these same ketones.[13] The results are seen to be essentially parallel for the two reactions.

While our results for cyclic ketones show the same trends as Wheeler's,[5] it is probably not meaningful to compare our numbers. His equilibrium constants are calculated for the hemiacetal reaction but our results demonstrate that they should be calculated for acetal formation. One cannot recalculate the data for his systems for the acetal equilibrium since the water concentrations for these systems are not known and thus his numbers are of only qualitative value.[3] One should note that whether the reaction involved only hemiacetal or only acetal formation one should expect the results to be parallel for the effects of ring size on equilibria because both involve a change from sp^2 to sp^3 geometries. We would also note a serious calculation error in Wheeler's results in that he used the molecular weights of methanol and of ethanol as the molarity of the alcohol.

Experimental Section

Materials.—Methanol was purified by the method of Lund and Bjerrum.[14] Each portion was distilled (on a column of 30 theoretical plates) until the transmittance was 97% or better when measured against distilled water at 250 mμ before collecting good material. In all cases the water content (Karl Fischer) was less than 0.010% and was usually 0.005% or less.

The ketones used in this study were purified just before use. The sources of the ketones, the purification method, and the observed physical properties have been previously reported[4] except for cyclobutanone, cycloheptanone, and cyclooctanone (these were obtained from Aldrich Chemical Co.). Cyclobutanone was distilled at atmospheric pressure, collecting only a middle cut [bp 96–97° (740 mm); $n^{25}D$ 1.4162; λ_{max}^{MeOH} 282 mμ ε 18.4)]. Cycloheptanone was extracted with dilute sodium bicarbonate solution, dried, and distilled under reduced pressure [$n^{25}D$ 1.4592; λ_{max}^{MeOH} 288 mμ (ε 20.3)]. Cyclooctanone was extracted with dilute sodium bicarbonate and distilled under reduced pressure [bp 70° (10 mm); $n^{25}D$ 1.4658; λ_{max}^{MeOH} 288 mμ (ε 16.5)].

Short-Cell-Path Measurements.—To permit the measurement of the ketone absorbances in concentrated methanol solutions, 1-cm quartz cells with matched quartz inserts were obtained from the Pyrocel Manufacturing Co., New York, N. Y. The inserts were made with two dimensions so that the path lengths could be varied as follows: 0.025, 0.045, 0.075, 0.095, 0.200, and 0.300 mm. The matching of the inserts was excellent and checked within 1% transmittance against each other at 288 mμ. The absolute values of the path lengths listed are not accurate because when the various inserts were used, the extinction coefficients for solutions of cyclohexanone in methanol (the ketone molarity varied from 0.05 to 5.2) varied by more than 20%, whereas for a given insert the variation in ε was less than 2%. For this reason we used the same insert (0.3 mm for all data reported) for a Beer's law check and for the equilibrium mixtures for any given ketone in methanol.

Portions of the ketone and of methanol were weighed into a glass-stoppered flask and the solutions were thoroughly mixed and maintained at 25 ± 0.01° in a constant-temperature bath. For each ketone studied, two to five mixtures were made. Samples of each solution were placed in the short-path cells and the absorbances determined to check Beer's law. One to two microdrops (drawn capillary) of 0.1 *M* hydrogen chloride in methanol were added to the solutions in the flasks which then remained in the constant-temperature bath until the absorbance readings were constant. All absorbances were measured with a Beckman DU spectrophtometer equipped with thermospacers by means of which the temperature could be maintained at 25 ± 0.02°. From 1 to 5 g of ketone with 12–19 g of methanol were used so that the weight of methanol added in the catalyst solution is insignificant. After the equilibrium absorption values were measured at 25°, the temperature of the bath was adjusted to 10 ± 0.02° and the mixtures were allowed to remain for several hours. Portions of each mixture were removed and poured onto solid sodium bicarbonate in a small flask and the mixtures were shaken to neutralize the acid; all operations were conducted as rapidly as possible to ensure that the equilibrium did not change from the values at 10°. After the bicarbonate had settled, a small sample of the solution was used for absorbance readings with the temperature regulated in the DU cell compartment at 25 ± 0.02°. This technique was effective in freezing the equilibrium and no significant drifting of the absorbances were observed over a period of 1 hr or longer. From the measured absorbances, from the weights of the reactants, and from the stoichiometry for acetal formation the mole-fraction equilibrium constants were calculated.

(13) V. Prelog and M. Kobelt, *Helv. Chim. Acta*, **32**, 1187 (1949).
(14) H. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1934).

Preparation of 3-Isopropenylcyclohexanone[1a]

HERBERT O. HOUSE, ROGER A. LATHAM,[1b] AND CARL D. SLATER

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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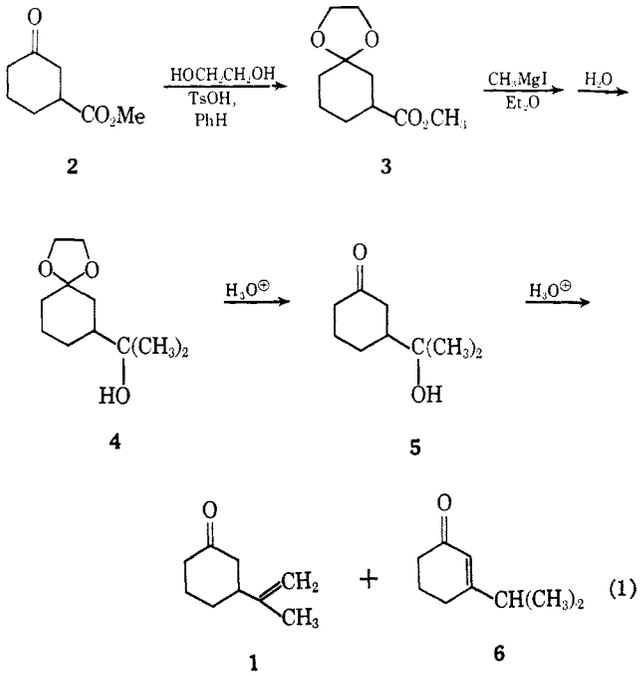
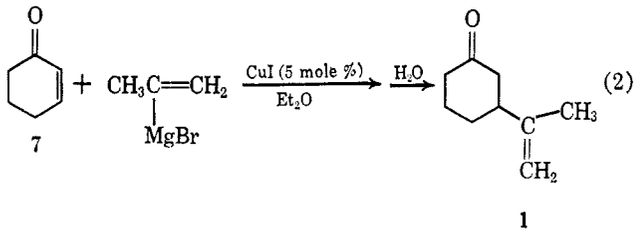
As a model for other synthetic work, we were interested in preparative routes to the isopropenyl ketone **1**. Our initial route illustrated in eq 1 was relatively unsatisfactory both because of the multistep procedure required and because the final acid-catalyzed dehydration step yielded a mixture of the desired ketone **1** and the more stable conjugated ketone **6** which had to be separated. None of the various dehydration methods



(1)

tried with the hydroxy ketal **4** or the keto alcohol **5** avoided this latter problem. Consequently, we were prompted to explore a different route (eq 2), the copper(I) iodide catalyzed addition of isopropenylmagnesium bromide to cyclohexenone (**7**). This route proved to be much more satisfactory, providing the pure un-

(1) (a) This research has been supported by a grant from the National Institutes of Health (No. GM-08761). (b) National Science Foundation Summer Fellow, 1963; Halcon International Predoctoral Fellow, 1963–1964.



7 (2)

1

saturated ketone **1** in 68% yield. This result also illustrates that vinylcopper intermediates, like their alkyl and aryl counterparts,[2] undergo conjugate addition to α,β-unsaturated ketones very efficiently.

Experimental Section[3]

Methyl 3-Ketocyclohexanecarboxylate (2).—Methyl *m*-hydroxybenzoate[4,5] was converted by hydrogenation[6] and subsequent oxidation to the keto ester **2**, bp 104–106° (4.2 mm), $n^{25.3}$D 1.4620 [lit.[7] bp 121–123° (16 mm), n^{24}D 1.4590]. In a more satisfactory procedure, Δ^3-cyclohexenecarboxylic acid[8] was brominated[9] and then treated successively with aqueous sodium carbonate and aqueous sodium hydroxide[10] to give 3-ketocyclohexanecarboxylic acid, bp 140–152° (0.4 mm), mp 72–72.5°, in 74% yield. Esterification yielded the keto ester **2**, bp 131–131.3° (18 mm), n^{26}D 1.4588.

Preparation of the Ketal Ester 3.—A solution of 51.30 g (0.328 mole) of the keto ester **2**, 38 g (0.61 mole) of ethylene glycol, and several milligrams of *p*-toluenesulfonic acid in 20 ml of benzene was refluxed for 5.5 hr with continuous separation of water and then subjected to the usual isolation procedure. Distillation separated 60.27 g (92%) of the ketal ester **3** as a colorless liquid, bp 99–104° (1.2–1.3 mm), $n^{27.5}$D 1.4641. A redistilled sample (n^{26}D 1.4645) was used for analysis. The product has infrared peaks[11] at 1735 (ester C=O), 1093, and 1043 cm^{-1} (ketal CO) with weak end absorption (ϵ 117 at 210 mμ) in the ultraviolet.[12]

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.84; H, 8.07.

Preparation of the Hydroxy Ketal 4.—To an ethereal solution containing 0.25 mole of methylmagnesium iodide was added, dropwise and with stirring over a 20-min period, a solution of 13.66 g (68.3 mmoles) of the ketal ester **3** in 25 ml of ether. The resulting solution was stirred at room temperature for 5 hr and then treated with an aqueous solution (pH ~8) of ammonia and ammonium chloride. The ethereal layer was separated, dried, concentrated, and distilled to yield 8.249 g (60%) of the hydroxy ketal **4**, bp 74.5–75.5° (0.10–0.15 mm), $n^{28.5}$D 1.4810, which was contaminated[13] with approximately 4% of the keto alcohol **5** (eluted after the ketal **4**). Redistillation afforded the pure[13] ketal **4**, bp 71° (0.05 mm), n^{26}D 1.4818, with infrared absorption[11] at 3610 (unassociated OH), 3480 (associated OH), 1080 and 1035 cm^{-1} (ketal CO). The product has nmr peaks[11] at δ 3.92 (4 H, CH_2O), 2.09 (1 H, OH, position shifted with added pyridine), and 1.13 (6 H, broad, $(CH_3)_2C$) as well as a multiplet in the region δ 1.2–2.0 (9 H, aliphatic CH).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.94; H, 10.13.

Preparation of the Hydroxy Ketone 5.—A solution of the crude hydroxy ketal **4**, obtained from 31.0 g (0.155 mole) of the ketal ester **3**, in 300 ml of chloroform was stirred with 150 ml of aqueous 1 *M* hydrochloric acid for 3 hr and then the organic layer was separated and combined with the chloroform extract of the aqueous phase. The combined organic solutions were washed with aqueous sodium bicarbonate, dried, concentrated, and distilled to separate 10.26 g of yellow liquid, bp 90–94° (0.1 mm), n^{25}D 1.4820, containing[14] primarily the hydroxy ketone **5** accompanied by small amounts of the ketal **4**, the unsaturated ketones **1** and **6**, and an unidentified lower boiling material. A series of fractional distillations separated a fraction, bp 147.5–148° (15 mm), n^{26}D 1.4812, containing[14] 95% of the hydroxy ketone **5** and 5% of the ketal **4** which was used for characterization. This product has infrared absorption[11] at 3610 and 3460 cm^{-1} (unassociated and associated OH) as well as a peak at 1715 cm^{-1} (C=O); the nmr spectrum[11] has singlets at δ 2.83 (1 H, OH, shifted by the addition of pyridine) and 1.17 (6 H, $(CH_3)_2C<$) as well as a complex multiplet in the region δ 1.2–2.6 (aliphatic CH).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.91; H, 10.32.

Dehydration of the Hydroxy Ketal 4. A. Acid Catalysis.—The crude hydroxy ketal **4** obtained from reaction of 20.01 g (0.100 mole) of the ester **3** with excess methylmagnesium iodide was mixed with 50 ml of ethanol and 25 ml of aqueous 6 *M* hydrochloric acid. After the mixture had been refluxed for 1.25 hr, it was cooled, diluted with ether, washed with saturated aqueous sodium chloride, dried, and concentrated. Distillation of the residue afforded 9.68 g of fractions, bp 101–113° (19 mm), which contained[15] two major components, ketones **1** (first eluted) and **6** (second eluted), in approximately equal amounts. Samples of each pure ketone were collected[15] for characterization. The **3-isopropenylcyclohexanone (1)** has infrared absorption[11] at 1710 (C=O) and 1645 cm^{-1} (weak, C=C) with an ultraviolet maximum[14] at 278 mμ (ϵ 33). The nmr spectrum[11] of the material has partially resolved multiplets centered at δ 4.68 (2 H, $>C=CH_2$, an AB pattern with further splitting) and 1.73 (3 H, $CH_3C=C<$) as well as a broad multiplet in the region δ 1.3–2.6 (aliphatic CH). The mass spectrum of the material has a molecular ion peak at *m/e* 138 with abundant fragment peaks at *m/e* 95, 81, 68, 67, 55, 42, 41, and 39.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.25; H, 10.28.

A collected[15] sample of **3-isopropyl-2-cyclohexen-1-one (6)**[16] has infrared absorption[11] at 1670 (conjugated C=O) and 1620 cm^{-1} (conjugated C=C) with an ultraviolet maximum[12] at 235 mμ (ϵ 14,900) and nmr peaks[11] at δ 5.87 (1 H, partially resolved multiplet, vinyl CH) and 1.16 (6 H, doublet with J = 7 cps, CH_3C) as well as a complex multiplet in the region δ 1.5–2.7 (aliphatic CH). The mass spectrum of the sample has a molecular ion peak at *m/e* 138 with relatively abundant fragment peaks at *m/e* 110, 95, 67, 41, and 39.

In subsequent experiments, the crude product was fractionally distilled to separate early fractions, bp 92–93° (16 mm), $n^{24.3}$D 1.4751, containing[15] 97% of the unconjugated ketone **1**, and final fractions, bp 100–102° (16 mm), $n^{24.3}$D 1.4864, containing 89% of the conjugated ketone **6**. After a mixture of approximately equal amounts of the two ketones **1** and **6** had been refluxed for 3 hr with a mixture of ether and aqueous 6 *M* hydrochloric acid, the recovered ketone mixture contained[14] approximately 90% of the conjugated isomer **6**.

(2) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, in press.

(3) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer, Model 237, infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The nmr spectra were determined at 60 Mc with a Varian, Model A-60, nmr spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by Scandinavian Microanalytical Laboratory.

(4) H. E. Ungnade and A. S. Henick, *J. Am. Chem. Soc.*, **64**, 1737 (1942).

(5) L. A. Duncanson, J. F. Grove, and J. Zealley, *J. Chem. Soc.*, 1331 (1953).

(6) (a) W. J. Bailey and R. Baylouny, *J. Am. Chem. Soc.*, **81**, 2126 (1959); (b) H. Goering and C. Serres, Jr., *ibid.*, **74**, 5908 (1952).

(7) D. K. Banerjee, J. Dutta, and G. Bagavant, *Proc. Indian Acad. Sci.*, **46A**, 80 (1957).

(8) F. X. Werber, J. E. Jansen, and T. L. Gresham, *J. Am. Chem. Soc.*, **74**, 532 (1952).

(9) W. H. Perkin, Jr., and G. Tattersall, *J. Chem. Soc.*, **91**, 480 (1907).

(10) R. Grewe, A. Heinke, and C. Sommer, *Chem. Ber.*, **89**, 1978 (1956).

(11) Determined as a solution in carbon tetrachloride.

(12) Determined as a solution in 95% ethanol.

(13) A gas chromatography column packed with silicone XE-60 suspended on base-washed Chromosorb W was employed for this analysis.

(14) A gas chromatography column packed with Carbowax 20M suspended on ground firebrick was employed for this analysis.

(15) A gas chromatography column packed with silicone fluid, no. 710, suspended on ground firebrick was employed for this analysis.

(16) Previous descriptions of this ketone are given by (a) M. Sharma, U. R. Ghatak, and P. C. Dutta [*Tetrahedron*, **19**, 985 (1963)], who report bp 80–90° (6–7 mm); (b) G. S. K. Rao and S. Dev [*J. Indian Chem. Soc.*, **33**, 539 (1956)], who report bp 112–113° (20 mm), $n^{27.5}$D 1.4845, λ_{max} 235 mμ (ϵ 10,000); and (c) G. F. Woods, P. H. Griswold, Jr., B. H. Armbrecht, D. I. Blumenthal, and R. Plapinger [*J. Am. Chem. Soc.*, **71**, 2028 (1949)], who report bp 59–60° (0.3 mm), nD 1.4842.

B. With Phosphorus Oxychloride and Pyridine.—To a solution of 3.0 ml (5.02 g or 33 mmoles) of phosphorus oxychloride in 50 ml of anhydrous pyridine was added 8.287 g (41.4 mmoles) of the hydroxy ketal **4**. After the reaction mixture had been heated on a steam bath for 1 hr, it was diluted with 10 ml of water and extracted successively with ether and with chloroform. The combined organic extracts were washed with dilute, aqueous hydrochloric acid and with aqueous sodium bicarbonate. After the organic phase had been dried and concentrated, the residual yellow liquid (10.44 g containing[14] three components believed to be ketones **1** and **6** and the ethylene ketal of ketone **1**) was diluted with 100 ml of chloroform and stirred at room temperature with 50 ml of aqueous 6 *M* hydrochloric acid for 24 hr. The chloroform layer was separated, combined with the chloroform extract of the aqueous phase, washed with aqueous sodium bicarbonate, dried, concentrated, and distilled to separate 4.699 g of pale yellow liquid, bp 83–100° (14 mm), which contained[14] the unconjugated ketone **1** (64%, eluted first), the conjugated ketone (31%, eluted third), and a minor, unknown component (5%, eluted second) thought to be the ethylene ketal of ketone **1**. The infrared and nmr spectra of this mixture are fully consistent with this composition. The product mixture from this reaction was combined with a comparable mixture from another reaction (total weight 11.25 g) and fractionally distilled to separate 2.83 g of the pure unconjugated ketone **1**, bp 78–79° (18 mm), $n^{22.5}$D 1.4756–1.4767.

***cis*-3-(2-Hydroxy-2-propyl)cyclohexanol.**—An ethereal solution containing 0.80 mole of methylmagnesium iodide was treated with 10.0 g (0.0794 mole) of the lactone of *cis*-3-hydroxycyclohexanecarboxylic acid.[17] After the reaction mixture had been stirred for 20 hr, it was hydrolyzed with an aqueous solution (pH ~8) of ammonia and ammonium chloride. The ethereal layer was combined with the ethereal extract of the aqueous phase and this organic solution was dried, concentrated, and distilled to separate 8.062 g of viscous liquid, bp 85–108° (0.05 mm), which crystallized on standing. Recrystallization from a carbon disulfide–ether mixture afforded 2.532 g of pure ***cis*-3-(2-hydroxy-2-propyl)cyclohexanol** as white prisms, mp 90.5–91°. The product has infrared absorption[18] at 3600 and 3440 cm^{-1} (unassociated and associated OH) with broad nmr peaks[19] in the regions δ 3.3–4.0 (1 H, >CHO) and 0.9–2.8 (aliphatic CH) as well as a singlet at 1.22 (6 H, CH_3C). The mass spectrum exhibits no molecular ion peak (the highest fragment peak is at *m/e* 125) but has relatively abundant fragment peaks at *m/e* 82, 67, 59, and 43.

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.11; H, 11.35.

Preparation of 3-Isopropenylcyclohexanone (1) from 2-Cyclohexen-1-one.—Commercial 2-bromopropene[20] was washed successively with aqueous sodium sulfite and with aqueous sodium bicarbonate, then dried over calcium sulfate, and fractionally distilled to give the bromo olefin, bp 48.6–49.0.[21] The reaction of this bromide with magnesium was initiated by adding a few drops of the alkenyl halide to a mixture of 3.65 g (0.15 g-atom) of magnesium, 100 ml of tetrahydrofuran, and a crystal of iodine.[22] Then a total of 24.90 g (0.21 mole) of 2-bromopropene in 40 ml of tetrahydrofuran was added over a 1.5-hr period; the reaction mixture was then refluxed for 15 min at which time all the magnesium had been consumed. The solution was diluted with 100 ml of tetrahydrofuran (to prevent precipitation of the reagent at 0°) and cooled to 0°; then 1.4 g (0.0074 mole, 5 mole % based on the magnesium employed) of anhydrous cuprous iodide was added. Although a transient yellow color (*cf.* ref 2) was observed during this addition, the final cold solution was essentially black in color presumably because of the presence of colloidal metal particles. A solution of 6.80 g (0.071 mole) of 2-cyclohexen-1-one in 50 ml of tetrahydrofuran was added, dropwise and with stirring over a 20-min period, to the cold (0°) organometallic solution, and the resulting mixture was stirred at 0° for 1 additional hr. The reaction mixture was then added to a cold (0°) aqueous solution (pH ~8) of ammonia and ammonium chloride and the organic layer was separated and combined with the ethereal extract of the aqueous phase. The combined organic solutions were dried, concentrated, and distilled in a short-path still. Fractional distillation of this product (which contained[14] the ketone **1** and low-boiling impurities) afforded 6.616 g (68%) of fractions, bp 80.5–84° (8 mm), n^{26}D 1.4743–1.4749, which contained[14] more than 97% of 3-isopropenylcyclohexanone (**1**). This product was identified with the previously described sample by comparison of infrared spectra and gas chromatographic retention times.

(17) The preparation of this lactone was described previously; see ref 10 and H. O. House, H. Babad, R. B. Toothill, and A. W. Noltes, *J. Org. Chem.*, **27**, 4141 (1962).

(18) Determined as a solution in chloroform.

(19) Determined as a solution in deuteriochloroform.

(20) Columbia Organic Chemicals Co., Inc., Columbia, S. C.

(21) (a) The commercial material contained[15] (in order of increasing retention times) an unidentified low-boiling component (2%), 2-bromopropene (60%), *cis*-1-bromopropene (26%), *trans*-1-bromopropene (11%), and 3-bromopropene (2%). The 2-bromopropene utilized in this experiment was approximately 96% pure.[15] (b) E. A. Braude and E. A. Evans [*J. Chem. Soc.*, 3333 (1956)] report bp 48°. (c) K. E. Harwell and L. F. Hatch [*J. Am. Chem. Soc.*, **77**, 1682 (1955)] report bp 47° (745 mm.).

(22) The general procedure of H. Normant, *Advan. Org. Chem.*, **2**, 1 (1960).

The Nentizescu Condensation of Ethyl 3-Aminocrotonate and 1,4-Benzoquinone[1]

S. A. MONTI

Department of Chemistry, Michigan State University, East Lansing, Michigan 48823

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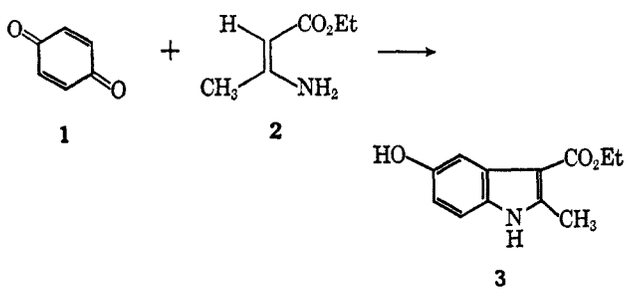
A general synthetic route to the 5-hydroxyindole nucleus, first described by Nenitzescu,[2,3] involves the condensation of a 1,4-benzoquinone with an appropriate 3-aminocrotonate as illustrated below for the preparation of 2-methyl-3-carbethoxy-5-hydroxyindole (**3**). Our interest in the construction of various indole skeletons, in particular those bearing a free hydroxyl group at C-5,[4] led us to investigate this reaction.



1 **2** **3**

Two products crystallized directly from the reaction of 1,4-benzoquinone (**1**) and excess ethyl 3-aminocrotonate (**2**) in refluxing dichloroethane. One component was identified as hydroquinone by comparison with authentic material. The other material, mp 200–201°, showed infrared absorptions anticipated for ethyl 2-methyl-3-carbethoxy-5-hydroxyindole (**3**). This assignment was confirmed by an nmr spectrum which verified the presence of an ethyl ester, a singlet methyl group at C-2, and three aromatic protons whose split-

(1) Partial support of this work by the Petroleum Research Fund (196-G) and by the Michigan State All-University Fund is gratefully acknowledged.

(2) C. D. Nenitzescu, *Bull. Soc. Chim. Romania*, **11**, 37 (1929); *Chem. Abstr.*, **24**, 1108 (1930).

(3) This reaction has subsequently been investigated by a number of workers: (a) R. J. S. Beer, K. Clark, H. F. Davenport, and A. Robertson, *J. Chem. Soc.*, 2029 (1951); (b) R. J. S. Beer, K. Clark, and A. Robertson, *ibid.*, 1262 (1953); (c) H.-J. Teuber and G. Thaler, *Chem. Ber.*, **91**, 2253 (1958); (d) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Org. Chem.*, **24**, 1750 (1959); (e) G. Domschke and J. Furst, *Chem. Ber.*, **92**, 3244 (1959); (f) A. N. Grinev, V. N. Ermakova, E. Vrotek, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **29**, 2777 (1959); *Chem. Abstr.*, **54**, 10992e (1960), and preceding papers.

(4) Several naturally occurring 5-hydroxyindole bases show pronounced pharmacological activity: *cf.* R. H. F. Manske, "The Alkaloids," Vol. VIII, Academic Press Inc., New York, N. Y., 1965, pp 12–19.