Syntheses of Polyhydroxybenzene Derivatives from Furfural

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It has been impressed that 2-substituted 2, 5-dimethoxydihydrofurans and 2, 5-dimethoxytetrahydrofurans are easily converted into aromatic compounds by hydrolysis in acid solution. For example, Clauson-Kass and co-workers[1] described the hydrolysis and spontaneous recyclization of 2-acetyl-2, 5-dimethoxytetrahydrofuran dimethylketal to catechol and Boehme[2] reported the formation of hydrourushiol (XVII) from the acid hydrolysis of 2-heptadecanoyl-2, 5-dimethoxytetrahydrofuran. Respect of the activated character of hydrogens in the α-position to carbonyl group (such as in the case of the compounds VI and XII) had let to the preparation of polyhydroxybenzenes (Fig. 1) and catechol derivatives including hydrourushiol (Fig. 2).

The compounds VI, VII, VIII and X are new substances. Their structures were determined from the synthetic process, analyses and from the infrared spectra.

The method of synthesis of VII was partly based on a route of its methyl analog developed by Clauson-Kass[1], VII was prepared by hydrolysis of VI at room temperature as well as at 100°C in dilute hydrochloric acid. The reaction at lower temperature produced a larger amount of VII (51.5% yield at room temperature and 21.2% at 100°C). VII showed a green color with ferric chloride and significant infrared

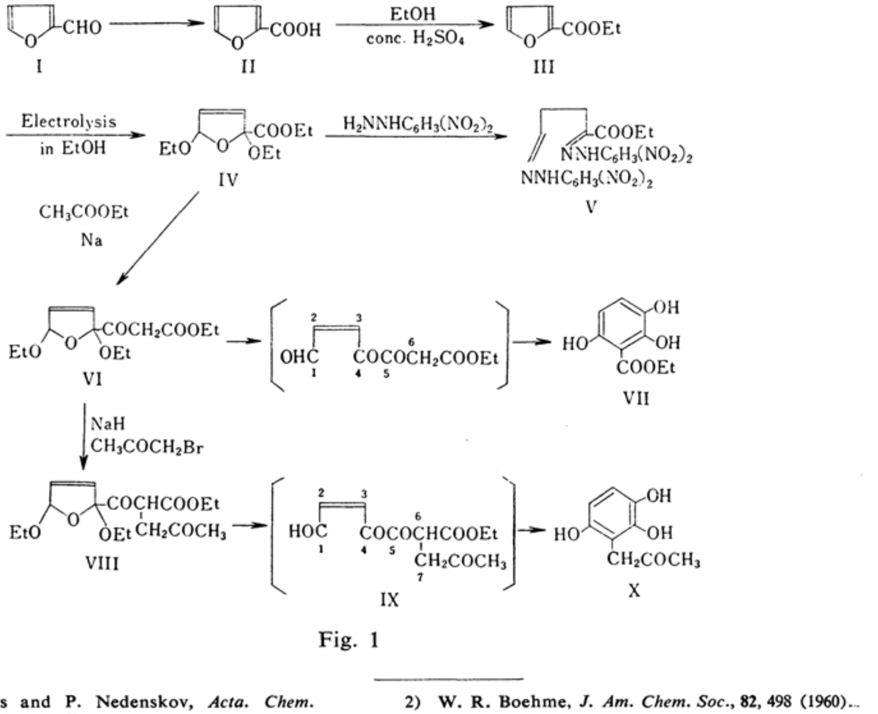

Fig. 1

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[1] N. Clauson-Kass and P. Nedenskov, *Acta. Chem. Scand.*, **9**, 27 (1955) and preceding papers.

[2] W. R. Boehme, *J. Am. Chem. Soc.*, **82**, 498 (1960).

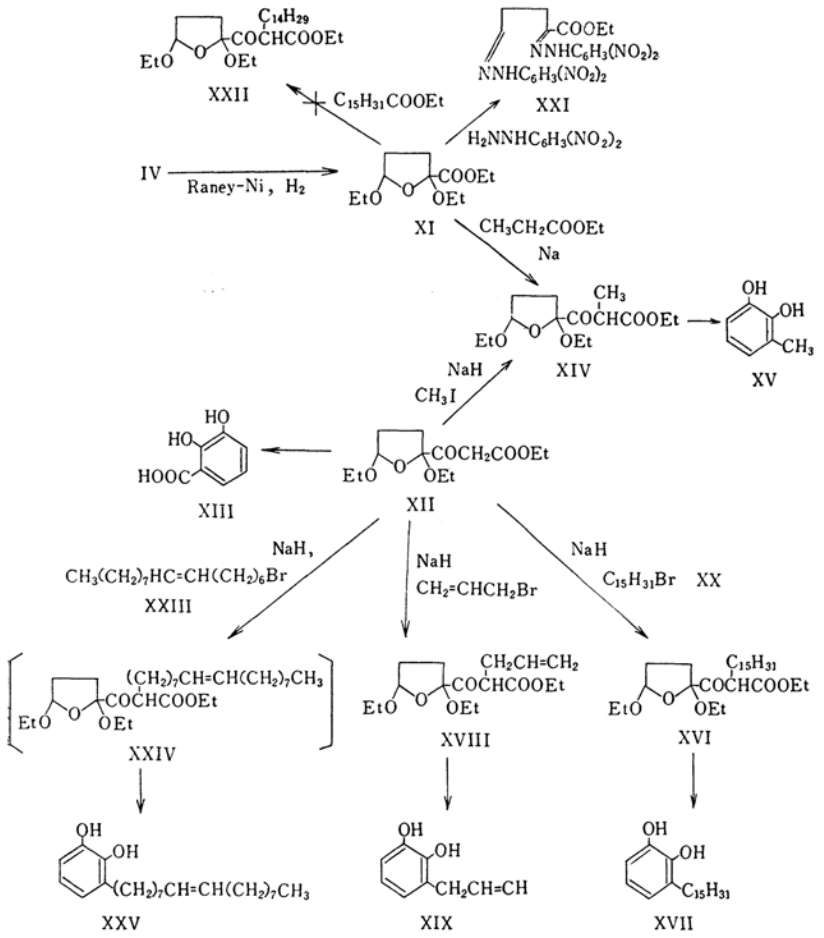

Fig. 2

absorption bands at 2.89~2.94 μ (-OH), and 5.92 μ (ester C=O).

X was obtained through 1,6-intramolecular condensation of the intermediate (IX) which was prepared by acid hydrolysis of VIII. X showed a green color with ferric chloride and gave a red 2,4-dinitrophenylhydrazone. The seven-membered ring compound which was expected from 1,7-intramolecular condensation of IX, was not found in the reaction mixture. The yield of X was 58% and the rest was polymerized in this reaction.

The compounds XII, XIV, XVI, XVIII and XXV are new substances.

XI was prepared by reduction of IV with Raney nickel as a catalyst. IV and XI are distinguished easily by the color of their bishydrazons (V and XXI). V is red and decomposes at 248°C, while XXI is yellow and melts at 194~196°C.

The compound XIII was identified with an authentic sample of commercial 2,3-dihydrobenzoic acid through mixed fusion test and by comparison of infrared spectra.

Pentadecyl bromide (XX) was prepared by the Hunsdiecker reaction[3] from silver salt of palmitic acid.

XVI was prepared (24.6%) by boiling the *n*-butyl ether solution of XII and XX for 5 hr. A large amount of XII and XX was recovered from the reaction mixture. A higher yield of XVI can be expected when the time of reaction is extended. At a lower temperature such as the boiling temperature of a mixture of ether and benzene, only a trace of XVI was obtained.

Very recently Hanafusa and Yukawa[4] have synthesized hydrourushiol (XVII) starting from catechol. Hydrourushiol, one of the Japanese lac urushiol[5] or poison-ivy compound[6], was prepared here by acid hydrolysis of XVI. The

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[3] H. Hunsdiecker and C. Hunsdiecker, *Ber.*, **75**, 291 (1942); C. V. Wilson, "Organic Reactions," Vol. 9, 332(1957).

[4] T. Hanafusa and Y. Yukawa, *Chem. & Ind.*, **1962**, 23.

[5] R. Majima and co-workers, *Ber.*, **55**, 172 (1922) and preceding papers.

[6] G. A. Holl, V. Mattcotti and W. D. Graham, *J. Am. Chem. Soc.*, **56**, 2736 (1934).

colorless, waxy crystals of synthetic hydrourushiol were identified with an authentic sample[7] by mixed fusion test and comparison of infrared spectra.

On the Claisen condensation of XI with ethyl acetate and ethyl propionate, the yields were 52.3 and 13.0% respectively. Ethyl palmitate failed to condense with XI in the presence of metallic sodium, sodium alkoxide, sodium hydride or triphenylmethyl-sodium using the ether, benzene or *n*-butyl ether as a solvent respectively. The condensation also failed when the timer of reaction was extended,

XVIII was a yellow oil and turned to brown when it was stored in the dark place for a long time. It reacted rapidly with bromine and permanganate. Infrared spectra of XVIII showed terminal double bond at the peaks of 6.06, 10.05, 10.83 μ and carbonyl groups at two peaks of $5.16\sim5.76\ \mu$.

XIX was obtained by acid hydrolysis of XVIII. 3-Allylcatechol was prepared formerly by the reaction of catechol and allyl bromide through the Claisen rearrangement of monoallyl ether of catechol[9]. XIX was practically colorless just after the distillation and rapidly became golden yellow, but it soon turned to reddish brown on exposure to air. The terminal olefinic bond of XIX was readily detected from the infrared spectra. XIX rapidly decolorized bromine and permanganate and gave an olive green color with ferric chloride.

1-Bromoheptadencen-8 (XXIII) was also prepared by the Hunsdiecker reaction[3] from silver salt of oleic acid. Acid hydrolysis was carried out after the reaction of XII and XXIII had been completed. Lead salt of XXV was isolated from the acid solution with lead acetate. XXV was obtained as a pale yellow oil by means of treating lead salt of XXV with hydrogen sulfide. This manner gave XXV in a high yield (52.4% yield based on reacted XII). When a solution of XXV in alcohol was treated with a drop of aqueous permanganate, the color disappeared after standing for a minute. XXV gave a green color with ferric chloride. Negative Beilstein test of XXX showed that bromine did not add to a double bond of oleic acid under the Hunsdiecker reaction.

It is interesting that application of XIX and XXV to the skin caused a marked blister within a few hours, but on application of hydrourushiol to the skin no blister edema was found. Dawson[9] reported that the 3-(8′-pentadecenyl)catechol caused the marked edema and blister characteristic of poison-ivy dermatitis. It is undoubted that 3-olefinic catechol caused dermatitis. Instead of urushiol, 3-allylcatechol (XIX) may be available for clinical study. Further study of olefinic catechols, some materials which have a characteristic of "Urushi" for paint will be expected. It is believed that the above methods will be available to synthesize the compounds having another substituent in 1-position of 2, 5, 6-trihydroxybenzene (method of Fig. 1) and substituents in 3-position of catechol (method of Fig. 2).

Experimental

2-Furoic Acid (II).—This compound was prepared by the method given earlier[10].

Ethyl 2-Furoate (III).—56.0 g. (0.50 mol.) of II was dissolved in amixture of 300 ml. of ethanol and 56 g. of concentrated sulfuric acid. After the reaction mixture had been heated at a reflux temperature for 6 hr, the ethanol was removed by distillation, the residue was dissolved in ether and a small amount of ice water was added. The ethereal solution was washed with saturated sodium hydrogen carbonate, with water and dried over magnesium sulfate. The ether was removed by distillation, the residue was distilled further, and 67.5 g. (96.5% yield) of III was obtained, b. p. 129~130°C (115 mmHg).

Found: C, 60.01; H, 5.75. Calcd. for $C_7H_8O_3$: C, 59.99; H, 5.75%.

2, 5-Diethoxy-2, 5-dihydrofurancarboxylic Acid Ethyl Ester (IV).—III (55.9 g., 0.40 mol.) was mixed with 230 ml. of methanol and 1.0 ml. of concentrated sulfuric acid. The electrolysis of the solution was carried out by the Clauson-Kaas method[1]. From the fraction at b. p. 115~136°C (11 mmHg), 56.25 g. (61.5%) of IV was obtained as a colorless liquid, n_D^{15} 1.4420.

Found: C, 57.80; H, 7.27. Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88%.

V was obtained in a quantitative yield from 1 mol. of IV and 2 mol. of 2, 4-dinitrophenylhydrazine. Crude crystals of V were twice recrystallized from nitrobenzene. V was red crystals, decomp. p. 248°C.

Found: C, 44.18; H, 3.65; N, 21.80. Calcd. for $C_{19}H_{16}O_{18}N_8$: C, 44.19; H, 3.12; N, 21.12%.

Ethyl (2, 5-Diethoxy-2, 5-dihydro)furfuroylacetate (VI).—14.0 g. (0.061 mol.) of IV and 20 ml. of benzene were placed in a three-necked flask fitted with a stirrer, a dropping funnel and a reflux condenser carrying a soda-lime tube and heated with stirring to about 100°C. 21.5 g. (0.244 mol.) of ethyl acetate and 5.6 g. (0.244 mol.) of sodium powder were added at the interval of 30 min. in six portions. After the reaction, ethanol was added dropwise to remove unreacted sodium and the

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7) The authors wish to thank the people of Yukawa Laboratory, Osaka University for a gift of the authentic sample.

8) S. Kawai, *Scient. Pap. Inst. Phys. Chem. Res.*, **3**, 267 (1926). W. H. Perkin and V. M. Trikojus, *J. Chem. Soc.*, **1927**, 1664.

9) B. Loev and C. R. Dawson, *J. Am. Chem. Soc.*, **24**, 980 (1959).

10) "Jikken Kagaku Koza" Vol. 17, Maruzen, Tokyo (1957), p. 626.

mixture was left to stand with stirring and heating for 10 hr. The solution was cooled to 0°C and acidified by acetic acid. The dark brown mixture was added to cold water and the benzene layer was separated, washed with saturated sodium hydrogen carbonate then with water, and dried over magnesium sulfate. Benzene was removed by distillation and the residue distilled further, 6.60 g. (40.0%) of VI was obtained as a slightly yellow oil, b. p. 130～140°C/5 mmHg, n_D^{15} 1.4420.

Found: C, 57.02; H, 7.10. Calcd. for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40%.

Ethyl 2, 3, 6-Trihydroxybenzoate (VII).—Two grams of VI was shaken at room temperature for 5 hr. with 20 ml. of 0.1 N hydrochloric acid and left to stand for 2 weeks. A light violet precipitate was collected by filtration, washed with water and dried. The yield of crude VII was 0.82 g. (56.1%), m. p. 149～151°C. Two recrystallizations from 30% ethanol raised the melting point to 154～155°C.

Found: C, 54.26; H, 5.20. Calcd. for $C_9H_{10}O_5$: C, 54.54; H, 5.09%.

VII was also obtained by heating 2.0 g. of VI in 20 ml. of 0.1 N hydrochloric acid at the boiling temperature for an hour. After cooled, a precipitate was removed by filtration, washed with water and dried. The yield of crude VII was 0.31 g. (21.2%). By two recrystallizations of this crude product from 30% ethanol, white crystals of VII, m. p. 154～158°C, were obtained. The product was identified with the sample which was prepared at room temperature by mixed fusion test and comparison of infrared spectra.

Found: C, 54.54; H, 5.20. Calcd. for $C_9H_{10}O_2$: C, 54.54; H, 5.09%.

Ethyl α-(2, 5-Diethoxy-2, 5-dihydro)furfuroyl-γ-oxovalerate (VIII).—Sodium hydride (0.0277 mol.) and 20 ml. of benzene were placed in a three-necked flask fitted with a mechanical stirrer, a dropping funnel and a reflux condenser carrying a soda-lime tube. 7.5 g. (0.0277 mol.) of VI was added dropwise to the stirred contents of the flask at room temperature. 4.56 g. (0.032 mol.) of bromoacetone was added after heating at reflux temperature for an hour, and the reaction mixture was heated for 10 hr. After the reaction, a small amount of ice water was added and acidified with acetic acid. The benzene layer was separated, washed with saturated sodium hydrogen carbonate solution then water, and dried over magnesium sulfate. Benzene and unreacted bromoacetone were removed by distillation, and further fractional distillation of the residue gave 0.7 g. of unreacted compound of VI, and 3.2 g. (45.0%) of VIII boiling at 114～120°C (1.8 mmHg). VIII was redistilled to give a yellow oil, b. p. 118～120°C (1.8 mmHg). n_D^{17} 1.4763. This yellow oil turned to brown when stored.

Found: C, 58.80; H, 6.91. Calcd. for $C_{16}H_{24}O_7$: C, 58.52; H, 7.73%.

2, 3, 6-Trihydroxyphenylacetone (X).—This compound was prepared from 1.90 g. (0.0071 mol.) of VIII as described above for preparation of VII (method of heating at reflux temperature). The yield was 0.80 g. (58.0%) of crude X. After two recrystallizations from water, white crystals of X, m. p. 140～142°C, were obtained. The product gave a green color with ferric chloride.

Found: C, 56.50; H, 6.18. Calcd. for $C_9H_{10}O_4$: C, 56.46; H, 5.92%.

2, 5-Diethoxytetrahydrofurancarboxylic Acid Ethyl Ester (XI).—XI was prepared in a quantitative yield by reduction of IV in ethanol under hydrogen of 50 kg./cm², using the W-6 Raney nickel[11] as a catalyst at room temperature for 7 hr. XI was a colorless liquid, b. p. 109～120°C (11 mmHg), n_D^{15} 0.4378.

XXI (quantitative yield) was prepared by the usual method from XI. Yellow crystals of XXI (m. p. 194～196°C) were obtained by three recrystallizations from nitromethane.

Found: C, 44.92; H, 3.62; N, 21.48. Calcd. for $C_{19}H_{18}O_{10}N_8$: C, 44.02; H, 3.49; N, 21.03%.

Ethyl (2, 5-Diethoxytetrahydro)furfuroylacetate (XII).—This compound was prepared from XI (21.0 g.) and ethyl acetate (23.9 g.) as described above for the preparation of VI. 12.9 g. (52.3%) of XIII was obtained as a light yellow liquid, b. p. 115～124°C (3.5 mmHg), n_D^{17} 1.4612.

Found: C, 57.28; H, 8.21. Calcd. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08%.

2, 3-Dihydroxybenzoic Acid (XIII).—One gram of XII in a mixture of 36 ml. of 0.1 N hydrochloric acid and 65 ml. of dioxane was heated at reflux temperature for 11 hr. After the reaction, the solvent was removed by distillation and the residue was sublimed under 6 mmHg on an oil bath (120～130°C). The product was identical with an authentic sample of commercial 2, 3-dihydroxybenzoic acid from mixed fusion test and comparison of infrared spectra.

Found: C, 54.73: H, 3.94. Calcd. for $C_7H_6O_4$: C, 54.55; H, 3.92%.

Ethyl α-(2, 5-Diethoxytetrahydro)furfuroyl-α-methylacetate (XIV).—This compound was prepared from 3.1 g. (0.0114 mol.) of XII and 2.61 g. (0.0171 mol.) methyl iodide by heating for 1.5 hr. in the ethereal solution as described above for the preparation of VIII. 2.20 g. (67.5%) of XIV was obtained as a yellow oil which turned to brown after a long time storage. B. p. 105～124°C (3 mmHg). This product was redistilled at 119～124°C (3 mmHg), n_D^{17} 1.4930.

Found: C, 56.25; H, 8.16. Calcd. for $C_{13}H_{24}O_6$: C, 56.56; H, 8.76%.

XIV was also prepared from 2.32 g. (0.01 mol.) of XI and 4.08 g. (0.04 mol.) of ethyl propionate as described above for preparation of VI. The yield of XIV was 0.37 g. (13.0%). Its infrared spectra showed this product was identical with the product which was prepared from XII and methyl iodide by the method described above.

1-Methyl-2, 3-dihydroxybenzene (XV).—0.90 g. of XIV in a mixture of 3.6 ml. of hydrochloric acid (0.1 N) and 6.5 ml. of dioxane was heated at reflux temperature for 3.5 hr. After the reaction, the solvent was distilled off at a reduced pressure. The residue was solidified on cooling. The product was purified by three recrystallizations from benzene to give 0.04 g. (13.0%) of XV which were

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[11] "Organic Syntheses", Vol. 29, 24 (1949).

colorless crystals, m. p. 46.5∼47°C (reported m. p. 47°C). The product gave a green color with ferric chloride.

Found: C, 67.68 : H, 6.62. Calcd. for $C_7H_8O_2$: C, 57.63; H, 6.50%.

Ethyl α-(2, 5-Diethoxytetrahydro)furfuroyl-α-heptadecylacetate (XVI).—This compound was prepared from 7.53 g. (0.026 mol.) of XII and 8.3 g (0.0263 mol.) of XX by reflux in *n*-butyl ether for 5 hr. as described above for preparation of VIII. After a fore-run of XII (1.90 g.), 2.0 g. (25.87% yield based on unrecovered XII) of XVI was obtained, b. p. 133∼135°C (0.1 mmHg). The product was solidified (colorless) at room temperature, m. p. 46∼47°C.

Found: C, 69.60; H, 11.58. Calcd. for $C_{28}H_{52}O_6$: C, 69.38; H, 10.81%.

Hydrourushiol (XVII).—One gram of XVI in a mixture of 10 ml. of 0.1 N hydrochloric acid and 10 ml. of dioxane was heated at reflux temperature for 10 hr. After the reaction, the solvent was distilled off. The residual oil[12] was dissolved in ethanol and treated with an excess of ethanolic solution of lead acetate trihydrate. The dense precipitate of lead salt was filtered off, washed with ether. The lead salt was suspended in ethanol and treated with hydrogen sulfide. The lead sulfide was removed by filtration and the solvent was distilled off from the filtrate, leaving an oil which solidified at room temperature as a colorless wax. The yield was 0.230 g. (34.7%) of XVII, m. p. 57∼68.5°C, which was recrystallized from ether. The infrared spectra and melting point of the synthetic product were identical with those of an authentic sample.

Found: C, 78.26; H, 11.21. Calcd. for $C_{21}H_{36}O_2$; C, 78.09; H, 11.32%.

Ethyl α-(2, 5-Diethoxytetrahydro)furfuroyl-α-allylacetate (XVIII).—This compound was prepared from 6.20 g. (0.0228 mol.) of XII and 4.14 g. (0.0342 mol.) of allyl bromide by reflux in benzene for 7 hr. as described above for the preparation of VIII. The yield was 3.2 g. (45.0%) of XVIII, b. p. 125∼134°C (3.5 mmHg), n_{D}^{20} 1.4640. The yellow oil XVIII turned to brown when stored for a few hr. A sample of XVIII reacted with bromine and permanganate.

Fund: C, 61.30; H, 8.72. Calcd. for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34%.

1-Allyl-2, 3-dihydroxybenzene (XIX).—This compound was prepared from 2.70 g. of XVIII in 86 ml. of 0.1 N hydrochloric acid and 50 ml. of dioxane by reflux for 9 hr. After the reaction the solvent was distilled off. The residue was distilled under a reduced pressure to give a colorless liquid of b. p. 140∼145°C/15 mmHg. The weight was 0.41 g. (32.0%) of XIX, which reacted rapidly with bromine and with permanganate. A sample of XIX gave an olive color with ferric chloride. The portion, b. p. 144∼145°C (15 mmHg.) was analyzed.

Found: C, 72.10; H, 6.65. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71%.

3-(8′-Heptadecenyl)catachol (XXV).—0.0246 mol. of sodium hydride in 30 ml. of *n*-butyl ether was placed in a three-necked flask with a mechanical stirrer, a dropping funnel and a reflux condenser carrying a soda-lime tube. 6.7 g. (0.0246 mol.) of XII was added dropwise to the stirred contents of the flask at room temperature for an hour, 5.2 g. (0.0164 mol.) of XXIV was added and the reaction mixture was heated for 10 hr. After the reaction, the reaction mixture was acidified with acetic acid and then *n*-butyl ether was removed by vacuum distillation. The residue was added to 30 ml. of 0.1 N hydrochloric acid and 20 ml. of dioxane and heated at reflux temperature for an hour. The reaction mixture was treated as described above for preparation of XVII. 0.298 g. (52.4%) of XXV was obtained as a pale yellow substance, b. p. 215∼220°C (0.8 mmHg), m. p. 33∼36°C, which gave a green color with ferric chloride and reacted with permanganate.

Found: C, 79.51; H, 11.19. Calcd. for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05%.

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[12] B. Loev and C. R. Dawson, *J. Am. Chem. Soc.*, **78**, 6095 (1959).