Condensation of Diethyl Malonate with Methyl Vinyl Ketone

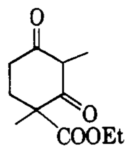
THOMAS A. SPENCER, MARSHALL D. NEWTON,[1a] AND STEVEN W. BALDWIN[1b]

Department of Chemistry, Dartmouth College, Hanover, New Hampshire

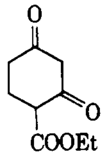
Received October 16, 1963

Ethoxide-catalyzed reaction of diethyl malonate with methyl vinyl ketone yields 1-carboxy-6-methylbicyclo-[3.3.1]non-6-ene-2,4-dione (VI) and, after hydrolysis, 1-methyl-2-acetyl-4-carboxycyclohexene-1 (XI). The separately prepared mono-Michael adduct (V) can be cyclized in very good yield to a mixture of 4-carboethoxycyclohexane-1,3-dione (II) and 3-ethoxy-6-carboethoxy-Δ^2-cyclohexenone (XIII).

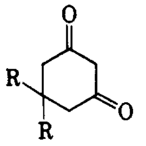
We have been engaged in a study of the synthesis of 4-carboalkoxycyclohexane-1,3-diones for use in elaboration of terpenoid carbocyclics, such as the diterpene resin acids (for which I would be a potential precursor) and isocamphorquinone.[2] The classical methods for preparing such systems consist in Michael addition of a suitably substituted malonic or acetoacetic ester to an α,β-unsaturated ketone or α,β-unsaturated ester, respectively, followed by ring-closing Claisen condensation. This paper reports the results of our investigation of the parent case of the first type: the reaction of diethyl malonate with methyl vinyl ketone. We were interested both in preparing 4-carboethoxycyclohexane-1,3-dione (II) and in the possibility of a simple one-step synthesis of dihydroresorcinol (III) that was analogous to the preparation of dimedone (IV) from mesityl oxide and diethyl malonate.[3] We were encouraged in the latter hope by the report of Mannich and Fourneau[4] that III could be isolated from sodium ethoxide treatment of the adduct V formed from diethyl malonate and N,N-diethylaminobutanone-3. However, when equimolar amounts of diethyl malonate and methyl vinyl ketone were subjected to the conditions of the first step in the preparation of dimedone,[3] the only pure products isolated were both the result of bis-Michael addition.



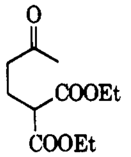
I



II

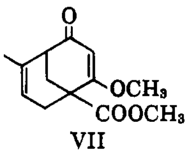


III, R = H
IV, R = CH$_3$

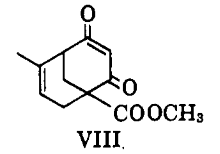


V

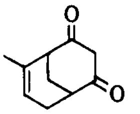
An acidic substance, m.p. 190–191° (with effervescence), was obtained in 20% yield; this had an elemental analysis indicating a formula $C_{11}H_{12}O_4$. Of the several structures with this formula which can be derived hypothetically from methyl vinyl ketone and diethyl malonate, only VI was consistent with the observed properties, which included neut. equiv. 107 (diacid), λ_{max} 270 mμ (ϵ 11,200), and λ_{max} 5.86, 6.14, and 6.4 μ (enolized β-diketone). The substance reacted with 2 moles of diazomethane to afford a compound, m.p. 87.5–88.5°, which was, accordingly, either VII or VIII. The n.m.r. spectrum of this diazomethane product was crucial in the assignment of structure VI to the diacid, for it showed bands completely consistent with the major structural features of VII or VIII.[5] The formation of VI from diethyl malonate and methyl vinyl ketone could occur as shown in Chart I. That the free acid VI rather than the ester IX was isolated can perhaps be explained as a case of the unusually facile hydrolysis (by water eliminated during condensation or upon work-up) undergone by enolized, hydrogen-bonded acetoacetic esters.[6a]



VII

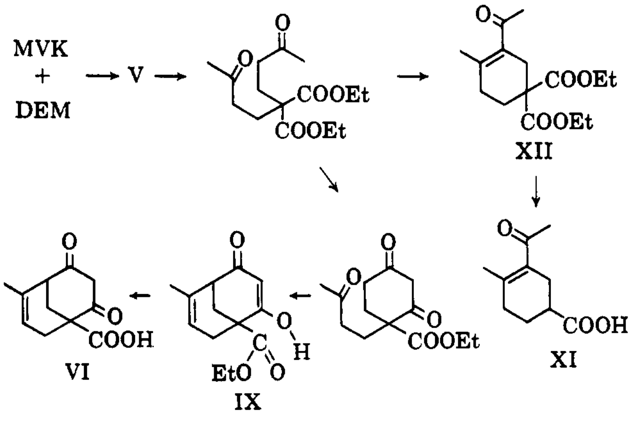


VIII



X

CHART I[6b]



When VI was heated at its melting point it yielded a substance, m.p. 120.5–121.5°, with an elemental analysis and ultraviolet and infrared spectra consistent with the decarboxylation product X. Similar decarboxylation of a bridgehead carboxyl in a bicyclo-[3.3.1]nonane β-keto acid has been observed when the participating ketone carbonyl is in a three-carbon bridge of the bicyclic system.[7]

The neutral material from this condensation of diethyl malonate with methyl vinyl ketone consisted of 23% recovered diethyl malonate and a higher-boiling fraction which afforded, upon saponification, a crystalline acid, m.p. 76.5–77.0°. The properties

---

[1] (a) National Science Foundation Undergraduate Research Participant, academic year, 1960–1961; recipient of support under the terms of an institutional research training grant from the U. S. Public Health Service, summer, 1961. (b) National Science Foundation Undergraduate Research Participant, academic year, 1962–1963, and summer, 1963.

[2] T. A. Spencer and M. D. Newton, *Tetrahedron Letters*, 1019 (1962).

[3] R. L. Shriner and H. R. Todd, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, 1943, p. 200.

[4] C. Mannich and J. P. Fourneau, *Ber.*, **71**, 2090 (1938).

[5] On the basis of a multiplet due to a single proton at τ 8.1, assigned to the methinyl proton of the 87–88° compound, we prefer structure VIII over VII, for, if this proton were adjacent to a carbonyl group (as in VII), it should appear at a lower field. See, *e.g.*, L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 57.

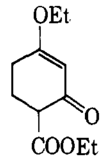
[6] (a) See M. L. Bender [*Chem. Rev.*, **60**, 70 (1960)] for a consideration of the exceptional reactivity toward nucleophiles of enolizable β-keto esters and for references. In Chart I, structure IX is shown in one such enolized, hydrogen-bonded form. (b) MVK, methyl vinyl ketone; DEM, diethyl malonate.

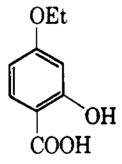
[7] H. Meerwein, *et al.*, *J. prakt. Chem.*, **104**, 163, 166 (1922).

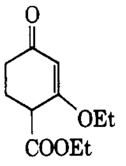
of this substance, *e.g.*, ultraviolet absorption at 248 mμ (ε 7000),[8] readily showed that it was 1-methyl-2-acetyl-4-carboxycyclohexene-1 (XI), which could be formed as indicated in Chart I. Wichterle[9] has reported the same structure for a compound, m.p. 97°, derived by treatment of diethyl bis(γ-chlorocrotyl)-malonate with concentrated sulfuric acid, followed by hydrolysis. He also reported preparation of the semicarbazone, m.p. 145–148°, of the cyclized malonic ester precursor XII. We were unable to obtain a semicarbazone of an α,β-unsaturated ketone from the neutral material which yielded XI upon hydrolysis, so that we were not thus able to check if the discrepancy between melting points for XI is due to dimorphism. Our spectral data (see Experimental) leave little room for doubt that at least our structural assignment is correct.

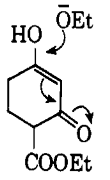
It was evident that, unlike mesityl oxide, methyl vinyl ketone very readily forms a bis-Michael adduct with diethyl malonate. It seemed that successful preparation of 4-carboethoxycyclohexane-1,3-dione would depend upon finding appropriate conditions, *e.g.*, those which would precipitate the enolate anion of II,[10] for cyclization of previously prepared mono-Michael adduct V. An improved method (71% yield) for the preparation of V was found in an adaptation of the method of Tsuruta[11] for the addition of methyl vinyl ketone to dimethyl malonate.

When V was treated with an equivalent of sodium ethoxide in a minimum amount of refluxing ethanol, a thick precipitate formed, which, upon acidification, afforded 79% of crude 4-carboethoxycyclohexane-1,3-dione. Pure II melted at 61.5–62.5° and absorbed at 256 mμ (ε 15,000) and at 5.77 and 6.2–6.3 μ. The structural assignment was confirmed by hydrolysis and decarboxylation to afford dihydroresorcinol (III) in 63% yield. Our hope of developing a convenient synthesis of III was frustrated, however, by the fact that, in subsequent cyclizations, the voluminous precipitate was not solely the anion of II but often largely the sodium salt of another solid substance, m.p. 98–99°, which proved to be the enol ether XIII.


XIII


XIV


XV


XVI

This structural assignment was made on the basis of elemental analysis and spectra, particularly the n.m.r. spectrum, which showed two nonequivalent ethyl groups, and by conversion of the substance in excellent yield (95%) to 4-ethoxysalicylic acid (XIV)[12] by treatment with N-bromosuccinimide, followed by basic hydrolysis, thereby establishing the location of the ethoxy group and showing that the substance was not the isomeric enol ether XV. Attempted basic hydrolysis of XIII led to no isolable product; mild acid hydrolysis gave II. Formation of XIII presumably occurs *via* II as indicated in XVI. Reaction variables which controlled the relative amounts of II and XIII formed upon cyclization of V were not found. Initiation of precipitation of a given enolate anion is probably important, for II is certainly a much stronger acid than XIII, and would be expected to form the predominant anion in an over-all equilibrium process.

Experimental[13]

Reaction of Diethyl Malonate with Methyl Vinyl Ketone at Reflux in the Presence of an Equivalent of Sodium Ethoxide.—In a modification of the procedure of Shriner and Todd,[3] 80.0 g. (0.50 mole) of freshly distilled diethyl malonate, b.p. 115–116° (65 mm.), was added to a solution of 11.5 g. (0.50 g.-atom) of metallic sodium in 200 ml. of absolute ethanol (distilled from calcium hydride) under a nitrogen atmosphere. While the clear solution was stirred in a water bath heated to 50° to prevent precipitation of the sodium enolate, 35.0 g. (0.50 mole) of methyl vinyl ketone (Matheson Coleman and Bell, technical) was added dropwise over 1 hr. The resulting light orange mixture was then brought to reflux, and after 2 hr. a salt began to precipitate. When the mixture had refluxed for 4 hr., it was reduced to a reddish brown slurry by evaporation of most of the ethanol *in vacuo*. This residue was then partitioned between 200 ml. of water and 250 ml. of chloroform. The chloroform layer was dried over magnesium sulfate and evaporated to yield 50 g. of mobile yellow oil, which was distilled to give two distinct fractions: 18 g. (23%) of recovered diethyl malonate, b.p. 55–62° (1 mm.), $n^{25}\text{D}$ 1.4118; and 3.5 g. of material with b.p. 115–120° (1.5 mm.).

The latter oil (1 g.) was stirred at room temperature for 24 hr. in 15 ml. of 1 *N* sodium hydroxide solution. Acidification of this mixture, followed by chloroform extraction in the usual manner, yielded 0.200 g. of white solid **1-methyl-2-acetyl-4-carboxycyclohexene-1 (XI)**, m.p. 68–71°. Recrystallization from benzene yielded material, m.p. 76.5–7.70°, which was soluble in 1 *N* sodium bicarbonate solution, and which gave a positive iodoform test and a neutralization equivalent of 182 (calculated for $C_{10}H_{14}O_3$: 182). The material had $\lambda_{\max}^{\text{EtOH}}$ 248 mμ (ε 7000) and $\lambda_{\max}^{\text{CHCl}_3}$ 5.85, 5.93, and 6.18 (w) μ; n.m.r.: singlet at τ −1.29 (-COO*H*), singlet at 7.85 $(-\overset{\overset{O}{\|}}{C}-CH_3)$, and singlet at 8.19 $(-\overset{|}{C}=\overset{|}{C}-CH_3)$.

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.92; H, 7.68.

The original aqueous solution obtained from the reaction of diethyl malonate and methyl vinyl ketone described above was cooled in an ice bath and acidified with 5 *N* sulfuric acid, whereupon a thick, dark oil precipitated. This gum was extracted with chloroform, leaving behind 15 g. of insoluble residue. The chloroform was dried over magnesium sulfate and evaporated to yield an oil which crystallized upon trituration with ether to give 10.5 g. (20%) of white crystalline **1-carboxy-6-methylbicyclo[3.3.1]non-6-ene-2,4-dione (VI)**, m.p. 187–188° (with definite evolution of gas). Recrystallization from ether–methanol yielded the analytical sample, m.p. 190–191° dec.; $\lambda_{\max}^{\text{EtOH}}$ 270 mμ (ε 11,200), shoulder at 242 (6600); $\lambda_{\max}^{\text{Nujol}}$ 3.7 (broad), 5.86, 6.14, and 6.4 (broad) μ. The material was soluble in 1 *N* sodium bicarbonate solution, gave a negative iodoform test, and turned methanolic ferric chloride solution deep red; a neutralization equivalent of 107 was obtained (calculated for a $C_{11}H_{12}O_4$ diacid: 104).

---

[8] R. B. Turner and D. M. Voitle [*J. Am. Chem. Soc.*, **73**, 1403 (1951)] report that 1-methyl-2-acetylcyclohexene-1 has $\lambda_{\max}$ 249 mμ (ε 6890).

[9] O. Wichterle, *Chem. Zentr.*, 348 (1944).

[10] In all cases of cyclization to cyclohexane-1,3-diones which we have investigated (see, *e.g.* ref. 2), no reasonable yield of desired product could be obtained unless conditions for enolate precipitation were found. Otherwise, reverse Michael reactions, other condensations, etc., occurred, as in the formation of VI and XI.

[11] T. Tsuruta, *Bull. Inst. Chem. Research Kyoto Univ.*, **31**, 190 (1953).

[12] (a) R. J. W. Byrde, D. F. Downing, and D. Woodstock, *Biochem. J.*, **72**, 344 (1959); (b) Ng. Ph. Buu-Hoï, N. D. Xuong, and D. Lavit, *Rec. trav. chim.*, **74**, 729 (1955); (c) R. Kuhn, F. Killiken, and H. Trischmann, *Ber.*, **83**, 304 (1950).

[13] Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Clark Microanalytical Laboratory, Urbana, Ill. Melting points were taken on a micro hot stage; those of analytical samples are corrected. Boiling points are uncorrected. Ultraviolet spectra were determined in 95% ethanol on a Bausch and Lomb Spectronic 505 recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer Model 21 recording spectrophotometer. N.m.r. spectra were determined on a Varian Model A-60 instrument in carbon tetrachloride solution using tetramethylsilane as reference.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.65; H, 5.86.

Monomethyl Enol Ether of 1-Carbomethoxy-6-methylbicyclo[3.3.1]non-6-ene-2,4-dione.—To an ethereal solution of diazomethane (prepared from Du Pont precursor EXR-101), was added a solution of 1.36 g. (6.54 mmoles) of the bicyclic compound VI, m.p. 187–188° dec., in 25 ml. of methanol. Excess diazomethane was decomposed with glacial acetic acid, and the solvent was evaporated to yield a yellow oil, which crystallized from methanol at −20°, affording 0.980 g. (64%) of white crystals, m.p. 60–70°. Three recrystallizations from cold methanol raised the melting point to 87.5–88.5°; $\lambda_{\max}^{\text{EtOH}}$ 259 mμ (ε 9200), shoulder at *ca.* 240 (8000); $\lambda_{\max}^{\text{CHCl}_3}$ 5.71, 6.00, and 6.17 μ; n.m.r.: multiplet at τ 4.7 $(-\overset{|}{\text{C}}=\overset{|}{\text{C}}-H)$, singlet at 4.9 $(\text{CH}_3-\text{O}-\overset{|}{\text{C}}=\overset{|}{\text{C}}-H)$, singlet at 6.3 (2 $\text{OC}H_3$), multiplets at 7.4 and 7.6 (2 $-\text{C}H_2-$), multiplet at 8.1 $(-\overset{|}{\text{C}}=\overset{|}{\text{C}}-\underset{|}{\overset{|}{\text{C}}}-H)$, and 8.3 $(-\overset{|}{\text{C}}=\overset{|}{\text{C}}-\ \text{C}H_3$, split, presumably by remote coupling).

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.12; H, 6.92.

6-Methylbicyclo[3.3.1]non-6-ene-2,4-dione (X).—A 0.200-g. (0.960 mmole) sample of the β-keto acid (VI), m.p. 190–191° dec., was placed in a small test tube filled with nitrogen and heated at 210° for 5 min. with the inert atmosphere maintained. The cooled contents of the tube crystallized upon addition of a small amount of ether. Four recrystallizations of the crude red product from acetone–hexane yielded 0.060 g. of colorless crystals, m.p. 120–121°. The analytical sample had m.p. 120.5–121.5°; $\lambda_{\max}^{\text{EtOH}}$ 270 mμ (ε 8400), shoulder at 240 (4400); $\lambda_{\max}^{\text{CHCl}_3}$ 3.1 (broad), 5.86 (shoulder at 5.78), and 6.22 μ.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.90; H, 7.35.

Diethyl (3-Oxobutyl)malonate (V).—In an adaptation of the method of Tsuruta,[11] 525 g. (3.28 moles) of diethyl malonate (Matheson Coleman and Bell, practical) was added to a solution of 11.3 g. (0.49 g.-atom) of sodium in 492 ml. of absolute ethanol (distilled from calcium hydride) in a nitrogen atmosphere. The mixture was cooled to −10° and stirred vigorously while a mixture of 490 g. (3.06 moles) of diethyl malonate, 286 g. (4.08 moles) of methyl vinyl ketone, and 490 ml. of absolute ethanol was added dropwise, causing the mixture to turn light yellow. When the addition was complete, the mixture was kept at −10° for 30 min. and then allowed to stand at room temperature for 48 hr. At the end of this time the bright yellow mixture was neutralized with 6% aqueous acetic acid and extracted with ether in the usual manner. After evaporation of the dried ether extracts, the residual oil was distilled *in vacuo* to give 660 g. (71%) of diethyl (3-oxobutyl)malonate (V), b.p. 129–138° (2 mm.). Redistillation afforded 602 g. (65%) of product, b.p. 134–138° (2.5 mm.); $n^{25}\text{D}$ 1.4377; $\lambda_{\max}$ 5.8 (broad) μ. The **semicarbazone**, prepared in the usual manner and recrystallized from ethanol, had m.p. 112.5–113.5° (lit.[4] m.p. 118°, lit.[14] m.p. 113°).

Anal. Calcd. for $C_{12}H_{21}N_3O_5$: C, 50.16; H, 7.37; N, 14.63. Found: C, 50.36; H, 7.33; N, 14.78.

4-Carboethoxycyclohexane-1,3-dione (II).—To a solution of 0.50 g. (0.022 g.-atom) of sodium in 8 ml. of absolute ethanol, cooled in an ice–acetone bath and protected with a nitrogen atmosphere was added 5.00 g. (0.022 mole) of diethyl (3-oxobutyl)-malonate (V), b.p. 134–138° (2.5 mm.). The resulting bright yellow mixture was stirred at −10° for 30 min. and then brought to reflux. After 20–30 min. of reflux a precipitate formed in sufficient amount to make the reaction mixture very difficult to stir. This thick slurry was refluxed for 2 hr. longer, then cooled, and partitioned between 25 ml. of saturated sodium chloride solution and 100 ml. of ether. The aqueous layer was acidified with 5 *N* sulfuric acid and extracted with ether. Evaporation of the ether yielded 4.34 g. of yellow, viscous oil, $\lambda_{\max}^{\text{EtOH}}$ 256 mμ (ε 14,300). This oil crystallized in the freezer when triturated with ether to give 2.31 g. (57%) of 4-carboethoxycyclohexane-1,3-dione (II), a colorless solid, m.p. 56–60°. A further 0.90 g., m.p. 50–60°, was isolated from the ether washings, making the total yield 3.21 g. (79%). Recrystallization from ether gave the analytical sample with m.p. 61.5–62.5°; $\lambda_{\max}^{\text{EtOH}}$ 256 mμ (ε 15,000); $\lambda_{\max}^{\text{CHCl}_3}$ 3.8 (broad), 5.77, and 6.2–6.3 μ.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.71; H, 6.64.

Conversion of II to Dihydroresorcinol.—A 0.208-g. (1.14 mmoles) sample of II was stirred for 24 hr. at 25° in 10 ml. of 3 *N* sodium hydroxide solution in a nitrogen atmosphere. The light yellow mixture was cooled, acidified with 5 *N* sulfuric acid, and partioned between 25 ml. of saturated sodium chloride solution and 300 ml. of chloroform. The chloroform was dried and evaporated to yield 0.080 g. (63%) of white solid, m.p. 87–95°. Recrystallization from benzene yielded a sample, m.p. 105–106°, which did not depress the melting point of an authentic sample of III, m.p. 105–106°.

3-Ethoxy-6-carboethoxy-Δ²-cyclohexenone (XIII).—Every time the cyclization of V was repeated, there was formed a mixture of II and, often as the predominant product, the enol ether XIII. For example, on a 5-g. scale, exactly as described above as far as we know, there was obtained a crude oily product which afforded, first, 1.1 g. of material, m.p. 84–87°, and then, from the mother liquors, a smaller amount of II. The ratio of XIII to II in different cyclizations varied and was not determined exactly.

The higher-melting material was recrystallized from ether to afford colorless crystals of XIII, m.p. 98–99°; $\lambda_{\max}^{\text{EtOH}}$ 252 (ε 16,000); $\lambda_{\max}^{\text{CHCl}_3}$ 5.78, 6.06, and 6.24 μ; n.m.r.: singlet at τ 4.7 $(-\overset{|}{\text{C}}=\overset{|}{\text{C}}-H)$, quartets centered at 5.8 and 6.1 (2 $-\text{O}-CH_2\text{-CH}_3$), multiplets at 6.8 $(-\underset{|}{\overset{|}{\text{C}}}-H)$ and 7.6 $(-\text{CH}_2-\text{CH}_2)$, and triplets centered at 8.6 and 8.7 (2 $-\text{O}-\text{CH}_2\text{-}CH_3$).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.22; H, 7.70.

On one occasion a 1-kg. sample of V was cyclized, the crude product was saponified (hopefully to III), and the basic mixture was treated with methyl iodide. Only 30 g. of methyldihydroresorcinol could be isolated from this sequence.

Conversion of XIII to II.—A solution of 2.12 g. (0.010 mole) of XIII in 350 ml. of 1 *N* hydrochloric acid was stirred for 24 hr. at 25° in a nitrogen atmosphere. The mixture was then partitioned between saturated sodium chloride solution and chloroform. Evaporation of the chloroform afforded 1.0 g. of yellow oil which crystallized in the freezer to afford 4-carboethoxycyclohexane-1,3-dione (II), identified by infrared spectrum and melting point. Treatment of XIII with dilute base gave only a very small amount of chloroform-soluble material; no dihydroresorcinol was obtained.

Conversion of XIII to 4-Ethoxysalicylic Acid (XIV).—To a solution of 6.36 g. (0.0300 mole) of enol ether XIII, m.p. 97.5–99.0°, in 125 ml. of reagent grade carbon tetrachloride was added 5.34 g. (0.300 mole) of N-bromosuccinimide. The resulting mixture was refluxed while being illuminated with two 100-watt light bulbs. Hydrogen bromide was evolved during reflux. After 90 min., the original precipitate was completely replaced by supernatant succinimide, which was removed by filtration of the cooled mixture. Evaporation of the filtrate afforded 11 g. of gummy solid residue which was stirred with 300 ml. of 3 *N* sodium hydroxide solution at room temperature for 11 hr., and then the mixture was heated on the steam bath for 2 hr. to complete dissolution of the solid. After being cooled, the reaction mixture was acidified with 3 *N* sulfuric acid, causing formation of a white precipitate, which was collected by filtration. The solid product was dissolved in ether, and the solution was dried over sodium sulfate. Evaporation of the ether afforded 5.20 g. (95%) of tan solid, m.p. 146–149°. This material was recrystallized from benzene to afford 4.51 g. of off-white needles, m.p. 151–153°. Comparison with 4-ethoxysalicylic acid, m.p. 151–153°, prepared by the reaction of resorcylic acid with diethyl sulfate,[12a] showed the two samples to have identical infrared spectra and an undepressed mixture melting point.

Acknowledgment.—This investigation was supported in part by Public Health Service Research Grant AM-05014. The authors are very grateful to Professor Paul R. Shafer who generously obtained the n.m.r. spectra and provided valuable and extensive discussion concerning their interpretation and many other aspects of this work.

---

[14] K. Nakazawa and S. Matsuura, *J. Pharm. Soc. Japan*, **71**, 178 (1951).