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Restricted Rotation in Aromatic Ketones. I. Substituent Effects on the Barrier to Rotation about the Benzene-to-Carbonyl Bond[1)]

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Several aryl isopropyl ketones and aryl benzyl ketones were synthesized and their NMR spectra were recorded at various temperatures. Their temperature dependence was accounted for in terms of the restricted rotation about the benzene-to-carbonyl bond, whose free energies of activation at the coalescence temperatures varied from 9 to 15 kcal/mol according to the steric effect of ortho substituents, the buttressing effect of meta substituents, and the steric effect of the side-chain groups.

Nuclear magnetic resonance spectroscopy has proved to be a powerful and convenient tool for the study of the relatively slow internal rotations, the representative being the PMR spectroscopic studies on amides, biphenyls, aromatic aldehydes, and diazoketones.[2)]

When the torsional process is slow enough and if the process produces the mirror images, there should exist a pair of optical antipodes even at the room temperature. Thus many successful results are to be seen in the resolution into the stable atropisomers whose pivot bonds are the sp^2-sp^2 hybridized. However, no example for which carbonyl carbon is involved as a carbon of sp^2-hybridization has been claimed to be resolved,[3)] though carbonyl group has been the subject of a large number of studies in organic chemistry because of its variety of reactions and reactivities.

The concept and the continuous interest in the torsional stereoisomerism led us to explore to what extent the rotation about the benzene-to-carbonyl bond could be hindered by the ortho substituents and to estimate whether the stable rotational isomers could be isolated at room temperature.

We now wish to report our results about the steric effects on the barrier to rotation about the benzene-to-carbonyl bond in some aromatic ketones using the

1) A part of this article was presented at the 21st anual meeting of the Chemical Society of Japan, Osaka, 1968.

2) a) M. T. Rogers and J. C. Woodbrey, *J. Phys. Chem.*, **66**, 540 (1962). b) W. L. Meyer and R. B. Meyer, *J. Amer. Chem. Soc.*, **85**, 2170 (1963). c) F. A. L. Anet and M. Ahmad, *ibid.*, **86**, 119 (1964). d) F. Kaplan and G. K. Meloy, *Tetrahedron Lett.*, **1964**, 2427. F. Kaplan and G. K. Meloy, *J. Amer. Chem. Soc.*, **88**, 950 (1966). e) N. Nakamura, *Kagaku no Ryoiki*, **23**, 154 (1969); N. Nakamura, *ibid.*, **23**, 262 (1969); H. Kessler, *Angew. Chem.*, **82**, 237 (1970).

3) During the course of our study, the cinchonine salt of *t*-butyl 3-carboxy-2,4,6-trimethylphenyl ketone was reported to exibit a mutarotation in solution, and the half-life time of the reacmization of the ketone was estimated to be 6.2 min at 0°C. See A. G. Pinkus, J. I. Riggs, Jr., and S. M. Broughton, *J. Amer. Chem. Soc.*, **90**, 5043 (1968).

variable temperature NMR technique which does not need the prior optical resolution.

It is well known that in *o*-substituted and *o,o'*-disubstituted aromatic ketones carbonyl group is not coplanar with the benzene ring at the ground state as a consequence of the steric requirements. When the rotation in question is sufficiently restricted, there should result the following two conformers A and $\bar{A}$, the latter being the mirror image of the former when X and Y are different from the each other.

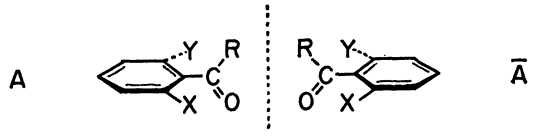


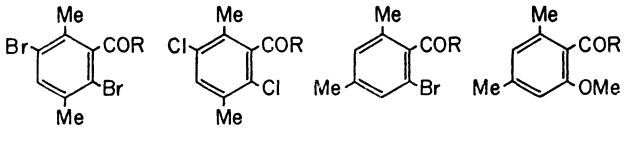
Fig. 1. Conformations of 2,6-disubstituted phenyl ketone.

Then, if R carries a methylene group or geminal methyl groups, the nonequivalence of the protons concerned is expected as in the case of a biphenyl[2] and an ansanoid compound.[4] Thus isopropyl and benzyl groups were chosen for the side chain groups for the convenience of the synthesis. If the coalescence or the change in line-shapes of these signals is observed in the NMR spectra, it should be possible to derive the kinetic data involving the internal rotation.

As for X and Y, they should provide magnetic environments of large difference in order to facilitate the distinguishing of the enantiomeric protons. Thus methyl, chlorine, bromine or methoxy groups were used in this study.

Syntheses

The following six compounds were prepared by the routes shown in the scheme 1.



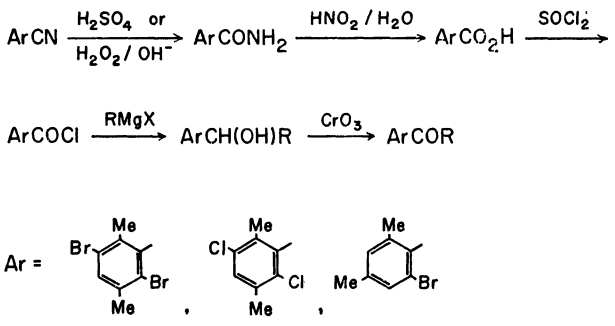
Ia,b IIa IIIa IVa,b

a, R = $CH(CH_3)_2$; b, R = CH_2Ph

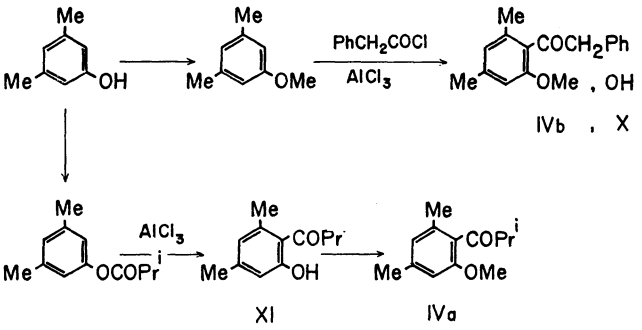
The appropriate nitriles which had been obtained by the several steps were hydrolysed in two steps to afford in relatively high yields the corresponding carboxylic acids, which were then converted to the acid chlorides by the action of thionyl chloride.

Treatment of the acid chloride with an ethereal solution of excess of isopropylmagnesium bromide gave after one distillation a mixture of the desired ketone and the corresponding secondary alcohol in a molar ratio of about 1 : 3 as clarified by vpc analysis. This mixture was oxidized with chromic acid in aqueous acetic acid at 0°C, and the oxidation product was purified by distillation and/or column chromatography on silica gel to give Ia, Ib, IIa, and IIIa.

4) M. Nakazaki, K. Yamamoto, and S. Okamoto, *Tetrahedron Lett.*, **1969**, 4597.



Scheme 1.



Scheme 2.

3,5-Xylenol was converted to the isobutyrate, which was treated with anhydrous aluminum chloride without solvent to rearrange to the phenolic ketone. The latter was then methylated to afford IVa. IVb was prepared by the Friedel-Crafts reaction of 3,5-dimethylanisol with phenylacetyl chloride in the presence of aluminum chloride (see Scheme 2).

Results

The NMR spectra of Ia in carbon tetrachloride, benzene, and pyridine were recorded at the ambient temperature, and the results were summarized in Table 1.

The methyl groups of isopropyl residue appeared as a sharp doublet (J=7 Hz, half-width 1.5 Hz) in carbon tetrachloride. However, when the solvent was changed to benzene and further to pyridine, the signals of isopropyl-methyl groups decreased in their heights, whose values relative to the methyl group attached directly to the aromatic ring were 1.0 in carbon tetrachloride, 0.54 in benzene, and 0.48 in pyridine. These figures apparently indicated that there were the chemical-shift differences between two methyl groups of the isopropyl-side-chain. That is, the rotation about the benzene-to-carbonyl bond was relatively slow on NMR time scale.

When the temperature of the pyridine solution was lowered to 18—20°C, the signal changed in its appearance to a single broad peak, which split into four peaks on further cooling and finally into the two sets of doublets at −35°C, the chemical-shift difference and the coupling constant being 13.5 Hz and 7.1 Hz, respectively. On the contrary, the signal increased in its height as the temperature was raised and at

Table 1. NMR Spectra of Ia in three solvents[a)]

Solvent	Chemical-shift[b)]			Peak-height Ratio (1/2)
	$CH(C\underline{H}_3)_2\cdots 1$	$C\underline{H}(CH_3)_2$	$Ar\text{–}C\underline{H}_3\cdots 2$	
CCl_4	1.19^{d}	3.07^{sep}	2.21^{s}, 2.37^{s}	1.0
C_6H_6	1.03^{d}	2.88^{sep}	1.88^{s}, 2.07^{s}	0.54
C_5H_5N	1.16^{d}	3.12^{sep}	2.24^{s}	0.48

a) The spectra were taken at 23°C in about 10% soln.
b) δ in ppm unit from TMS as an internal standard. d, sep, and s refer to doublet, septet and singlet, respectively.

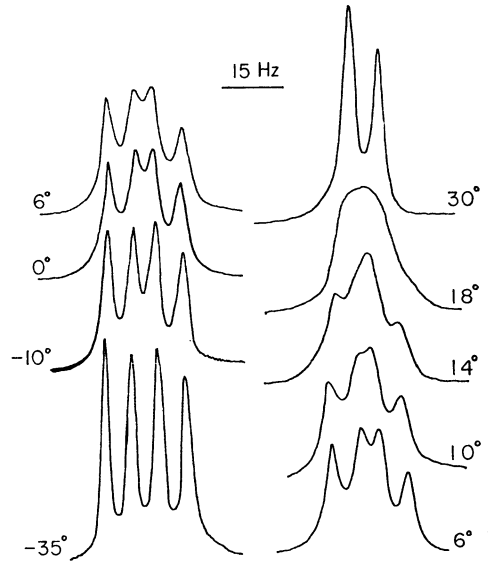


Fig. 2. Methyl signals of isopropyl group at various temperatures.

last a sharp doublet resulted at 60°C.

From these temperature dependence of the spectra shown in Fig. 2, the rates and free energies of activation for rotation were evaluated using the following approximation methods.[5)] For the isopropyl ketones, the approximate rates k_c at the coalescence temperatures T_c were calculated by

$$k_c = \frac{\pi\delta\nu}{\sqrt{2}} \quad (1)$$

and the free energies of activation by

$$\Delta G_c^{\ddagger} = 4.57\,T_c\left(9.97+\log_{10}\frac{T_c}{\delta\nu}\right) \quad (2)$$

whereas for the benzyl ketones, k_c and $\Delta G_c^{\ddagger}$ at T_c were calculated by

$$k_c = \frac{\pi\sqrt{\delta\nu^2+6J^2}}{\sqrt{2}} \quad (3)$$

and

$$\Delta G_c^{\ddagger} = 4.57\,T_c\left(9.97+\log_{10}\frac{T_c}{\sqrt{\delta\nu^2+6J^2}}\right) \quad (4)$$

The variable-temperature spectra of the other compounds were also taken and the results together with those of Ia were sammarized in Tables 2 and 3.

In each case, the coalescence temperature for the isopropyl ketone was assigned to the temperature at which a single broad peak was observed ($\delta\nu > J_{CH_3CH}$) or at which two broad peaks were observed ($\delta\nu < J_{CH_3CH}$).

As the chemical-shift difference of the two methyls in IIIa could not obtained experimentally, $\delta\nu$ of 13.5 Hz was assumed for IIIa because the free energy of activation at the coalescence temperature was mainly decided by the T_c value as shown in Eq. (2), and because the two ortho substituents of IIIa were the same as those of Ia, for which $\delta\nu$ of 13.5 Hz had been obtained experimentally. Substitution of $T_c=-77$°C and $\delta\nu=13.5$ Hz in Eq. (2) gave the $\Delta G_c^{\ddagger}$ value of 10 kcal/mol for IIIa. Similarly, the free energy of activation for IVa was estimated to be about 9 kcal/mol at the experimental coalescence temperature of −95°C, the same chemical-shift difference and coupling constant being assumed for compound IVb with those of Ib.

Discussion

Comparison of the free energies of activation gives the following sequence in the decreasing order:

Ia > IIa—Ib > IIIa > IVa—IVb

The free energies of activation of the ketones studied here are equal or greater than those of benzaldehyde studied by Anet. This fact is apparently ascribed to the steric effects of the ortho substituents and side chain. When Ia is compared with IIIa, that is, when the compounds with the same pair of substituents at 2,6-positions but with the different substitution patterns, the former being 2,3,5,6-tetrasubstituted and the latter 2,4,6-trisubstituted, are compared with each other, the barrier to rotation in the former is greater than that in the latter by 5 kcal/mol.

This surprisingly large value can be best accounted for by the idea that the buttressing effect of the meta substituents is operating substantially in Ia. Such an effect is well known especially for biphenyl derivatives, where 10—2000 times of the slow-down effect on the rate of racemization are reported.[6)]

5) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance", McGraw-Hill Book Co., Inc., New York (1959); J. W. Emsley, J. Feeney, and L. H. Sutcliff, "High Resolution Nuclear Magnetic Resonance Spectroscopy", Pergamon Press (1965).

6) L. N. Ferguson, "The Modern Structural Theory of Organic Chemistry", Japanese language ed., Tokyo Kagaku Dojin, Tokyo (1965), p. 286. See also M. Rieger and F. H. Westheimer, *J. Amer. Chem. Soc.*, **72**, 19 (1950), where about 10^5 times of the slow-down effect of the 5,5′-diiodo substituents on the racemization of 3,3′-dicarboxy-5,5′,6,6′-tetraiodobiphenyl is reported. This effect corresponds to the about 7 kcal/mol difference of the free energies of activation.

Table 2. NMR Parameters and free energies of activation for rotation

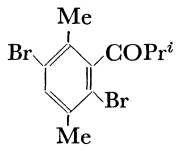
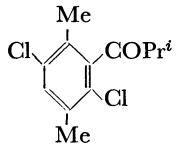
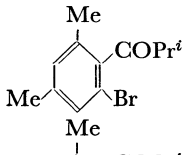
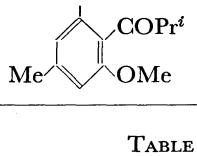
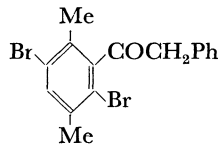
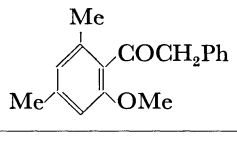
Compound	Solvent	T_c, °C	$\delta\nu$, Hz	$\Delta G_c^{\neq}$, kcal/mol	k_c, sec^{-1}
	C_5H_5N	20	13.5	15.0±0.2	30
	$(CD_3)_2CO$	−3	4.8	14.5±0.2	11
	$(CD_3)_2CO$	−40	3.6	12.5±0.2	11
	C_5H_5N–CS_2	−77	13.5	10.1	—
	$(CD_3)_2CO$	−73	4.8		—
	C_5H_5N–CS_2	−95	13.5	9.0	—

Table 3. NMR Parameters and free energies of activation for rotation

Compound	Solvent	T_c,°C	$\delta\nu$, Hz	J, Hz	$\Delta G_c^{\neq}$, kcal/mol	k_c, sec^{-1}
	C_5H_5N–CS_2	−27	7.9	9.0	12.4±0.2	52
	C_5H_5N–CS_2	−95	7.9	9.0	8.8	—

Comparison of the data of Ia and IIa gives the difference of the barriers by 2.5 kcal/mol, which clearly shows the effectiveness of the steric hindrance, the former having a larger substituent in an ortho position than the latter.[7]

The difference between IIIa and VIa is much lesser than that expected from the ground of van der Waals' radii. However, it may be necessary to obtain more accurate data to discuss the similarness or dissimilarness of the steric effect of the substituents in detail.

The steric effect of the side-chain groups may be also shown when Ia and Ib are compared. The magnitude of the difference in this case amounts to *ca.* 2.5 kcal/mol to indicate that the side-chain group is also involved in slowing down the rotation about the benzene-to-carbonyl bond.[8] It is, of course, understandable if the coplanar transition state for rotation is assumed, where the steric interference between the ortho substituents and the side-chain is playing the main role in determining the energy barrier.

Experimental

NMR spectra were recorded on either a Jeol Model JNM-C-60H, or a HITACHI Model R-20B spectrometer both operating at 60 MHz. Samples were run as dilute solutions in an apropriate solvent indicated using TMS as an internal reference. Chemical shifts are recorded as parts per million downfield from TMS on the δ scale. Sample temperatures were measured and calibrated by the chemical shift differences between the hydroxyl protons and the methylene protons of ethylene glycol for the higher temperatures, or by those between the hydroxyl proton and the methyl protons of methanol for the lower temperatures. IR spectra were taken with a HITACHI Model G-2 grating spectrophotometer. The purities of the oily final compounds were checked by analytical vpc using a Shimadzu GC-4APF gas chromatograph equipped with flame ionization detectors using nitrogen as carrier gas, the flow rate of which was set to 40 ml/min. Glass tubing columns, designed for on-column injection, 2 m in length and 3 mm of inner diameter, and packed with 10% SE-52 on Diasolid M of 60—80 mesh, were used. Melting points are uncorrected.

7) The van der Waals radii of bromine, chlorine and methyl groups are 1.95, 1.80, and 2.0 Å, respectively. L. Pauling, "Nature of the Chemical Bond", 3rd ed., Cornel U. P., Ithaca, N. Y. (1960), pp. 260, 263. The bond lengths of C(sp^3)–Br and C(sp^2)–Cl are 1.875 and 1.711 Å, respectively. M. G. Brown, *Trans. Faraday Soc.*, **55**, 694 (1959).

8) Slow-down of the internal rotation of amides due to the side-chain groups has been also reported. See A. Mannschreck, *Tetrahedron Lett.*, **1965**, 1341.

2,5-Dibromo-3,6-dimethylbenzonitrile (V). *(a)*: Diazotization of 2,5-Dibromo-3,6-dimethylaniline. To a solution of 42 g of the aniline in 360 m*l* of ethanol, 36 m*l* of concentrated sulfuric acid was added dropwise below 0°C, and the mixture was cooled to −10°C. To this mixture 20.5 g of butyl nitrite was added with vigorous stirring over a period of 30 min and the stirring was continued at this temperature for an additional 1 hr, at the end of which time 180 m*l* of cold ether was added and the mixture was stirred for 30 min to complete the separation of solid. The diazonium sulfate was collected on a glass filter, washed with cold anhydrous ethanol and finally dissolved in ice-water.

(b): The Sandmeyer Reaction. To a cuprous cyanide solution obtained from 100 g of cupric sulfate according to the standard method, the diazonium salt solution prepared in (*a*) was added slowly with vigorous stirring. The stirring was continued for 10 hr at room temperature and then at 50°C for 2 hr. After cooling, the organic layer was separated, washed with water, and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the crystalline residue was recrystallized from ethanol to yield 20.5 g (47% of the theoretical) of the desired product, mp 123°C.

Found: C, 37.20; H, 2.44; N, 4.85%. Calcd for $C_9H_7Br_2N$: C, 37.40; H, 2.88; N, 4.64%.

2,5-Dichloro-3,6-dimethylbenzonitrile (VII). VII was prepared in a similar way as described for (V), mp 109.5—111.0°C.

Found: C, 53.84; H, 3.81; N, 6.82%. Calcd for $C_9H_7Cl_2N$: C, 54.03; H, 3.53; N, 7.00%.

2,5-Dibromo-3,6-dimethylbenzoic Acid (VI). A mixture of 5.0 g of 2,5-dibromo-3,6-dimethylbenzonitrile, 10 m*l* of water and 30 m*l* of concentrated sulfuric acid was heated at 160°C for 1 hr, cooled to room temperature, and poured into 70 m*l* of cold water. The resulting solid was collected and recrystallized from ethanol to yield 3.0 g of 2,5-dibromo-3,6-dimethylbenzamide, mp 214—217°C. The half of the amide was dissolved in dilute sulfuric acid (obtained from 15 g of concentrated sulfuric acid and 7.6 g of water) and treated with 1 g of sodium nitrite in 1.5 m*l* of water at 0°C. The mixture was then maintained at 80—90°C for 10 min and again cooled to 0°C. The carboxylic acid was collected and dissolved in sodium bicarbonate solution, which was then acidified to give 1.3 g of the desired compound, mp 160°C. NMR ($CDCl_3$): 2.42 (3H, singlet), 2.49 (3H, singlet), 7.53 (1H, singlet), 9.08 (1H, singlet).

Found: C, 34.97; H, 2.40; Br, 52.56%. Calcd for $C_9H_8Br_2O_2$: C, 35.10; H, 2.62; Br, 51.89%.

6-Bromo-2,4-dimethylbenzoic Acid (IX). Starting from 2.5 g of 6-bromo-2,4-dimethylbenzonitrile,[9] 1.9 g of 6-bromo-2,4-dimethylbenzamide, mp 178—180°C, was obtained in a similar way as described for (VI). IR (Nujol): $\nu_{N=H}$ 3400, 3170 cm^{-1}, $\nu_{C=O}$ 1690 cm^{-1}. NMR ($CDCl_3$): 2.27 (3H, singlet), 2.33 (3H, singlet), 5.96 (1H, singlet), 6.48 (1H, singlet), 6.92 (1H, singlet), 7.15 (1H, singlet).

A mixture of 1.5 g of the amide, 14 g of concentrated sulfuric acid, and 7.6 g of water was treated with 1 g of sodium nitrite in 2 m*l* of water as described for (VI) to yield 1.3 g of the carboxylic acid, mp 153—155°C. IR (Nujol): $\nu_{C=O}$ 1700 cm^{-1}. NMR ($CDCl_3$): 2.27 (3H, singlet), 2.38 (3H. singlet), 6.93 (1H, singlet), 7.20 (1H, singlet), 9.64 (1H, singlet).

Found: C, 47.06; H, 4.16; Br, 35.21%. Calcd for $C_9H_9BrO_2$: C, 47.19; H, 3.96; Br, 34.88%.

2,5-Dichloro-3,6-dimethylbenzoic Acid (VIII). To a solution of 10 g of 2,5-dichloro-3,6-dimethylbenzonitrile in 140 m*l* of 95% ethanol, 4 m*l* of 6N sodium hydroxide solution was added followed by 60 m*l* of 30% hydrogen peroxide solution at 50°C. After heating for 2 hr at 50°C, the reaction mixture was neutralized with 5% sulfuric acid and diluted with water. The precipitated amide was collected, dissolved in 50% (v/v) sulfuric acid and treated with a saturated sodium nitrite solution as described for (VI). Yield 7 g, mp 145.5—148.0°C. NMR ($CDCl_3$): 3.31 (3H, singlet), 3.37 (3H, singlet), 7.26 (1H, singlet), 9.22 (1H, singlet). For the elemental analysis, the acid was methylated with diazomethane to the corresponding methyl ester, mp 36.5—37.0°C. NMR ($CDCl_3$): 2.28 (3H, singlet), 3.31 (3H, singlet), 3.94 (3H, singlet), 7.27 (1H, singlet).

Found: C, 51.37; H, 4.27; Cl, 30.62%. Calcd for $C_{10}H_{10}Cl_2O_2$: C, 51.53; H, 4.32; Cl, 30.42%.

2,5-Dibromo-3,6-dimethylphenyl Isopropyl Ketone (Ia). To an ethereal solution of isopropyl magnesium bromide prepared from 21 g of isopropyl bromide, 4.0 g of magnesium ribbon, and 70 m*l* of anhydrous ether under nitrogen atmosphere, a solution of 2,5-dibromo-3,6-dimethylbenzoyl chloride in anhydrous ether, prepared from 5.0 g of 2,5-dibromo-3,6-dimethylbenzoic acid and thionyl chloride, was added dropwise at room temperature. The stirring was continued for 2 hr after the addition was completed, at the end of which time the reaction mixture was poured into the mixture of crushed ice and hydrochloric acid. The organic layer was separated, washed and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residual oil was chromatographed on silica gel to yield the desired ketone, yield 1.4 g, mp 24°C. The vpc analysis of the product showed only a single peak, whose retention time was 11.5 min at the column temperature of 180—200°C with the program rate being 2°C/min.

Found: C, 43.04; H, 3.95; Br, 48.01%. Calcd for $C_{12}H_{14}Br_2O$: C, 43.15; H, 4.22; Br, 47.84%.

2,5-Dibromo-3,6-dimethylphenyl Benzyl Ketone (Ib). A mixture of 4.0 g of 2,5-dibromo-3,6-dimethylbenzoic acid and 5 m*l* of thionyl chloride was heated. After the evolution of gases ceased, the excess of thionyl chloride was evaporated *in vacuo* and the residual solid was dissolved in 5 m*l* of anhydrous ether. The solution was again evaporated *in vacuo* to remove any thionyl chloride or hydrogen chloride. The acid chloride was dissolved in 80 m*l* of anhydrous ether, and added over a 1 hr period to an ethereal solution of benzyl magnesium chloride prepared from 25.5 g of benzyl chloride, 4.0 g of magnesium ribbon, and 100 m*l* of anhydrous ether under nitrogen atmosphere. The product was distilled under reduced pressure to give a fraction boiled at 200—210°C/2 mmHg. The distillate solidified and recrystallized from petroleum ether to afford the desired ketone, yield 2.0 g, mp 108—109°C. IR: $\nu_{C=O}$ 1713 cm^{-1} (liq.), 1705 cm^{-1} (solid). NMR (CCl_4): 1.92 (3H, singlet), 2.36 (3H, singlet), 3.99 (2H, singlet), 7.14 (5H, singlet), 7.35 (1H, singlet).

Found: C, 50.49; H, 3.64; Br, 42.02%. Calcd for $C_{16}H_{14}Br_2O$: C, 50.29; H, 3.69; Br, 41.83%.

2,4-Dimethyl-6-bromophenyl Isopropyl Ketone (IIIa). The reaction between 2,4-dimethyl-6-bromobenzoyl chloride from 6.9 g of the corresponding acid and isopropyl magnesium bromide from 37 g of isopropyl bromide afforded 4.5 g of an oil boiling at 113—116°C/2 mmHg, which was proved by vpc analysis to be a 1:3 mixture of the ketone and the corresponding secondary alcohol.

To a solution of the above mixture in 10 m*l* of acetic acid, a solution of 0.93 g of chromic anhydride in 40 m*l* of acetic acid and 13 m*l* of water was added at 0°C with vigorous stirring, which was continued for 30 min after the addition

9) A. S. Wheeler and R. E. Thomas, *J. Amer. Chem. Soc.*, **50**, 2287 (1928).

was completed. The reaction mixture was poured into ice-water and extracted with ether. The ether extract was washed with saturated sodium bicarbonate solution and with water and then dried over magnesium sulfate. The solvent was evaporated and the residual oil (*ca.* 4.3 g) was chromatographed on 129 g of silica gel and eluted with petroleum ether–benzene (5: 1). The yield of the ketone was 3.2 g. The vpc analysis of the product showed only a single peak, whose retention time was 9.3 min at the column temperature of 160—200°C with the program rate being 4°C/min. IR (neat): $\nu_{C=O}$ 1700 cm^{-1}. NMR (CCl_4): 1.16 (6H, doublet, J=7 Hz), 2.15 (3H, singlet), 2.26 (3H, singlet), 3.13 (1H, septet, J=7 Hz), 6.88 (1H, singlet), 7.11 (1H, singlet).

Found: C, 56.29; H, 5.98; Br, 31.54%. Calcd for $C_{12}H_{15}BrO$: C, 56.49; H, 5.93; Br, 31.32%.

2,5-Dichloro-3,5-dimethylphenyl Isopropyl Ketone (IIa). 2,5-Dichloro-3,6-dimethylbenzoyl chloride prepared from 6.6 g of the corresponding acid was treated similarly as above. Chromic acid oxidation of the products followed by chromatography on silica gel yielded 2.8 g of the desired ketone, the vpc analysis of which showed only a single peak; retention time, 8.2 min at the column temperature of 180—200°C with the program rate being 2°C/min. IR (neat): $\nu_{C=O}$ 1700 cm^{-1}. NMR (CCl_4): 1.18 (6H, doublet, J=7.5 Hz), 2.17 (3H, singlet), 2.34 (3H, singlet), 3.02 (1H, septet, J=7.5 Hz), 7.23 (1H, singlet).

Found: C, 58.93; H, 5.97; Cl, 28.81%. Calcd for $C_{12}H_{14}Cl_2O$: C, 58.79; H, 5.76; Cl, 28.92%.

2,4-Dimethyl-6-methoxyphenyl Benzyl Ketone (IVb). To 14.7 g of anhydrous aluminum chloride covered with 30 m*l* of carbon disulfide, a solution of 13.6 g of 3,5-dimethylanisole and 15.4 g of phenylacetyl chloride in 70 m*l* of carbon disulfide was added dropwise with vigorous stirring. The mixture was stirred at room temperature for 1 hr and then kept at the reflux temperature for an additional 1 hr. The mixture was cooled to room temperature and the solvent was removed by decantation. The residual complex was decomposed by the addition of 150 g of crushed ice and 50 m*l* of hydrochloric acid, and the mixture was extracted with benzene. The combined extract was washed with 5% sodium hydroxide solution, then with water, and dried over calcium chloride. After the removal of the solvent the residual oil was distilled under reduced pressure. Yield 7.5 g, bp 157—159°C/1 mmHg, $n_D^{23.2}$ 1.5685. IR (neat): 1670 cm^{-1}. NMR (CS_2): 1.82 (3H, singlet), 2.17 (3H, singlet), 3.64 (3H, singlet), 3.88 (2H, singlet), 6.40 (2H, singlet), 7.04 (5H, singlet).

Found: C, 80.44; H, 7.27%. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13%.

2,4-Dimethyl-6-hydroxyphenyl Benzyl Ketone (X). The alkaline wash of the benzene extract of (IVb) was acidified and the product extracted with ether. The ether extract was washed with water and dried over sodium sulfate. After the evaporation of the solvent, the residual oil was distilled to yield the *o*-hydroxy ketone. Yield 10.2 g, bp 168—173°C/1 mmHg, $n_D^{23.2}$ 1.5921. IR (neat): ν_{O-H} 3300 cm^{-1}, $\nu_{C=O}$ 1650 cm^{-1}. NMR (CS_2): 2.10 (3H, singlet), 2.33 (3H, singlet), 4.04 (2H, singlet), 6.35 (1H, singlet), 6.40 (1H, singlet), 7.08 (5H, singlet), 11.24 (1H, singlet).

Found: C, 79.71; H, 6.82%. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71%.

2,4-Dimethyl-6-hydroxyphenyl Isopropyl Ketone (XI). To 24 g of 3,5-dimethyl phenyl isobutyrate, bp 95°C/2 mmHg, was added 22 g of anhydrous aluminum chloride at once, and the mixture was heated at 90°C for a few minutes, at he end of which time the reaction temperature was raisetd to 120°C as fast as possible and maintained at 120°C for 10 min. The reaction was completed by heating the mixture at 140°C for 30 min. After cooling the reaction mixture was treated with 50 g of crushed ice and 30 m*l* of hydrochloric acid and steamdistilled. The *o*-hydroxy ketone was recrystallized from petroleum ether. Yield 6.0 g, mp 82—82.5°C and 91—91.5°C (dual mp). IR (Nujol): ν_{O-H} 3330 cm^{-1}, $\nu_{C=O}$ 1680 cm^{-1}. NMR (CCl_4): 1.15 (6H, doublet, J= 7.1 Hz), 2.20 (3H, singlet), 2.45 (3H, singlet), 3.40 (1H, septet, J=7.1 Hz), 6.40 (1H, singlet), 6.46 (1H, singlet), 10.62 (1H, singlet).

Found: C, 74.78; H, 8.31%. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%.

2,4-Dimethyl-6-methoxyphenyl Isopropyl Ketone (IVa). The corresponding *o*-hydroxy ketone was methylated with dimethyl sulfate to afford the desired product. Bp 109—110°C/2 mmHg, $n_D^{23.2}$ 1.5118. IR (neat): $\nu_{C=O}$ 1680 cm^{-1}. NMR (CCl_4): 1.05 (6H, doublet, J=7.1 Hz), 2.08 (3H, singlet), 2.25 (3H, singlet), 3.00 (1H, septet, J=7.1 Hz), 3.74 (3H, singlet), 6.43 (1H, singlet), 6.49 (1H, singlet).

Found: C, 75.63; H, 8.97%. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%.