[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

The Preparation of Hydroxypyrazines and Derived Chloropyrazines

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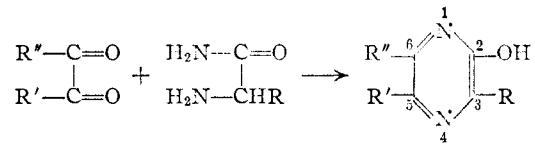
A recent synthesis of hydroxypyrazines from α-dicarbonyl compounds and aminoacid amides has been shown to be practicable using the more accessible hydrohalides of the amides. Several new hydroxypyrazines have been prepared and evidence is presented for the actual formation of isomeric condensation products from unsymmetrical reagents. Pyrazyl chlorides have been prepared from all the hydroxypyrazines herein described, and the influence of ring substituents on the replacement of hydroxyl by chlorine is briefly discussed.

The direct synthesis of hydroxypyrazines devised by R. G. Jones,[2] in which an α-aminoacid amide is condensed with a 1,2-dicarbonyl compound, has made pyrazines of this type readily available.



As reported, yields usually range from good to excellent for a wide variety of groups R, R′ and R″. The principal difficulty encountered is the preparation of α-aminoacid amides of low molecular weight, such as glycine amide and alanine amide, by ammonolysis of the esters.[3,4]

Our primary objective in beginning this investigation was to avoid this difficulty by employing the hydrohalides of α-aminoacid amides in the condensation, since these are far more easily prepared than are the free bases. Such halides as α-chloroacetamide, α-bromopropionic ester, and α-bromobutyric ester have previously been treated with 28% aqueous ammonia, forming the corresponding α-aminoacid amide hydrohalides in fair yields.[5] We have found that the use of a more concentrated solution of aqueous ammonia (saturated at 0°) produces purer products in much better yields. Ammonolysis and amination of the three above mentioned halides occurs at 0° with this reagent, but at this temperature α-chloropropionic ester, α-bromovaleric ester and α-bromoisovaleric ester form only the α-haloamides within a few days. However, at higher temperatures (see Table I) these α-haloamides react readily to form the α-aminoacid amide hydrohalides. These crude, stable, non-hygroscopic amide salts are isolated simply by concentration of the ammoniacal solutions and drying in air. While recrystallization of these salts furnishes pure materials, it was found that the crude products are perfectly satisfactory for condensation with 1,2-dicarbonyl compounds.

α-Aminobutyramide, α-aminovaleramide (norvaline amide) and α-aminoisovaleramide (valine amide) may be isolated by neutralization of the hydrobromides with saturated aqueous potassium carbonate at 0° and extraction with chloroform. This method is *not* satisfactory for glycine amide and alanine amide, because both are extremely soluble in aqueous solutions. Isolation of these free bases was not further investigated.

It was found that all the α-aminoacid amide hydrohalides which we prepared could be condensed with glyoxal, methylglyoxal and biacetyl in methanol at low temperature, using two equivalents of concentrated sodium hydroxide; these are the original conditions of Jones,[2] except for the extra amount of alkali used. In the convenient modified procedure of Jones,[2b,c] sodium carbonate or organic amines are used as condensing agents in aqueous solution at room temperature, but unfortunately this method gives very poor yields with the amide hydrohalides.

No single, simple technique could be devised for the isolation of all the hydroxypyrazines in a pure state. Hydroxypyrazine (I) and 2-hydroxy-3-isopropylpyrazine (XV) were most effectively and economically separated from troublesome by-products and tars by precipitation of their silver derivatives from aqueous solution—such a procedure is applicable to all of our hydroxyalkylpyrazines, but is not generally necessary. Compounds II-X, XII, XIII, XVI were isolated by exhaustive extraction of concentrated aqueous solutions with chloroform and were then purified by distillation at 20 mm. or less (of those with melting points below 160°), followed by recrystallization. Compounds XI, XIV and XVII precipitated on removal of methanol from the neutralized reaction mixtures, and were easily purified by recrystallization.

Glycine amide hydrochloride reacted with sodium hydroxide and benzil in refluxing methanol to form 2-hydroxy-5,6-diphenylpyrazine (XVIII) in good yield. However, under these conditions only 3% of the 3-methyl homolog was formed from alanine amide hydrobromide. Apparently destruction of alanine amide by the strong alkali proceeds much more rapidly than the formation of 2-hydroxy-3-methyl-5,6-diphenylpyrazine. A procedure finally developed for the preparation of the 2-hydroxy-3-alkyl-5,6-diphenylpyrazines (XIX–XXII) involves neutralization of the α-aminoacid amide hydrohalides with silver oxide, followed by condensation with benzil in refluxing methanol, using a small amount of piperidine as the base.

Condensations of α-aminoacid amides with methylglyoxal were of particular interest because, although two isomeric hydroxypyrazines might be expected in each case, only one type of product has been observed,[2a] namely, that isomer in which the alkyl (or aryl)[6] group of the substituted glyoxal is found in the para-position to the hydroxyl. Thus alanine amide and methylglyoxal had been found to

(1) Ortho Pharmaceutical Corporation, Raritan, New Jersey.

(2) (a) R. G. Jones, THIS JOURNAL, **71**, 78 (1949); (b) R. G. Jones, U. S. Patent 2,520,088 (1950); (c) private communication from R. G. Jones.

(3) E. Koenigs and B. Mylo, *Ber.*, **41**, 4427 (1908).

(4) P. S. Yang and M. S. Rising, THIS JOURNAL, **53**, 3183 (1941).

(5) P. Bergell and H. V. Wulfing, *Z. physiol. Chem.*, **64**, 348 (1910).

(6) G. Dunn, *et al.*, *J. Chem. Soc.*, 2707 (1949).

TABLE I

α-AMINOACID AMIDE HYDROHALIDES

Compound	Starting material	Conditions[a]	Yield, % (recryst.)	Crystallization solvent	Highest m.p., °C.[b]
Glycine amide·HCl[c]	α-Chloroacetamide	3 days at −5°	85	EtOH–H_2O	203–205
Alanine amide·HCl[d]	Ethyl α-chloropropionate	30 hr. at 48°[h]	60	EtOH (abs.)	172–173
Alanine amide·HBr[e]	Ethyl α-bromopropionate	2 days at −5°	(85)[e]	Acet.–EtOH	(156–160)[f]
α-Aminobutyramide·HBr[c]	Ethyl α-bromobutyrate	10 days at −5°	90	EtOH (95%)	190–192
Norvaline amide·HBr	α-Bromovaleramide	3 days at 25°[g]	76	Acet.–MeOH	218–219
Valine amide·HBr	α-Bromoisovaleramide	1 day at 60°[h]	70	Acet.–MeOH	233–235

[a] The common reagent is 0°-saturated aqueous ammonia. [b] These melting points are considerably higher than those previously observed, and are strongly depressed by small amounts of water. [c] Previously prepared using 28% aqueous ammonia (ref. 4). [d] Previously prepared from alanine amide: A. P. N. Francimont and H. Friedmann, *Rec. trav. chim.*, **25**, 77 (1906). [e] Since this salt is very difficult to recrystallize, this figure represents its percentage in the crude product. [f] Once recrystallized material. [g] Reacted in stoppered, screened suction flask. [h] Reacted in an Aminco bomb.

yield only 2-hydroxy-3,5-dimethylpyrazine.[2a] It was startling to find that our first reaction of alanine amide hydrobromide with methylglyoxal and sodium hydroxide yielded 25% of 2-hydroxy-3,6-dimethylpyrazine (VI) and *none* of the 3,5-dimethyl isomer (VII). However, numerous attempts at reproducing this result were completely unsuccessful—only the 3,5-dimethyl isomer could thereafter be isolated, in yields averaging 65%. The only apparent difference in the reactions was that a very old sample of methylglyoxal was used for the first run (but in *none* of the other condensations described in this publication).

With glycine amide hydrochloride and alkali, methylglyoxal formed a separable mixture of 2-hydroxy-6-methylpyrazine (8%) and 2-hydroxy-5-methylpyrazine (27%). The latter isomer had the surprising property of decomposing rapidly above 110°. All the other hydroxypyrazines are stable even at 170–200°. Since the 5-methyl isomer is the more soluble, it was never obtained from the mixture in purity better than 90%. However, the structure of each isomer was proven by conversion, through the 2-chloro derivatives, to the 2-amino-5- and 6-methylpyrazines which have previously been prepared.[7]

The products of condensation of methylglyoxal and alkali with the hydrobromides of α-aminobutyramide, norvaline amide and valine amide were presumably the 2-hydroxy-3-alkyl-5-methylpyrazines, in view of their solubilities and low melting points (*cf.* III and VII). There was, however, evidence of their being contaminated with small amounts of 6-methyl isomers, for after each product had first been isolated through its silver salt (specific for hydroxypyrazines in these reaction mixtures), followed by distillation, none could be brought to a melting point range of less than 3° by repeated recrystallization. Complete removal of the presumed, since always less soluble, 6-methyl isomers was effected by treatment with one-fifth of a molecular equivalent of *o*-tolyldiazonium chloride–hydroxypyrazines with a free 5-position couple very readily.[8] After removal of the azo compounds, the remaining uncoupled hydroxypyrazines, X, XIII and XVI, were distilled and brought to sharp melting points by a *single* recrystallization.

It is to be noted that pyrazines XV and XVII are formed from valine amide hydrobromide in poorer yield than are their lower homologs from the hydrobromides of α-aminobutyramide and alanine amide.[9] Presumably a steric factor here commences to be of significance, lowering the reactivity of the amide, with the result that the very strong alkali destroys a large part of the reactants while promoting some condensation to the desired hydroxypyrazines.

All of the hydroxypyrazines listed in Table II have been converted to the 2-chloro derivatives, using either phosphorus oxychloride alone, or admixed with phosphorus pentachloride.[10] Some interesting consequences of substitution about the 2-hydroxypyrazine nucleus were observed using oxychloride alone. An alkyl group *in the 3-position only* in no case hinders replacement of hydroxyl by chlorine, and the reaction occurs rapidly in refluxing phosphorus oxychloride. When ethyl, propyl and isopropyl are at 3 and methyl is at 5, replacement is more difficult and requires heating in a sealed tube at 140°. The 2-hydroxy-3-ethyl (and propyl, isopropyl) - 5,6 - dimethyl (and diphenyl) - pyrazines must be heated with $POCl_3$ at 190–200° to form the chlorides in good yield. Thus alkyl and aryl groups in the remote 5- and 6-positions effectively hinder the replacement of the 2-hydroxyl by chlorine when an alkyl group is in the 3-position.

One of the favored current mechanisms of chlorination by displacement of hydroxyl[11] is represented by $ROH + POCl_3 \longrightarrow HCl + ROPOCl_2 \xrightarrow{Cl^-} RCl + (OPOCl_2)^-$. Our reactions are apparently of this type, for all of our hydroxypyrazines readily evolve hydrogen chloride with refluxing phosphorus oxychloride. However, those for which a higher reaction temperature is indicated in Table III give only very poor yields of the chloride at temperatures below those specified. The dichlorophosphites are easily formed, without appreciable hindrance from alkyl groups in any position. It must then be the second step, displacement of dichlorophosphite by

(7) J. Weijlard, M. Tishler and A. E. Erickson, THIS JOURNAL, **67**, 805 (1945).

(8) E. Principalle, *Gazz. chim. ital.*, **60**, 298 (1930).

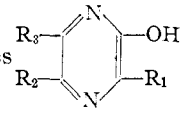
(9) Pyrazines XV and XVII are formed in yields of 60 and 50%, respectively, by the preferred technique of Jones, adding the 1,2-dicarbonyl compound to a solution of free valine amide and sodium carbonate in water at room temperature.

(10) The use of phosphorus pentachloride at temperatures above 100° leads to complex reaction products, possibly due to radical chlorination of alkyl groups. Even at 200°, phosphorus oxychloride yields only the desired 2-chloro compounds, with no rearrangements. This has been proven by reconversion in excellent yield of representative chlorides, through the butyl ethers, to the original hydroxypyrazines.

(11) E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 92f.

TABLE II

HYDROXYPYRAZINES

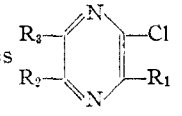


Compound	R_1	R_2	R_3	Yield, %	M.p., °C.	Crystallization solvent	Analyses, % N Calcd.	Found
I[a]	H	H	H	51	188–190	*i*-BuOH	...	...
II[b]	H	H	CH_3	8	250–251	H_2O	C, 54.62 H, 5.50	C, 54.88 H, 5.42
III	H	CH_3	H	27	126–128	MEK; acet.	C, 54.62 H, 5.50	C, 55.12 H, 5.69
IV[a]	CH_3	H	H	85	151–152	EtOAc	...	...
V[a]	H	CH_3	CH_3	30	201–202	*i*-BuOH	...	...
VI[c]	CH_3	H	CH_3	25	210–211	BuOAc	...	...
VII[a]	CH_3	CH_3	H	70	146–147	bz.; BuOAc	...	...
VIII[a]	CH_3	CH_3	CH_3	70	204–205	BuOAc	...	...
IX	C_2H_5	H	H	82	96–97	bz + pentane	22.56	22.42
X	C_2H_5	CH_3	H	32	99–100	Hexane	20.28	20.33
XI	C_2H_5	CH_3	CH_3	60	149–150	H_2O	18.42	18.26
XII	C_3H_7	H	H	80	79–80	Heptane	20.28	19.90
XIII	C_3H_7	CH_3	H	60	75–76	Hexane	18.42	18.51
XIV	C_3H_7	CH_3	CH_3	64	119–120	H_2O + MeOH	16.85	16.78
XV	*i*-C_3H_7	H	H	46	76–77	Hexane	20.28	20.20
XVI	*i*-C_3H_7	CH_3	H	30	91–92	Hexane	18.42	18.58
XVII	*i*-C_3H_7	CH_3	CH_3	23	144–145	H_2O + MeOH	16.85	16.91
XVIII[a]	H	C_6H_5	C_6H_5	69	243–244	BuOH	...	...
XIX	CH_3	C_6H_5	C_6H_5	47	213–214	Acet.	10.68	10.37
XX	C_2H_5	C_6H_5	C_6H_5	46	207–208	Acet.	10.13	10.17
XXI	C_3H_7	C_6H_5	C_6H_5	60	205–206	MeOH	9.65	9.43
XXII	*i*-C_3H_7	C_6H_5	C_6H_5	47	234–235	Acet.	9.65	9.65

[a] Previously prepared by Jones (ref. 2a, b). [b] D. M. Sharefkin, Doctoral Dissertation, Polytechnic Institute of Brooklyn, 1950. [c] Previously prepared by a different method, see Baxter, Newbold and Spring, *J. Chem. Soc.*, 373 (1947); obtained by us only once (see Discussion).

TABLE III

CHLOROPYRAZINES

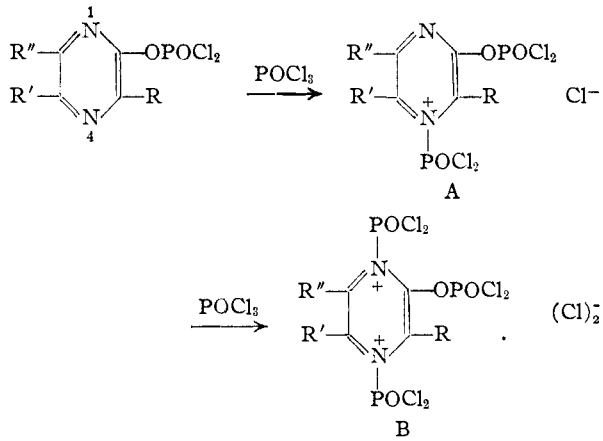


R_1	R_2	R_3	Conditions[a]	Yield, %	B.p. °C.	Mm.	M.p.,[b] °C.	*t*	n_D^t	Cl, % Calcd.	Found
H	H	H[c]	A: reflux 1 hr.	65	62–63	31	L	25	1.5342	...	...
H	H	CH_3	B: ½ hr. at 90°	69	84–85	40	50–51	..	....	27.61	27.61
H	CH_3	H	A: refl. ¼ hr.	30	94–96	60	L	..	....	...	...
CH_3	H	H	A: refl. 1 hr.	65	94–96	65	L	25	1.5302	27.61	27.77
H	CH_3	CH_3	B: 1.5 hr. at 90°	60	86–88	20	L	23	1.5290	24.89	24.90
CH_3	H	CH_3[d]	B: ¾ hr. at 90°	26	112–113	70	L	26	1.5243	24.89	24.94
CH_3	CH_3	H	A: refl. ¾ hr.	67	111–112	70	L	24	1.5230	24.89	24.68
CH_3	CH_3	CH_3	A: refl. 20 hr.	75	100–101	25	56–57	..	....	22.68	22.53
C_2H_5	H	H	A: refl. 3 hr.	75	110–111	72	L	22	1.5244	24.89	24.72
C_2H_5	CH_3	H	A: refl. 6 hr. 16 hr. at 142°	32 82	93–94	20	L	23	1.5186	22.68	22.62
C_2H_5	CH_3	CH_3	A: 5 hr. at 195°	50	106–107	20	L	25	1.5205	20.80	20.66
C_3H_7	H	H	A: refl. ¾ hr.	53	124–125	65	L	24	1.5144	22.68	22.57
C_3H_7	CH_3	H	A: 16 hr. at 142°	77	106–107	20	L	22	1.5130	20.80	20.82
C_3H_7	CH_3	CH_3	A: 27 hr. at 195°	36	121–122	20	L	24	1.5147	19.22	18.93
i-C_3H_7	H	H	A: refl. 2 hr.	60	112–113	65	L	25	1.5104	22.68	22.57
i-C_3H_7	CH_3	H	A: 15 hr. at 142°	76	95–96	18	L	25	1.5092	20.80	20.80
i-C_3H_7	CH_3	CH_3	A: 30 hr. at 190°	65	105–106	15	L	25	1.5120	19.22	19.25
H	C_6H_5	C_6H_5	A: refl. 15 hrs.	70	140–145	10^{-3}	126–127			13.31	13.51
CH_3	C_6H_5	C_6H_5	A: 6 hr. at 165°	84	140–150	10^{-3}	136–137			12.64	12.95
C_2H_5	C_6H_5	C_6H_5	A: 30 hr. at 195°	85	145–150	10^{-3}	77–78			12.06	12.40
C_3H_7	C_6H_5	C_6H_5	A: 30 hr. at 200°	97	155–160	10^{-3}	L			11.49	11.68
i-C_3H_7	C_6H_5	C_6H_5	A: 30 hr. at 200°	75	155–160	10^{-3}	96–97			11.49	11.27

[a] A means $POCl_3$ alone; B means $POCl_3$ + PCl_5. [b] L means liquid at 25°. [c] B. Klein and P. E. Spoerri, THIS JOURNAL, **73**, 2951 (1951). [d] R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, 1183 (1947).

chloride ion, which depends on substitutions at positions-5 and -6 when an alkyl is also at 3.

The considerable decrease in the ease of displacement from 2-hydroxytrimethylpyrazine to 2-hydroxy-3-propyl-5,6-dimethylpyrazine makes an explanation in terms of steric hindrance more reasonable than any based on electronic effects. If the reaction mechanism presented is substantially correct, the rate of the displacement on C_1 is proportional to the concentration of chloride ion, and consequently this must be dependent on the extent and character of nuclear substituents. Presumably the major source of chloride ion is the quaternary compounds which may be formed from phosphorus oxychloride and the basic ring nitrogens



When N_4 or N_1 and N_4 are flanked by alkyl or aryl groups the tendency to quaternize (and thus form chloride ion) is decreased in proportion to the size of the groups. It seems probable that the 2-dichlorophosphite participates to a lesser degree in the blocking of N_1.

All of our 2-chloropyrazines readily formed ethyl ethers in refluxing ethanolic sodium ethoxide, further demonstrating that hydrocarbon substituents in the 3-, 5- and 6-positions do not hinder displacement reactions at C_1 when this attacking anion is present in equivalent concentration.

Experimental

Glyoxal (30%) and methylglyoxal (33%) were the commercial products of Carbide and Carbon Corporation. All melting points were determined with a Fisher–Johns apparatus and are uncorrected. Concentrations were carried out from a water-bath at 50°, under water-pump vacuum, using a long spiral condenser to speed the process. Applicator sticks were used as ebulliators because, unlike capillaries, they do not cease functioning when solids form in a concentrate.

I. **α-Bromovaleramide and α-Bromoisovaleramide.**—α-Bromovaleric acid and α-bromoisovaleric acid were refluxed for seven hours with a 50% excess of thionyl chloride to form α-bromovaleryl chloride (b.p. 93–95° at 60 mm.) and α-bromoisovaleryl chloride (b.p. 84–85° at 53 mm.) in 75–80% yield. The amides were most simply prepared by adding dropwise one mole of the acid chloride to 1.2 l. of vigorously stirred 28% aqueous ammonia at −30°. After partial drying in air the crude amides were dissolved in a warm acetone–benzene mixture and the solutions were dried with magnesium sulfate. Concentration of these warm filtered solutions gave an 80% yield of the amides, which were converted without further purification to the amino-acid amide hydrohalides.

II. Aminoacid Amide Hydrohalides.—One liter of 28% aqueous ammonia was stirred at 0° while tank ammonia gas was rapidly bubbled under the surface to effect saturation. To this was added one mole of the starting material (Table I). When an ester was used, stirring and passage of ammonia through the cold mixture were continued until the oily phase had disappeared. After these mixtures had been kept at the specified temperatures for the indicated lengths of time in proper reaction vessels (Table I), the resulting clear solutions were concentrated in suction flasks, at about 40°, to damp solid residues. These were dried in air for one week with occasional breaking of lumps. When recrystallization was desired (and a mixed solvent is specified) the crude material was dissolved in a minimum of warm second solvent and precipitated by addition of a threefold volume of the first-named solvent. Recrystallized products were used only to determine yields in the hydroxypyrazine syntheses. The crude, air-dried amide hydrohalides are satisfactory for general preparative purposes, since the only significant impurity is 5–15% water. These salts are all stable, non-hygroscopic compounds which present no storage problem.

III. Condensations with 30% Aqueous Glyoxal, 33% Aqueous Methylglyoxal, and Biacetyl. A. General Procedure.—The technique of condensation was substantially that of Jones.[2] A solution of 0.1 mole of the aminoacid amide hydrohalide in 200 ml. of methanol (with an added 20 ml. of water when using the glycine amide and alanine amide salts) was stirred at −30 to −40° while 0.12 mole of the α-dicarbonyl compound was added rapidly. This was followed by dropwise addition, over 20 minutes, of 0.25 mole of 12.5 *N* aqueous sodium hydroxide. The stirred reaction mixture was maintained at −30° for one-half hour and at room temperature for three hours, and then it was stirred in an ice-bath and treated with 25 ml. of 12 *N* hydrochloric acid, followed by 20 g. of solid sodium bicarbonate. After filtration and addition of 20 ml. of water, the neutral filtrates were concentrated to remove methanol. (Hydroxyalkylpyrazines XI, XIV and XVII have a low solubility in water and were filtered off at this point.) The tacky concentrates were leached with 250 ml. of methanol and filtered to remove salts. The filtrates were again concentrated to a tacky mass which was shaken with 100 ml. of chloroform and just enough added water to make the dark aqueous phase supernatant. This aqueous phase was extracted 5–9 times more with 100-ml. portions of chloroform.[12] Drying of the combined extracts with magnesium sulfate, followed by concentration and air-drying, yielded the crude hydroxypyrazines II-X, XII, XIII and XVI, of which IV, V, VII, VIII, IX and XII could be purified simply by recrystallization from the solvents indicated in Table II. As a purification procedure, IV, VII, IX and XII may also be distilled in the range 150–180° at 10–20 mm. The other hydroxyalkylpyrazines were best isolated by the special procedures described below.

B. Hydroxypyrazine (I).—This compound has a low solubility in chloroform, and is accompanied by hygroscopic and tarry impurities in the crude reaction product, which make direct recrystallization very difficult. The methanolic product from a 0.2-mole run performed as described above was twice concentrated, leached with methanol, and filtered to remove sodium chloride. The last methanolic filtrate was again concentrated and the residue was stirred vigorously in 300 ml. of water with 50 g. of powdered silver acetate for one-half hour at 35°. The gray silver salt of hydroxypyrazine was filtered off and washed with water, and then the damp filter cake was stirred vigorously for 20 minutes with 200 ml. of 2 *N* hydrochloric acid. After filtration, the aqueous solution of hydroxypyrazine was neutralized with potassium bicarbonate and concentrated to dryness. The residue was dried under vacuum, ground in a mortar with 5 g. of Super-Cel, and this mixture was extracted with chloroform for 16 hours in a soxhlet unit, yielding 10.1 g. of hydroxypyrazine in two crops from the chloroform.

C. 2-Hydroxy-5-methylpyrazine (III) **and 2-Hydroxy-6-methylpyrazine** (II).—In a 0.2-mole run with methylglyoxal and glycine amide hydrochloride, the chloroform residue

(12) The volume of chloroform used may be kept to a minimum by using a cyclic extractor in which chloroform is distilled into a flask containing the aqueous concentrate. Extraction is accomplished by stirring vigorously for a few minutes, and the solvent is returned through a stopcock to the chloroform pot, from which the same chloroform is distilled into the extraction flask for the next cycle.

(General Procedure[13]) was dried under vacuum and then leached at 25° with two 100-ml. portions of acetone. Compound II was almost insoluble in acetone and was filtered off and recrystallized from a minimum of hot water.

Concentration of the acetone extracts gave brown, crude 2-hydroxy-5-methylpyrazine in variable yield. This was difficult to purify because it decomposes on warming in solution. It could be recrystallized from a small amount of acetone or methyl ethyl ketone, with considerable loss.

The structure of each isomer was demonstrated by conversion to the 2-amino compounds (see below).

D. 2-Hydroxy-3-isopropylpyrazine (XV).—The chloroform-extracted product from a 0.05-mole condensation of valine amide hydrobromide with glyoxal (General Procedure) could not be purified by distillation or recrystallization. It was stirred at 90° for 20 minutes with 7.0 g. of silver acetate in 100 ml. of water to form the insoluble silver salt of 2-hydroxy-3-isopropylpyrazine, from which the pyrazine was regenerated in aqueous solution as described for hydroxypyrazine. The final neutralized solution was concentrated and hydroxyisopropylpyrazine was extracted with chloroform and distilled (b.p. 112–115° at 0.05 mm.). A single recrystallization from hexane yielded 46% of the pure compound.

E. 2-Hydroxy-3-ethyl (and propyl, isopropyl)-5-methylpyrazine (X, XIII and XVI).—Condensations on a 0.2-mole scale were performed in the usual manner, using 33% methylglyoxal and the hydrobromides of α-aminobutyramide, norvaline amide and valine amide. The chloroform-extracted products were distilled at 0.1 mm. (b.p. 110–120°), but it was observed that repeated recrystallization from various solvents failed to yield products with a melting point range of less than three degrees. Purification with only 20% loss was achieved by adding all at once a cold solution of *o*-tolyldiazonium chloride (from 2.15 ml. of *o*-toluidine plus 2.17 ml. of 12 *N* hydrochloric acid in 25 ml. of water and 20.7 ml. of 1.0 *N* sodium nitrite) to a cold (5°) solution of 0.1 mole of crude distilled alkylhydroxypyrazine and 14 g. of sodium carbonate in 500 ml. of water. After the mixture had been held at 0° for 20 minutes, the orange tolylazohydroxyalkylpyrazines were filtered off and the filtrates were concentrated until the pyrazines oiled out. The latter were extracted with four 100-ml. portions of chloroform and were distilled at 0.1 mm. A single recrystallization from hexane yielded products of sharp melting point in the yields indicated in Table II. If crystallized from water, the pyrazines form hydrates which slowly effloresce above room temperature.

The tolylazo compounds melt with decomposition above 200° and have little diagnostic value.

F. 2-Hydroxy-3-ethyl-6-methylpyrazine.—From one condensation of α-aminobutyramide hydrobromide with methylglyoxal there was isolated 4% of a product which melted at 181–182°, was sparingly soluble in benzene, and formed an insoluble silver salt. Presumably it is the 6-methyl isomer of X.

Anal. Calcd. for $C_7H_{10}N_2O$: N, 20.28. Found: N, 20.42.

IV. Condensations with Benzil. A. 2-Hydroxy-5,6-diphenylpyrazine.—To a stirred and refluxing mixture of 22 g. (0.2 mole) of glycine amide hydrochloride and 42 g. (0.2 mole) of benzil in 500 ml. of methanol was added over one-half hour 32 ml. (0.4 mole) of 12.5 *N* sodium hydroxide. After one-half hour of refluxing, the mixture was treated with 25 ml. of 12 *N* hydrochloric acid, followed by 20 g. of solid potassium bicarbonate. The yellow solid was filtered off, washed well with water, dried in air, and recrystallized from butanol.

B. 2-Hydroxy-3-methyl (and ethyl, propyl, isopropyl)-5,6-diphenylpyrazine.—A mixture of 0.07 mole of the pulverized appropriate aminoacid amide hydrobromide, 15.4 g. (0.07 mole) of benzil and 25 g. (0.108 mole) of silver oxide in 400 ml. of methanol was stirred at 20° for one hour. Then 3 ml. of piperidine was added and the mixture was refluxed with vigorous stirring for two hours. After slight cooling of the pasty dark reaction mixture, 20 ml. of 12 *N* hydrochloric acid was added and refluxing was continued for 20 minutes more. The silver halides were filtered from the hot mixture and were washed well with two 100-ml. portions of methanol. The filtrate was concentrated to remove methanol, and the residual pasty mass was shaken with 500 ml. of 5% aqueous potassium carbonate. The insoluble yellow mixture of benzil and 2-hydroxy-3-alkyl-5,6-diphenylpyrazine was recrystallized from methanol or acetone to yield the pure pyrazines.

V. Pyrazyl Chloride. Procedure A.—To 15 ml. of phosphorus oxychloride containing one drop of sulfuric acid was added 0.04 mole of purified hydroxy compound, and the mixture was refluxed for the period of time indicated in Table III. After cooling to room temperature, the chlorination mixture was poured onto 200 g. of chopped ice layered with 100 ml. of ether. This was stirred to effect hydrolysis and then the acidic mixture was neutralized with 28% ammonia, while keeping it below 10°. The aqueous phase was finally made strongly alkaline with sodium hydroxide. If an emulsion formed at this point 5 g. of Super-Cel was added and the mixture was filtered. Another extraction with 100 ml. of ether was performed, and the combined ether solution was dried with magnesium sulfate. Concentration at atmospheric pressure and careful fractionation yielded the pure pyrazyl chlorides (except for 2-chloro-5-methylpyrazine, which has not been obtained analytically pure).

The ratio of reagents for the 5,6-diphenyl compounds XVIII–XXII was 0.02 mole in 15 ml. of phosphorus oxychloride containing one drop of sulfuric acid. The isolation of these chlorides was as described above, except that they were extracted from the hydrolysis mixture with chloroform and were recrystallized from methanol.

In those cases where a reaction temperature higher than 115° is indicated, the mixture of hydroxy compound and phosphorus oxychloride (plus one drop of sulfuric acid) was refluxed gently in an open pressure tube until evolution of hydrogen chloride had apparently ceased. Then the tube was sealed and heated in an oil-bath. Working up was as described above.

Procedure B.—A mixture of 0.1 mole of the hydroxypyrazine, 0.1 mole of phosphorus pentachloride and 40 ml. of phosphorus oxychloride was stirred at 90° for 30–45 minutes. The working up followed Procedure A.

VI. 2-Amino-5-methylpyrazine and 2-Amino-6-methylpyrazine.—A mixture of 0.3 g. of crude 2-chloro-5-methylpyrazine and 9 ml. of 28% aqueous ammonia was heated for 20 hours at 200° in a sealed tube.[14] The clear yellow solution was saturated with flake sodium hydroxide and extracted with ether. Recrystallization of the ether residue three times from benzene gave 2-amino-5-methylpyrazine of m.p. 117.5–118° (lit. 116–118°[7]).

The same procedure applied to the isomeric pyrazyl chloride gave 2-amino-6-methylpyrazine of m.p. 127–128° (lit. 124–125°[7]).

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(13) If a lustrous, water-insoluble material appears in the concentrates, it should be filtered off and retained, for it is compound II.

(14) A. E. Erickson and P. E. Spoerri, THIS JOURNAL, **68**, 400 (1946).