marin animals were analyzed. The amines which had not been fully investigated. The quantitative data obtained here are shown in Table III.

Table III. Amines produced by Putrefaction of Marine Animals

Amines \ Kinds	Mackerel	Sea bream	Octopus	Crab	Short-necked clam	Shark	Carp	
hr	24	24	24	24	24	24	18	24
Histamine	9.26		.15	1.41			.94	3.91
Tyramine	1.77	.23	.10	2.58	.47	.31	.04	.27
Putrescine	1.08	.41	4.43	13.70	1.06	.30	.31	.81
Cadaverine	5.72	1.22	2.27	3.27	2.15	.85	2.56	4.59

μmoles/meat 1 g

In this method effluent speed of the developer is 30 ml/hr, but if effluent speed is increased, analytical times should be shortened. Developer were effluent on three times of stepped change, but effluent on graded change or connection of stepped and graded change, it will be successful furthermore.

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The Reimer-Tiemann Reaction of *m*-Halophenols. III.[1] Formation of Dialdehydes[2]

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The preceding paper[1] reported that in addition to the three isomers, 2-bromo-4-hydroxybenzaldehyde and 4- and 6-bromosalicylaldehydes, a new dialdehyde was isolated in the Reimer–Tiemann reaction with *m*-bromophenol.

There have been reports about the isolation of dialdehydes in the Reimer–Tiemann reaction with resorcinol,[4] with resorcinol methyl ether,[5] with thymol,[6] and with orcin.[7] A dialdehyde obtained from resorcinol was confirmed to be 2,4-dihydroxyisophthalaldehyde on the basis of chemical evidence[8] and the structure was supported by its nuclear magnetic resonance (NMR) spectrum.[9] In the case of orcin, two isomeric dialdehydes isolated were

1) Part II: S. Kobayashi, M. Azekawa, and H. Morita, *Chem. Pharm. Bull.* (Tokyo), **17**, 89 (1969).
2) This forms Part IV of "Studies on the Syntheses of Benzoheterocyclic Compounds," by S. Kobayashi.
3) Location: *No.* 78, *Sho-machi-1-chome, Tokushima.*
4) F. Tiemann and L. Lewy, *Ber.*, **10**, 2210 (1877).
5) F. Tiemann and A. Parrisius, *Ber.*, **13**, 2354 (1880).
6) H. Kobek, *Ber.*, **16**, 2096 (1883).
7) F. Tiemann and E. Helkenberg, *Ber.*, **12**, 999 (1879).
8) W. Baker, A.W.W. Kirby, and L.V. Montgomery, *J. Chem. Soc.*, **1932**, 2876.
9) K.K. Ramaswamy and D.N. Sen, *Indian J. Chem.*, **4**, 142 (1966).

assinged to be 2,6-dihydroxy-4-methyl- and 4,6-dihydroxy-2-methyl-isophthalaldehydes from their NMR spectra.[10]

This paper reports that the structure of the new dialdehyde mentioned above has been established as 2-bromo-4-hydroxyisophthalaldehyde (I). Furthermore, the formation of I in the reaction prompts us to re-examine the products of the Reimer–Tiemann reaction[11] with *m*-iodophenol. On re-examination, two hitherto undescribed dialdehydes, 4-hydroxy-2-iodo-, (II), and 2-hydroxy-4-iodo-isophthalaldehydes (III) have been isolated along with the three monoaldehydes[11] previously obtained. Their structures were confirmed by spectral examination and chemical evidence.

The NMR spectrum of dialdehyde (I) showed two doublets at $\delta=7.05$ ($J=9.0$ cps) and 8.07 ($J=9.0$ cps) due to protons with an AB pattern for 1,2,3,4-substituted benzene. The latter doublet is ascribed to the aromatic hydrogen in the *ortho* position to the formyl group. The former one seemed to be due to the aromatic proton *ortho* to the phenolic hydroxyl group, rather than to the bromo substituent. This seems to agree with the interpretation that both the formyl proton peaks[1] of I were shifted downfield by the proximity effect[12] of the bromo substituent *ortho* to the formyl groups, which accordingly were in the *meta* position to each other. Therefore, of the three possible structures for the dialdehyde derived from *m*-bromophenol, 2-bromo-4-hydroxy-, 4-bromo-2-hydroxy-, and 4-bromo-6-hydroxy-isophthalaldehydes, the first was suggested for the compound (I).

To confirm this, dimethyl methoxybiphenyldicarboxylate (VI) synthesized from compound (I) was compared with dimethyl 3-methoxy-2,4-biphenyldicarboxylate (XI). The latter could be obtained from 3-hydroxy-2,4-biphenyldicarboxylic acid which was easily prepared by the method of Prelog, *et al.*[13] Oxidation of dialdehyde (I) with silver oxide and methylation of the resulting acid (IV) with diazomethane gave the O-methylated ester (V). A product (VI), $C_{17}H_{16}O_5$, bp 104—107° (0.12 mmHg), which was obtained by Ullmann condensation of the ester (V) with iodobenzene, was found to differ from a sample of XI. However, in the Ullmann condensation three by-products, biphenyl (VII), compounds VIII ($C_{22}H_{22}O_{10}$, mp 211—212°) and IX (mp 91—93°), were isolated besides the ester (VI). The quantity of the compound (IX) was insufficient for elemental analysis, but its structure was suggested to be dimethyl 4-methoxyisophthalate by a mixed melting point determination with an authentic sample.[14] It seems obvious that in the Ullmann condensation the isophthalate (IX) was derived by reductive dehalogenation of dimethyl bromoisophthalate in which the position of the bromo substituent is ambiguous. These results show that the compound (V) might be dimethyl 2- or 6-bromo-4-methoxyisophthalate, of which the former structure was assigned to the compound (V) by identification of V with an authentic sample of dimethyl 2-bromo-4-methoxyisophthalate prepared from 2-bromo-4-hydroxy-*m*-xylene (XII).[15] The conclusion adds a proof to the assignment of the precursor (I) deduced from NMR data. Consequently, it is clear that the compounds (VI) and (VIII) are dimethyl 3-methoxy-2,6-biphenyldicarboxylate and tetramethyl 3,3′-dimethoxy-2,6,2′,6′-biphenyltetracarboxylate, respectively, from their elemental analyses and from the fact that the structure of the starting material was confirmed as V.

On the basis of a) elemental analyses of compound (II) and its dioxime, b) its NMR spectrum, in which the formyl and aromatic proton peaks (see Experimental) were inter-

10) C. Grundmann and R. Richter, *Chem. Ber.*, **99**, 2705 (1966).
11) S. Kobayashi, S. Tagawa, and S. Nakajima, *Chem. Pharm. Bull.* (Tokyo), **11**, 123 (1963).
12) C. Postmus, Jr., I.A. Kaye, C.A. Craig, and R.S. Matthews, *J. Org. Chem.*, **29**, 2693 (1964).
13) V. Prelog, O. Metzler, and O. Jeger, *Helv. Chem. Acta.*, **30**, 675 (1947).
14) *a*) O.E. Fanchar, *J. Am. Chem. Soc.*, **63**, 1277 (1941); *b*) S.E. Hunt, J.I. Jones, and A.S. Lindsey, *Chem. Ind.* (London), **1955**, 417; *c*) M. Tomita and S. Uyeo, *Nippon Kagaku Zasshi*, **64**, 70 (1943); F. Wessely and E. Shinzel, *Monatsh*, **84**, 969 (1953).
15) E. Norting, A. Brawn, and G. Thesmar, *Ber.*, **34**, 2242 (1901).

preted in the same way as for I, and c) the similarity between its IR spectrum and that of I, compound (II) was concluded to be an iodo compound corresponding to I. This was confirmed by the conversion of compound (II) to the biphenyl derivative (VIII); oxidation of compound (II) with silver oxide and methylation of the resulting acid (XV) with diazomethane gave O-methylated dimethyl ester (XVI) which underwent Ullmann condensation in the presence of copper bronze. The condensation product was found to be identical in all respects with an authentic sample of VIII. This conclusion was supported by the facts that dehalogenation of XV with Raney nickel gave 4-hydroxyisophthalic acid and that its methylation with diazomethane afforded the corresponding O-methylated ester (IX).

Oxidation of the dialdehyde (III) and dehalogenation of the resulting acid (XVII) with Raney nickel afforded crystals which were identical with an authentic sample of 2-hydroxyisophthalic acid obtained from 3-methylsalicylic acid by the method of Graebe, *et al.*[16] It follows from this result that the second dialdehyde (III) obtained in the Reimer–Tiemann reaction with *m*-iodophenol must be 2-hydroxy-4-iodoisophthalaldehyde.

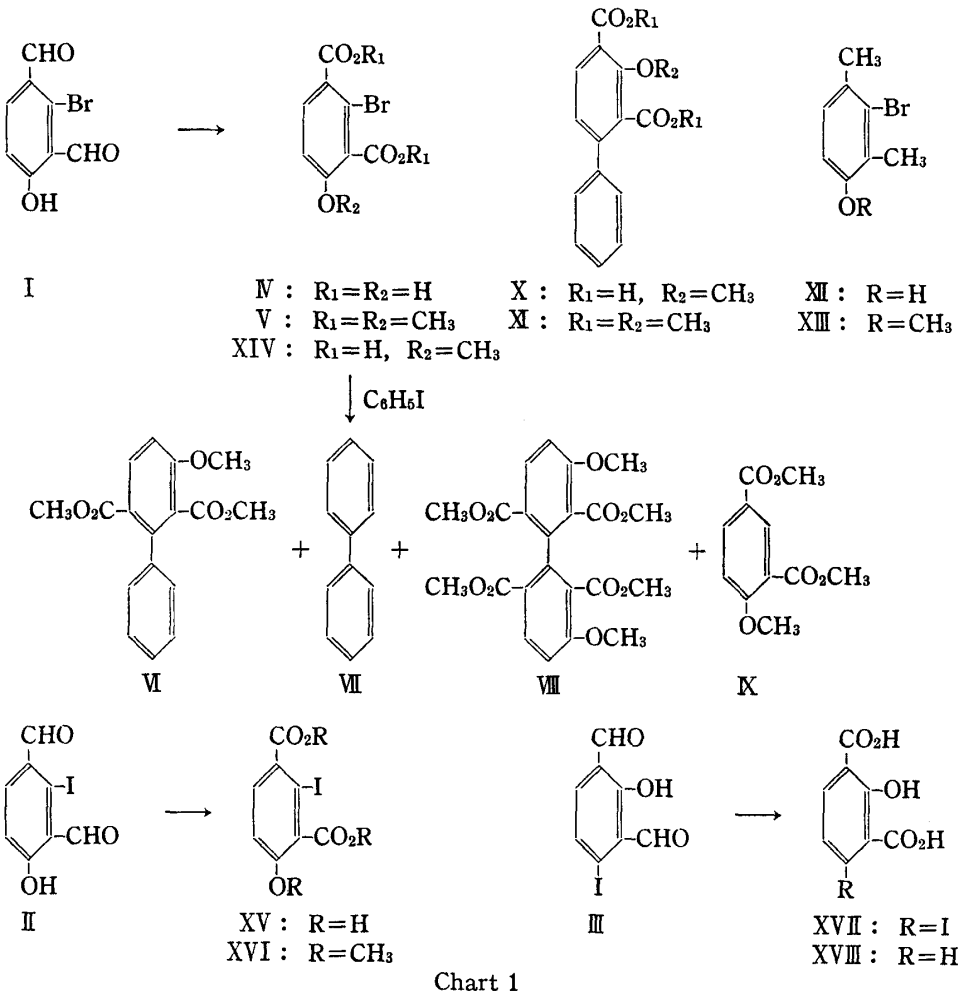

Chart 1

Experimental[17]

2-Bromo-4-hydroxyisophthalaldehyde (I)——This compound was described as IV in the preceding paper.[1]

16) C. Graebe and H. Kraft, *Ber.*, **39**, 794 (1906).

17) All melting points are uncorrected. IR spectra were taken on Hitachi EPI-G2 in KBr pellets and Hitachi EPI-2 in CCl_4 and $CHCl_3$ solution, and NMR spectra on Varian A-60 using TMS as an internal standard.

2-Bromo-4-hydroxyisophthalic Acid (IV)——To a mixture of Ag_2O (from 320 mg of $AgNO_3$ and excess 10% NaOH) and 10% NaOH (3.5 ml) was added I (86 mg) at 55° and the temperature was raised to 84° for 30 min. The mixture was filtered, the filtrate was acidified with SO_2, and the acid solution was extracted with ether. The extracts were evaporated to yield crude crysatls (40 mg), which were recrystallized from ether as white cubes, mp 194—196.5°. *Anal.* Calcd. for $C_8H_5O_5Br$: C, 36.81; H, 1.93. Found: C, 36.84; H, 1.94.

Dimethyl 2-Bromo-4-methoxyisophthalate (V)——(i) From IV: A mixture of diazomethane (from 8 g of nitrosomethylurea and 27 ml of 50% KOH) in dry ether and IV (60 mg) was allowed to stand overnight at room temperature. Evaporation of the ether and recrystallization of the resulting residue from ether–petr. ether gave white cubes (31 mg), mp 88—88.5°. *Anal.* Calcd. for $C_{11}H_{11}O_5Br$: C, 43.58; H, 3.66. Found: C, 44.33; H, 3.84.

(ii) From 2-Bromo-4-methoxyisophthalic Acid (XIV): The crude compound (V), prepared from XIV (48 mg) and diazomethane (from 10 g of nitrosomethylurea and 30 ml of 50% KOH), was recrystallized from ether–petr. ether as white cubes (14 mg), mp 88—89°. Found: C, 43.91; H, 3.86. IR cm^{-1} (KBr): $\gamma_{C=O}$ 1745, 1720. The samples of ester (V) obtained by methods (i) and (ii) were identical.

Ullmann Condensation of V with Iodobenzene——The ester (V) (200 mg), iodobenzene (500 mg), and copper bronze (640 mg) were heated in a sealed tube at 202—203° for 3 hr and then at 207—208° for 1 hr. The reaction mixture was taken up in $CHCl_3$, the solution was evaporated, and to the residue ether was added to give a brown precipitate.

Tetramethyl 3,3′-Dimethoxy-2,6,2′,6′-biphenyltetracarboxylate (VIII): The brown precipitate was chromatographed in $CHCl_3$ on alumina and then recrystallized from MeOH to give white prisms (11 mg), mp 211—212°. *Anal.* Calcd. for $C_{22}H_{22}O_{10}$: C, 59.19; H, 4.97. Found: C, 58.92; H, 5.00. IR cm^{-1} (KBr): $\gamma_{C=O}$ 1740, 1720.

Biphenyl (VII): The ether solution which was separated from the brown precipitate was evaporated and chromatographed in petr. ether on sillica gel. The first petr. ether eluate gave 95 mg of VII, mp 67—68° (from petr. ether). *Anal.* Calcd. for $C_{12}H_{10}$: C, 93.46; H, 6.54. Found: C, 93.60; H, 6.51.

Dimethyl 3-Methoxy-2,6-biphenyldicarboxylate (VI): The second petr. ether eluate afforded a colorless oil (118 mg), which was vacuum distilled to give VI as a viscous oil, bp 104—107° (0.12 mmHg). *Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.84; H, 5.07. IR cm^{-1} ($CHCl_3$): $\gamma_{C=O}$ 1728. Mass Spectrum *m/e*: 300 (M^+).

Dimethyl 4-Methoxyisophthalate (IX): When VI was vacuum distilled, the first fraction, bp up to 42° (0.12 mmHg), gave 10 mg of white crystals, mp 91—93°. The product was identical with an authentic sample of dimethyl 4-methoxyisophthalate, which was prepared by methylation of 4-hydroxyisophthalic acid with diazomethane, by mixed melting point test and IR comparison.

3-Methoxy-2,4-biphenyldicarboxylic Acid (X)——3-Hydroxy-2,4-biphenyldicarboxylic acid (0.5 g), which was prepared by the method of Prelog, *et al.*,[13] was treated with Me_2SO_4 (25.2 g) and 6.7% NaOH at 70° for 17 hr in the usual way to give white prisms of X, mp 192—193°, after recrystallization from etherbenzene. *Anal.* Calcd. for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.46; H, 4.56.

Dimethyl 3-Methoxy-2,4-biphenyldicarboxylate (XI)——A mixture of diazomethane (from 1.5 g of nitrosomethylurea) in dry ether and X (50 mg) was allowed to stand overnight at room temperature. Evaporation of the ether and recrystallization of the residue from ether–petr. ether afforded white cubes of a new compound, XI, mp 65—67°. *Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 68.13; H, 5.51. IR cm^{-1} ($CHCl_3$): $\gamma_{C=O}$ 1724. The IR curve was different in the finger print region from that of VI.

2-Bromo-4-methoxy-*m*-xylene (XIII)——A mixture of diazomethane (from 10 g of nitrosomethylurea and 30 ml of 50% KOH) and an ethereal solution of 2-bromo-4-hydroxy-*m*-xylene (XII) (1.29 g), which was obtained from 2-bromo-4-nitro-*m*-xylene by the procedure of Norting, *et al.*,[15] was allowed to stand at room temperature for 48 hr. After removal of the solvent, the residue was dissolved in ether, which was washed with 2% NaOH and water, dried over Na_2SO_4, and evaporated to give an oil. The oil was vacuum distilled to afford XIII (0.65 g) as a colorless oil, bp 84—88° (1.5 mmHg). *Anal.* Calcd. for $C_9H_{11}OBr$: C, 50.25; H, 5.16. Found: C, 50.54; H, 5.32. Unchanged XII (0.32 g) was recovered from the alkaline washing.

2-Bromo-4-methoxyisophthalic Acid (XIV)——To a suspension of the xylene (XIII) (394 mg) in water (25 ml) was added powdered $KMnO_4$ (1.06 g) in portions with stirring at 95—98° for 11.5 hr. The filtrate of the reaction mixture was acidified with HCl and extracted with ether. The extracts were washed with water, dried, and concentrated to give white needles of XIV, mp 227—230°, after recrystallization from ether. *Anal.* Calcd. for $C_9H_7O_5Br$: C, 39.30; H, 2.57. Found: C, 39.65; H, 2.83.

4-Hydroxy-2-iodoisophthalaldehyde (II) and 2-Hydroxy-4-iodoisophthalaldehyde (III)——The precipitate (0.6 g),[18] mp 137—146°, which was obtained from the steam distillate of the acidified reaction mixture together with the three monoaldehydes in the Reimer–Tiemann reaction[11] with 50 g of *m*-iodophenol, was recrystallized from EtOH to give crystals. Recrystallization of the crystals from benzene afforded white

18) The precipitate had not been examined further at the time when we reported "The Reimer–Tiemann Reaction of *m*-Iodophenol"[11] and had been preserved.

needles of II (68 mg), mp 166—168.5°. *Anal.* Calcd. for $C_8H_5O_3I$: C, 34.81; H, 1.83. Found: C, 34.87; H, 1.71. IR cm^{-1} (CCl_4): $\gamma_{C=O}$ 1694, 1655. NMR δ ($CDCl_3$): 12.81 (-OH), 10.37 (-CHO), 10.16 (-CHO), 7.97 (doublet, $J=9.0$ cps, aromatic proton at the C_6-position), 7.05 (doublet, $J=8.5$ cps, aromatic proton at the C_5-position).

The dialdehyde (II) (80 mg), $NH_2OH \cdot HCl$ (400 mg), pyridine (3 ml), and dry EtOH (4 ml) were heated in a sealed tube at 98—100° for 3 hr. The crude dioxime thus obtained was recrystallized from MeOH to afford white crystals, mp 196—199°. *Anal.* Calcd. for $C_8H_7O_3N_2I$: C, 31.51; H, 2.23; N, 9.14. Found: C, 31.24; H, 2.62; N, 9.08.

On the other hand, after recrystallization of the precipitate, mp 137—146°, the EtOH mother-liquor was evaporated and the residue was crystallized from benzene to yield a trace of III, mp 191—192.5°. *Anal.* Calcd. for $C_8H_5O_3I$: C, 34.81; H, 1.83. Found: C, 34.51; H, 1.81. IR cm^{-1} (CCl_4): $\gamma_{C=O}$ 1692, 1654.

4-Hydroxy-2-iodoisophthalic Acid (XV)——A mixture of the dialdehyde (II) (100 mg), Ag_2O (from 308 mg of $AgNO_3$ and excess NaOH), and 10% NaOH (3.5 ml) was treated by the same procedure as for IV. The crude acid was recrystallized from ether–petr. ether to afford white prisms of XV (86 mg), mp 203—205°. *Anal.* Calcd. for $C_8H_5O_5I$: C, 31.19; H, 1.64. Found: C, 31.69; H, 1.65.

Dimethyl 2-Iodo-4-methoxyisophthalate (XVI)——A mixture of XV (200 mg) in dry EtOH (5 ml) and diazomethane (from 5 g of nitrosomethylurea and 18 ml of 50% KOH) in ether was kept at room temperature overnight. After working up in the usual way, the crude ester (XVI) was recrystallized from ether–petr. ether to give 150 mg of colorless prisms, mp 95—95.5°. *Anal.* Calcd. for $C_{11}H_{11}O_5I$: C, 37.74; H, 3.16. Found: C, 38.08; H, 3.09.

Tetramethyl 3,3′-Dimethoxy-2,6,2′,6′-biphenyltetracarboxylate (VIII)——The ester (XVI) (100 mg) and copper bronze (500 mg) were heated in a sealed tube at 205—210° for 4 hr. The reaction mixture was extracted with $CHCl_3$ and the extracts were concentrated to afford a crystalline mass, which was recrystallized from MeOH yielding 42 mg of VIII as cubes, mp 210—211°. *Anal.* Calcd. for $C_{22}H_{22}O_{10}$: C, 59.19; H, 4.97. Found: C, 58.92; H, 5.00. The ester (VIII) thus obtained was identical with a sample which was prepared by Ullmann condensation of V with iodobenzene as mentioned above.

4-Hydroxyisophthalic Acid——To a solution of the acid (XV) (98 mg) in 10% NaOH (3 ml) was gradually added Raney nickel (300 mg) with stirring at 60°. Stirring was continued at 60—70° for another 30 min. The reaction mixture was filtered and the filtrate was acidified with HCl to afford a precipitate. The precipitate was recrystallized from MeOH to give crystals (43 mg), mp 290—293°. *Anal.* Calcd. for $C_8H_6O_5$: C, 52.75; H, 3.32. Found: C, 53.01; H, 3.29. The acid thus obtained was identical with an authentic sample of 4-hydroxyisophthalic acid by mixed melting point test and IR comparison.

Dimethyl 4-Methoxyisophthalate (IX)——A mixture of 4-hydroxyisophthalic acid (26 mg), prepared from II, in dry EtOH and diazomethane (from 8.4 g of nitrosomethylurea and 25.2 ml of 50% KOH) in ether (50 ml) was kept at room temperature overnight. Working up in the usual way gave white needles of IX (6 mg), mp 96.5—97°, after recrystallization from ether–petr. ether (lit.,[14a] mp 94°, lit.,[14b] mp 95°, lit.,[14c] mp 96°). The ester (IX) was identical with an authentic sample of IX which was prepared from commercial 4-hydroxyisophthalic acid.

2-Hydroxyisophthalic Acid (XVIII)——(i) From 3-Methylsalicylic Acid: According to the method reported by Graebe, *et al.*,[16] the acid (XVIII) was synthesized by heating a mixture of 3-methylsalicylic acid (1 g), KOH (6 g), PbO_2 (4.8 g), and water (1.2 ml) and had mp 224—230° as white needles (from MeOH) (lit.,[16] mp 230°). *Anal.* Calcd. for $C_8H_6O_5$: C, 52.75; H, 3.32. Found: C, 52.79; H, 3.28.

(ii) From III: A crude product (22 mg) of 2-hydroxy-4-iodoisophthalic acid (XVII) was prepared from III (25 mg), Ag_2O (from 92 mg of $AgNO_3$ and excess 10% NaOH), and 10% NaOH (1 ml) by the same procedure as for IV and formed white cubes, mp 232.5—235.5°, on recrystallization from benzene–ether. To a solution of the acid (XVII) (29 mg) in 10% NaOH (2.5 ml) was added Raney nickel (200 mg) with stirring at 85° for 15 min. Stirring was continued for another 40 min. The reaction mixture was treated in the same way as 4-hydroxyisophthalic acid to give pale yellow crystals (11 mg), mp 230—235° (from MeOH). The samples of acid (XVIII) prepared by procedures (ii) and (i) were identical by mixed melting point test and IR comparison.

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