40 g) in 650 m*l* of methanol, 5% Pd-charcoal (5 g) and 36 m*l* of concentrated hydrochloric acid were added, and the hydrogenation was carried out at room temperature under atmospheric pressure with vigorous stirring. Exothermic hydrogen uptake ceased after four hours. The catalyst was filtered and the filtrate was evaporated under reduced pressure and the residue was dissolved in 250 m*l* of water. The pH of the solution was brought to 7 by the addition of concentrated ammonia and the undissolved precipitates (2—3 g) were filtered. The filtrate was made alkaline by further addition of ammonia and the resulting colorless crystals were filtered and washed with water. The crude salicylamine was dried over calcium chloride in a vacuum and recrystallized from CCl$_4$. Yield, 27 g (75%), mp 126°C.

General Procedure for the Preparation of 2,2′-Bibenz-1,3-oxazines. To a suspension of freshly purified salicylamine or its derivative (1 mol) in methanol was added a slight excess of calculated amount (0.5 mol) of α-diketone or aqueous 40% glyoxal, and the mixture was stirred for thirty minutes at a temperature below 20°C. Salicylamine was once dissolved into solution and colorless crystals then gradually separated out. After stirring for additional thrity minutes, the crystals were filtered and washed with cold methanol. Purification of each oxazine except I was carried out by recrystallization from the solvent listed in Table 1. In the case of the acetyl, the reaction was carried out in ice-cold methanol to avoid otherwise inevitable transamintion. The yield of each oxazine is described in Table 1.

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[4] D. B. Witkop and T. W. Beiler, *J. Amer. Chem. Soc.*, **76**, 5596 (1954).

[5] M. Yamaguchi, *Nippon Kagaku Zasshi*, **73**, 393 (1952).

[6] K. W. Rosenmund and E. Phankuch, *Ber.*, **56**, 2258 (1923).

Decomposition of 2,2′-Dimethyl-2,2′-bibenzoxazine (III): Formation of Salicylidenesalicylamine. A solution of III (0.9 g, 0.003 mol) in 30 m*l* of 95% methanol was gently refluxed in a nitrogen stream for four hours. The solution turned yellow and it was concentrated to about 5 m*l* under vacuum and kept in a refrigerator overnight. The resulting yellow crystals were filtered and recrystallized from methanol. A pure sample of salicylidenesalicylamine, mp 183—184°C was obtained in 50% yield.

The filtrate from which salicylidenesalicylamine was separated was evaporated to dryness in a vacuum and the residue was colloected. It was sublimed at 80°C in a vacuum (30 mmHg) and colorless crystals, mp 85°C were obtained. The compound was identified as tetramethylpyrazine by infrared spectra and by mixed melting point determination.

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