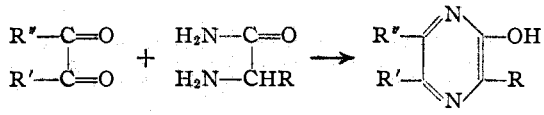
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Pyrazines and Related Compounds. I. A New Synthesis of Hydroxypyrazines

BY REUBEN G. JONES

A new general synthesis of hydroxypyrazines (I) has been devised which involves the condensation of 1,2-dicarbonyl compounds with α-amino acid amides



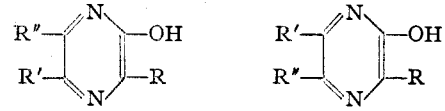
(I)

This appears to be a direct and convenient method for the preparation of hydroxypyrazines which, heretofore, have been obtained in poor yields and by laborious procedures.[1] It also appears to be one of the few satisfactory methods for preparing compounds containing the isolated pyrazine nucleus.[2]

In starting out to explore this reaction the first condensations were carried out with glyoxal and aminomalonamide. When these compounds were mixed in water solution and allowed to stand, or warmed, dark brown reaction products resulted from which no pure materials could be isolated. It was then found that in the presence of base, preferably one equivalent of sodium or potassium hydroxide, glyoxal and aminomalonamide reacted rapidly to form the sodium or potassium salt of 2-hydroxy-3-carboxamidopyrazine. Under these conditions aminomalonamide was also found to condense readily with other 1,2-diketones and ketoaldehydes to give high yields of substituted hydroxycarboxamidopyrazines. Subsequently it was found that diacetyl reacted with aminomalonamide in the absence of any added base to give a practically quantitative yield of 2-hydroxy-3-carboxamido-5,6-dimethylpyrazine. In one experiment in which a solid glyoxal polymer was heated in water with aminomalonamide, several drops of aqueous sodium hydroxide was sufficient to bring about condensation.

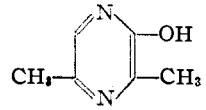
In order to determine the scope of the reaction glyoxal, methylglyoxal, diacetyl, phenylglyoxal and benzil were condensed with a number of typical α-amino acid amides. The results of these experiments are summarized in Table I. Usually, when the reagents were mixed at room temperature, reaction took place immediately with the evolution of heat and the formation of black intractable tars. The reactions were suitably controlled, however, to yield the desired pyrazine compounds by operating at temperatures of about -10 to $-20°$. For the most part the reactions were carried out in water or methanol solution and with the use of one equivalent of aqueous sodium hydroxide. However, other solvents and bases may be used. For example, methionine amide and diacetyl were allowed to react in dry chloroform solution using one equivalent of piperidine to give a 70% yield of 2-hydroxy-3-(β-methylmercaptoethyl)-5,6-dimethylpyrazine. Hydroxypyrazine, the parent member of the series, was obtained in good yield by the condensation of glycine amide with glyoxal.

The condensation of an α-amino acid amide with an unsymmetrical dicarbonyl compound might be expected to yield a mixture of the two possible isomeric hydroxypyrazines (II and III).



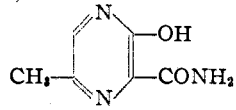
(II) (III)

However, in each case where methylglyoxal or phenylglyoxal has been condensed with an α-amino acid amide, only one compound has been isolated. The melting point of the product from the reaction of methylglyoxal with alanine amide differed from that of the known 2-hydroxy-3,6-dimethylpyrazine.[1b] Therefore, the compound must be 2-hydroxy-3,5-dimethylpyrazine (IV).



(IV)

Methylglyoxal and aminomalonamide underwent reaction to yield 2-hydroxy-5-methyl-3-pyrazinecarboxamide (V).



(V)

Proof of structure (V) was obtained by hydrolyzing to the acid and comparing the melting point with that of 2-hydroxy-6-methyl-3-pyrazinecarboxylic acid (VI). The latter was synthesized from the known 2-amino-6-methyl-3-pyrazinecarboxylic acid.[3] The melting points of the two acids differed widely.

(VI)

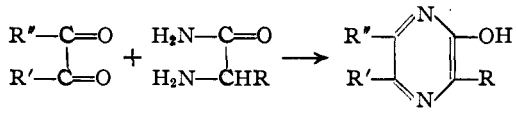
(1) (a) Tota and Elderfield, *J. Org. Chem.*, **7**, 313 (1942); (b) Baxter, Newbold and Spring, *J. Chem. Soc.*, 370 (1947); (c) Newbold and Spring, *ibid.*, 373 (1947); (d) Erickson and Spoerri, THIS JOURNAL, **68**, 400 (1946).

(2) Krems and Spoerri, *Chem. Revs.*, **40**, 279 (1947).

(3) Weijlard, Tishler and Erickson, THIS JOURNAL, **67**, 862 (1945).

TABLE I

2-HYDROXYPYRAZINES



R	R′	R″	Empirical formula	Yield, %	M. p., °C.	Analyses, nitrogen, % Calcd.	Found
$CONH_2$	H	H[a]	$C_5H_5N_3O_2$	90	265 (dec.)	30.21	29.80
$CONH_2$	CH_3	H	$C_6H_7N_3O_2$	59	243–244 (dec.)	27.46	27.60
$CONH_2$	CH_3	CH_3	$C_7H_9N_3O_2$	93	231–232 (dec.)	25.13	25.34
$CONH_2$	C_6H_5	H[b]	$C_{11}H_9N_3O_2$	75	213–216	19.53	19.80
$CONH_2$	C_6H_5	C_6H_5	$C_{17}H_{13}N_3O_2$	83	174–175	14.46	14.57
CH_3	H	H	$C_5H_6N_2O$	83.7	140–142	25.44	25.12
CH_3	CH_3	H	$C_6H_8N_2O$	42	145–146	22.57	22.43
CH_3	CH_3	CH_3[c]	$C_7H_{10}N_2O$	77.5	193–194	20.28	20.42
CH_3	C_6H_5	H[b]	$C_{11}H_{10}N_2O$	56.5	212–213	15.05	14.71
H	CH_3	CH_3[d]	$C_6H_8N_2O$	11.3	199–200	22.57	22.65
H	C_6H_5	C_6H_5	$C_{16}H_{12}N_2O$	97	225–227	11.29	11.22
$CH_2CH_2—S—CH_3$	H	H	$C_7H_{10}N_2OS$	97	96–97	16.46	16.94
$CH_2CH_2—S—CH_3$	CH_3	CH_3	$C_9H_{14}N_2OS$	88	128–129	14.13	13.81
C_6H_5	H	H	$C_{10}H_8N_2O$	88.5	172–173	16.27	16.04
C_6H_5	CH_3	CH_3	$C_{12}H_{12}N_2O$	45	222–226	13.99	13.91
p-$CH_2C_6H_4OH$	H	H	$C_{11}H_{10}N_2O_2$	76	212–213	13.86	13.81
p-$CH_2C_6H_4OH$	CH_3	H[b]	$C_{12}H_{12}N_2O_2$	47	202–203	12.96	12.78
p-$CH_2C_6H_4OH$	CH_3	CH_3	$C_{13}H_{14}N_2O_2$	77.5	236–237	12.17	11.88

[a] Previously prepared by a different method, see McDonald and Ellingson, THIS JOURNAL, 69, 1034 (1947). [b] Structure not proved. [c] Previously prepared by a different method, see ref. 1c. [d] Previously prepared by a different method, see ref. 1a.

The structures of the hydroxypyrazines obtained from the reaction of phenylglyoxal with alanine amide and with aminomalonamide are now under investigation. It is hoped that these and other studies currently under way will provide an insight into the mechanism of the reaction.

Experimental

α-Amino Acid Amides.—Aminomalonamide,[4] m. p. 187–188° (dec.), separated in 97% yield by allowing a solution of aminomalonic ester[5] in seven volumes of absolute alcohol saturated with ammonia to stand at room temperature seven days. The yellow to orange colored product was pure enough for the condensation with dicarbonyl compounds.

Anal. Calcd. for $C_3H_7N_3O_2$: N, 35.88. Found: N, 35.83.

Glycine amide and *dl*-alanine amide were prepared by treating the corresponding amino acid ethyl esters with ten volumes of saturated absolute alcoholic ammonia instead of liquid ammonia as described by Koenigs and Mylo.[6] The reaction with glycine ethyl ester was allowed to proceed for four days and then worked up[6] to give a 38% yield of amide. With a longer reaction time the yield was lower. In the preparation of alanine amide the reaction mixture stood for thirty days before it was worked up to give a 63% yield of amide and 17% of unchanged ester.

A solution of *l*-tyrosine ethyl ester in absolute alcoholic ammonia was allowed to stand for ten days. When the solution was evaporated to dryness, unchanged tyrosine ethyl ester was quantitatively recovered. Tyrosine amide was obtained in 90% yield from tyrosine ethyl ester and liquid ammonia as described by Koenigs and Mylo.[6]

For the preparation of *dl*-methionine amide a solution of 287 g. (1.62 moles) of *dl*-methionine ethyl ester, b. p. 132° (14 mm.), in two liters of absolute alcohol saturated at 0° with ammonia was allowed to stand in a closed flask for thirty days. The clear solution was evaporated in vacuum at about 40° until all alcohol appeared to have been removed. The residual semicrystalline mass was treated with one liter of anhydrous ether and cooled to 0°. The snow-white crystalline product was collected on a filter, washed with dry ether and dried in vacuum: The ether filtrate was distilled to yield 57 g. (20%) of unreacted methionine ethyl ester. The yield of amide was 175 g. (93% based on unrecovered ester); m. p. 48–49°. A sample for analysis was dissolved in chloroform, the solution filtered, and evaporated in vacuum.

Anal. Calcd. for $C_5H_{12}N_2OS$: C, 40.51; H, 8.17. Found: C, 40.66; H, 8.14.

α-Aminophenylacetamide was prepared in 88% yield by allowing a solution of ethyl α-aminophenylacetate in seven volumes of absolute alcoholic ammonia to stand at room temperature for two weeks. The product was isolated as described above for methionine amide; m. p. 128–129°.

Anal. Calcd. for $C_8H_{10}N_2O$: N, 18.66. Found: N, 18.32.

Samples of the amino acid amides were kept in the refrigerator for several months without decomposition. At room temperature, however, alanine amide and especially glycine amide lost ammonia and changed to the diketopiperazines.

Condensations with Aminomalonamide.—To 25 g. (0.166 mole) of 40% aqueous glyoxal solution diluted with 25 ml. of water was added 11.7 g. (0.10 mole) of finely powdered aminomalonamide. The mixture was cooled in an ice–salt-bath, and with stirring 10 ml. (0.125 mole) of 12.5 *N* sodium hydroxide solution was added dropwise while the temperature was maintained below 10°. The resulting solution was allowed to stand at room temperature, and after a few minutes it had set to a semisolid mass of finely-divided crystals (sodium salt of 2-hydroxy-3-carboxamidopyrazine). After several hours, 10 ml. of glacial acetic acid was added with stirring. The precipitate of 2-hydroxy-3-carboxamidopyrazine was collected on a filter,

(4) Piloty and Nerensheimer, *Ber.*, **39**, 514 (1906).
(5) Locquin and Cerchez, *Compt. rend.*, **186**, 1360 (1928).
(6) Koenigs and Mylo, *Ber.*, **41**, 4427 (1908).

washed with water, then with acetone and air dried. The yield of crude product was 12.5 g. (90% based on aminomalonamide). A sample for analysis was recrystallized from water and dried at 150° for several hours (see Table I).

The yields were lower when the reaction was conducted at higher temperatures or when smaller proportions of glyoxal were used. Potassium hydroxide or diethylamine was used in place of the sodium hydroxide with equally good results. Also, solid glyoxal polymer or glyoxal sodium bisulfite could be substituted for aqueous glyoxal solution.

Diacetyl was condensed with aminomalonamide in the manner described above for glyoxal. Later it was discovered that diacetyl reacted with powdered aminomalonamide in water suspension without any basic catalyst to give a practically quantitative yield of 2-hydroxy-3-carboxamido-5,6-dimethylpyrazine. This compound was very sparingly soluble in water, acetic acid or alcohol, but readily soluble in pyridine.

The condensation of aminomalonamide with methylglyoxal proceeded best when an excess of the amide was used.[7] A solution of 36 g. (0.50 mole) of freshly prepared methylglyoxal[8] (b. p. 60–64° at 50 mm.) in 50 ml. of water was cooled to −20° and 60 g. (0.51 mole) of finely powdered aminomalonamide was added. With stirring, 40 ml. (0.50 mole) of 12.5 *N* sodium hydroxide solution was added dropwise while the temperature was kept below 0°. The mixture was then allowed to stand at room temperature for eighteen hours before it was acidified with 50 ml. of 12 *N* hydrochloric acid. After standing for an additional two days, the mixture was chilled, and the 2-hydroxy-3-carboxamido-5-methylpyrazine was collected on a filter, washed with a little water and air dried. The yield was 45 g. (59%). For analysis the compound was recrystallized from water in which it appeared to be appreciably soluble.

A mixture of 21 g. (0.10 mole) of benzil and 11.7 g. (0.10 mole) of powdered aminomalonamide in 350 ml. of 50% aqueous alcohol was heated to about 70° and 10 ml. (0.125 mole) of 12.5 *N* sodium hydroxide solution was added with stirring. A clear brown solution formed and then suddenly it became almost solid with crystalline precipitate. The cooled mixture was filtered, and the solid was washed by suspension in 300 ml. of acetone. This sodium salt was very sparingly soluble in all of the common solvents, including boiling water. It was suspended in 200 ml. of acetone and treated with 20 ml. of concentrated hydrochloric acid. The resulting almost-clear solution was diluted with 500 ml. of water to precipitate 2-hydroxy-3-carboxamido-5,6-diphenylpyrazine as an oil which soon crystallized. The compound was readily recrystallized from acetone–petroleum ether, acetone–water or alcohol–water.

Condensations with Glycine Amide, Alanine Amide, Methionine Amide and α-Aminophenylacetamide.—The following typical experiment will illustrate the method used for the preparation of most of the compounds in Table I.

A solution of 8.8 g. (0.10 mole) of alanine amide in 50 ml. of methanol was cooled to −30° and to it was added a solution of 24 g. (0.10 mole) of commercial 30% methylglyoxal in 25 ml. of methanol also precooled to −30°. With stirring, 10 ml. (0.125 mole) of 12.5 *N* aqueous sodium hydroxide solution was added dropwise while the temperature was maintained below −10°. The mixture was allowed to stand in the refrigerator at −5° for two hours, then at room temperature for several hours. To the mixture was added 10 ml. of 12 *N* hydrochloric acid followed by 5 g. of solid sodium bicarbonate to neutralize any excess acid, and the whole was evaporated to dryness in vacuum on the steam-bath. The residue was extracted with three 100-ml. portions of boiling chloroform. Evaporation in vacuum of the chloroform left 8.5 g. of gummy solid. This was recrystallized successively from 25-ml., 15-ml. and 10-ml. portions of ethyl acetate to yield 3.5 g. of white crystals, m. p. 144–146°. The ethyl acetate mother liquors were evaporated and cooled, and after several recrystallizations there was eventually obtained an additional 1.7 g. of pure product making the total yield 5.2 g. (42%). A small sample recrystallized from acetone melted at 145–146° and a sample sublimed in vacuum also melted at 145–146°.

Anal. Calcd. for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.33; H, 6.57; N, 22.42.

The melting point of the known 2-hydroxy-3,6-dimethylpyrazine is reported[1b] to be 210–211°. This difference in melting point in conjunction with the analytical data proves that the present compound must be 2-hydroxy-3,5-dimethylpyrazine.

The condensation of glycine amide with benzil was carried out in *hot* methanol solution.

Hydroxypyrazine.—To a solution of 12 ml. of 12.5 *N* sodium hydroxide in 50 ml. of methanol cooled to −20° was added 7.4 g. (0.10 mole) of glycine amide in 20 ml. of methanol. Then with stirring 30 g. (0.15 mole) of 30% aqueous glyoxal was added slowly while the temperature was maintained below −10°. After the solution had stood at room temperature for two hours, 15 ml. of acetic acid was added, and the mixture was evaporated to dryness under vacuum on the steam-bath. The residue was exhaustively extracted with acetone, and after evaporation of the acetone extract there was obtained 8.1 g. (84% yield) of crude hydroxypyrazine, m. p., 140–150°. This product was difficult to purify, but, eventually, after three recrystallizations from absolute alcohol using liberal quantities of activated carbon there was obtained 4.6 g. (48% yield) of pure hydroxypyrazine, m. p. 187–189°, and mixed m. p. with an authentic sample,[3] 187–189°.

Condensation with Tyrosine Amide.—The following example is typical. To a suspension of 8.5 g. (0.05 mole) of tyrosine amide in 50 ml. of methanol at −20° was added 12 g. (0.06 mole) of 30% aqueous glyoxal followed by 9 ml. (0.11 mole) of 12.5 *N* sodium hydroxide solution. The mixture was removed from the cooling-bath and allowed to stand overnight at room temperature. With stirring, 10 ml. of 12 *N* hydrochloric acid and 10 ml. of water were added and the solution was chilled to 0°. The white crystalline precipitate of 2-hydroxy-3-(*p*-hydroxybenzyl)-pyrazine (Table I) was collected on a filter, washed with water and air dried. It was recrystallized from methanol–ethyl acetate or methanol–water.

2-Hydroxy-5,6-dimethyl-3-pyrazinoic Acid.—A suspension of 11.5 g. (0.069 mole) of 2-hydroxy-3-carboxamido-5,6-dimethylpyrazine in 75 ml. of 3 *N* sodium hydroxide solution was heated on the steam-bath for several hours. Ammonia was evolved, and a clear brown solution formed. The solution was acidified with excess (25 ml.) concentrated hydrochloric acid and chilled to 0°. The crystalline precipitate was collected and air dried. It weighed 9.0 g. (79% yield). A sample was recrystallized from water; m. p. 172–174° (dec.).

Anal. Calcd. for $C_7H_8N_2O_3$: N. 16.66. Found: N, 16.86.

In the same way 2-hydroxy-3-carboxamidopyrazine was hydrolyzed to 2-hydroxy-3-pyrazinoic acid in 84% yield; m. p. 218–220°. The mixed melting point with a specimen prepared by the method of Weijlard, Tishler and Erickson[3] was also 218–220°.

2-Hydroxy-5-methyl-3-pyrazinoic Acid.—A suspension of 20 g. (0.13 mole) of crude 2-hydroxy-3-carboxamido-5-methylpyrazine in 75 ml. of 5 *N* sodium hydroxide solution was heated on the steam-bath for sixteen hours. The resulting solution was acidified and chilled to yield 6.0 g. (30%) of 2-hydroxy-5-methyl-3-pyrazinoic acid. A sample was recrystallized from water, in which it was appreciably soluble.

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.75; H, 3.92; N, 18.18. Found: C, 46.79; H, 3.99; N, 18.52.

The recrystallized compound melted with decomposition at 155–157°. Authentic 2-hydroxy-6-methyl-3-pyrazin-

(7) Very small yields of the desired 2-hydroxy-3-carboxamide-5-methylpyrazine were obtained when methylglyoxal was used in excess. With commercial 30% methylglyoxal (obtained from Carbide and Carbon Chemicals Corporation) the best yields of pyrazine compound were only 25 to 30%.

(8) Riley, Morley and Friend, *J. Chem. Soc.*, 1875 (1932).

oic acid (see below) melted and decomposed at 182–183°, and a mixture of the two melted and decomposed over the range 150–155°.

2-Hydroxy-6-methyl-3-pyrazinoic Acid.—A solution of 3.5 g. (0.023 mole) of 2-amino-6-methyl-3-pyrazinoic acid[3] in 100 ml. of 1.00 *N* hydrochloric acid was cooled to 10° and with stirring 4.5 g. (0.065 mole) of solid sodium nitrite was added in small portions. The solution stood at room temperature for one hour, and then it was heated at 70° for one-half hour. With stirring 3.0 g. (0.035 mole) of sodium bicarbonate was added, and the solution was evaporated to dryness in vacuum. The residue was extracted with 150 ml. of hot absolute alcohol, the alcohol solution was evaporated to 25 ml., and 200 ml. of dry ether was added. The resulting brown hygroscopic precipitate was recrystallized from 20 ml. of water to give 1.2 g. of tan powder. This was recrystallized from 4 ml. of water using carbon to decolorize, and 0.8 g. of light tan crystals were obtained; m. p. 183–184° (dec.).

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.75; H, 3.92; N, 18.18. Found: C, 47.04; H, 4.23; N, 18.65.

Summary

A new pyrazine synthesis has been evolved in which 1,2-dicarbonyl compounds are caused to condense with α-amino acid amides to yield substituted hydroxypyrazines.

INDIANAPOLIS, INDIANA RECEIVED JULY 26, 1948

[CONTRIBUTION NO. 59 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Catalytic Hydrogenation of the Benzene Nucleus. IV. The Hydrogenation of Methyl-substituted Benzoic Acids

BY HILTON A. SMITH AND JAMES A. STANFIELD

Introduction

In an earlier paper[1] it was demonstrated that for the polymethylbenzenes the rate of catalytic hydrogenation of the benzene nucleus was governed not only by the number of substituents but also by their position. Those compounds which were symmetrically substituted reacted much faster than did others with the same number of substituents. Evidence that this was a question of symmetrical substitution and not of symmetry in the molecule itself was found in the fact that *p*-cymene hydrogenated more rapidly than did isopropylbenzene.

In order to study this matter further, a number of compounds have now been prepared which have both methyl groups and carboxyl groups attached to a benzene ring. With such compounds it should be possible to confirm the evidence that symmetrical substitution rather than molecular symmetry is the important factor.

Experimental

Benzoic, ortho-, meta- and para-toluic acids were all obtained from the Eastman Kodak Company and were Eastman best grade materials.

2,3-Dimethylbenzoic acid was prepared from 3-nitro-1,2-dimethylbenzene. The nitro group was reduced with iron and hydrochloric acid[2] to form the amino compound, which was then converted to 3-iodo-1,2-dimethylbenzene.[3] This was then converted to 2,3-dimethylbenzoic acid using an adaptation of the Grignard reaction.[4]

2,4-Dimethylbenzoic acid was prepared by diazotization of the corresponding amino compound followed by treatment of the diazonium salt with potassium iodide.[5] The iodo compound was converted to the acid by treatment of the corresponding Grignard reagent with carbon dioxide.

2,5-Dimethylbenzoic acid was prepared by bromination of *p*-xylene[6] which was then converted to the acid by carbonation of the corresponding Grignard reagent.

2,6-Dimethylbenzoic acid was prepared from 2-amino-1,3-dimethylbenzene using the same general procedure as that employed in the preparation of the 2,3-dimethylbenzoic acid.

3,4-Dimethylbenzoic acid was prepared from *o*-xylene in a manner analogous to that used for the 2,5-dimethylbenzoic acid.

3,5-Dimethylbenzoic acid was prepared from mesitylene by oxidation with dilute nitric acid.[7]

2,3,4-Trimethylbenzoic acid was prepared; 3-iodo-1,2-dimethylbenzene was treated with magnesium and dimethyl sulfate to form hemimellitene in the same manner as that used in the preparation of isodurene.[8] The hydrocarbon was converted to 2,3,4-trimethylbenzaldehyde through the action of zinc cyanide in the presence of hydrogen chloride gas and aluminum chloride.[9] The aldehyde was then oxidized to the desired acid by means of a 20% permanganate solution.

2,4,5-Trimethylbenzoic acid was prepared by bromination of pseudocumene[10] followed by a Grignard reaction similar to that used in the preparation of 2,3-dimethylbenzoic acid.

2,4,6-Trimethylbenzoic acid was prepared from bromomesitylene by means of a Grignard synthesis.

2,3,6-Trimethylbenzoic acid was prepared from pseudocumene.[10] The pseudocumene was first sulfonated to form pseudocumenesulfonic acid-5[11] which was then brominated. This bromination to form a mixture of 5-bromopseudocumene and 3-bromopseudocumenesulfonic acid-5 has been previously carried out by Smith and Kiess[12] but the procedure was sufficiently modified to warrant description: 136 grams of pseudocumenesulfonic acid-5 ($C_6H_2(CH_3)_3SO_3H \cdot 1.5H_2O$) was suspended in 300 ml. of 20% hydrochloric acid solution; 122 g. of bromine suspended in 56

(1) Smith and Pennekamp, THIS JOURNAL, **67**, 279 (1945).

(2) Mahood and Shaffner, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 160.

(3) Lucas and Kennedy, *ibid.*, p. 351.

(4) Fuson and Kelton, *ibid.*, **63**, 1500 (1941).

(5) Smith and Lund, *ibid.*, **52**, 4144 (1930).

(6) Smith, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 95.

(7) Fittig, *Ann.*, **141**, 144 (1867); Snyder, Adams and McIntosh, THIS JOURNAL, **63**, 3280 (1941).

(8) *Cf.* Smith, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 360.

(9) *Cf.* Fuson, Horning, Rowland and Ward, "Organic Syntheses," **23**, 57 (1947).

(10) This was prepared by Mr. Comer Shacklett of this Laboratory by chloromethylation of mixed xylenes followed by a Grignard reaction.

(11) Smith and Cass, THIS JOURNAL, **54**, 1603 (1932).

(12) Smith and Kiess, *ibid.*, **61**, 284 (1939).