Preparation and Spectral Characterization of Substituted 2-Hydroxyacetophenones and 2-Ethylphenols

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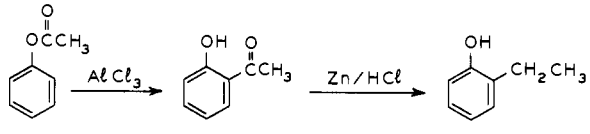
Preparation of substituted 2-hydroxyacetophenones and 2-ethylphenols is reported, along with their mass spectra and NMR data. 2-Hydroxyacetophenones were prepared by the Fries rearrangement of aryl acetates. 2-Ethylphenols were prepared by Clemmensen reduction of these hydroxyacetophenones or direct halogenation of 2-ethylphenol. Both types of compounds fragment under electron impact, predominantly with loss of methyl radical. The loss of acetyl group (*m/e* 43), either as cation or radical, is of less importance for the hydroxyacetophenones. Chemical shifts and coupling constants for these compounds have been calculated. Intramolecular hydrogen bonding in the 2-hydroxyacetophenones gives rise to low-field hydroxyl proton resonances. A coupling between the hydroxyl proton and a meta aromatic proton is observed for both the acetophenones and ethylphenols, but on opposite sides of the ring.

SEVERAL substituted 2-hydroxyacetophenones and 2-ethylphenols have been prepared, some of which are new. The 2-hydroxyacetophenones were prepared by the Fries rearrangement of appropriately substituted phenyl acetates. Clemmensen reduction of these aryl ketones produced the corresponding 2-ethylphenols. 4-Bromo-, 4,6-dibromo-,



4-chloro, 6-chloro, and 4,6-dichloro-2-ethylphenol were prepared by direct halogenation of 2-ethylphenol in chloroform. 4,6-Dichloro-2-ethylphenol was prepared also from 3,5-dichloro-2-hydroxyacetophenone.

EXPERIMENTAL

All melting points were obtained on a Fisher-Johns melting point block. The infrared spectra were determined with a Perkin-Elmer Model 337 grating spectrophotometer, as either neat liquids or suspensions in potassium bromide pellets. The NMR spectra were determined on a Varian Model A-60 NMR spectrometer, using tetramethylsilane as internal reference. Calculation of chemical shifts and coupling constants were performed on a computer using the LAOCOON II program of Castellano and Bothner-By (*13*). The mass spectra were obtained with a CEC Model 21-103 mass spectrometer at an ionizing potential of 70 e.v., using an all-glass inlet system heated to 250° C. for the 2-hydroxyacetophenones and up to 350° C., although usually 100° C., for the 2-ethylphenols, without any apparent thermal effects. However, at 350° C., the 2-hydroxyacetophenones started to decompose. Gas-liquid partition chromatography was performed with an F & M Model 810 gas chromatograph.

2-Hydroxyacetophenones. 2,4-Dichloro-, 4-ethyl-, 4-fluoro- (*12*), and 2-fluorophenyl (*24*) acetate were prepared in excellent yield from the appropriate phenol and acetyl chloride. By the Fries rearrangement (*4*) of these acetates, the hydroxyacetophenones were obtained. The procedure is illustrated for 5-fluoro-2-hydroxyacetophenone, previously prepared by this method (*12*). With cooling, 86 grams (0.64 mole) of aluminum chloride was added to 90 grams (0.58 mole) of 4-fluorophenyl acetate. After complete addition, the mixture was heated in an oil bath. A reaction commenced at 70° C., and the cake was completely dissolved at 115° C. Heating was continued for two hours at 115° C., and the mixture was then cooled. After adding 200 ml. of 2*N* hydrochloric acid, the solid mass was stirred 30 minutes until completely dissolved. The product was extracted into ether and purified by taking up in 10% sodium hydroxide solution. The alkaline solution was acidified and the product extracted with ether. The ether layer was dried and the solvent evaporated. Crystallizing and recrystallizing from hexane gave 5-fluoro-2-hydroxyacetophenone [m.p. 55° C., lit. (*12*) 56.6° to 57° C.].

Essentially the same method was used to prepare these compounds: 3,5-dichloro-2-hydroxyacetophenone was recrystallized from hexane [m.p. 95° to 96° C., lit. (*9, 19*) 95° to 97° C.]; 5-ethyl-2-hydroxyacetophenone (*1*) was distilled (b.p. 94° to 96° C. at 2.3 mm.); 3-fluoro-2-hydroxyacetophenone [m.p. 75° to 76° C., lit. (*7*) 72° to 73° C.] and 3-fluoro-4-hydroxyacetophenone [m.p. 128° to 128.5° C., lit. (*24*) 125° to 126.6° C.] were obtained from rearrangement of 2-fluorophenyl acetate and separated by fractional crystallization from benzene-hexane mixtures.

2-Ethylphenols. The Clemmensen reduction of the 2-hydroxyacetophenones gave the corresponding 2-ethylphenols (*23*).

3,5-Dichloro-2-hydroxyacetophenone gave 4,6-dichloro-2-ethylphenol (*9, 19*) (b.p. 98° to 101° C. at 0.9 mm.). 5-Ethyl-2-hydroxyacetophenone gave 2,4-diethylphenol (*1*) (b.p. 65° C. at 0.1 mm.). 4,5-Dimethyl-2-hydroxyacetophenone gave 4,5-dimethyl-2-ethylphenol [m.p. 49.5° to 50.5° C. (lit. (*1*) 51° to 52° C.)]. 2-Hydroxy-5-methylacetophenone gave **2-ethyl-4-methylphenol (b.p. 85° to 87° C. at 0.5 mm.) (*22*). 5-Fluoro-2-hydroxyacetophenone gave 2-ethyl-4-fluoro**phenol (*20*), which was distilled in a short-path distillation apparatus (b.p. 47° C. at 0.1 mm.).

3-Fluoro-2-hydroxyacetophenone gave the previously unreported 2-ethyl-6-fluorophenol, which was distilled in a short-path distillation apparatus (b.p. 40° C. at 0.1 mm.). Anal. calcd. for C_8H_9FO: C, 68.58; H, 6.48. Found: C, 68.65; H, 6.58. Infrared bands appear at 3570(s), 3450(s), 2970(s), 2940(w), 2880(w), 1630(m), 1600(w), 1500(shoulder), 1490(s), 1260(s), 1085(m), 990(m), 910(s), 830(m), 775(m), 730(m) and 670(w) cm.$^{-1}$.

4-Bromo-2-ethylphenol, prepared earlier by other methods (*21*), was prepared by addition of 28.8 grams (0.18 mole) of bromine in 200 ml. of chloroform to an ice-cooled solution of 24.4 grams (0.20 mole) of 2-ethylphenol in 200 ml. of chloroform (93% yield, b.p. 90° to

Table I. Mass Spectra of 2-Hydroxyacetophenones (70 Ev.)[a]

Acetophenone	Ion Fragments (m/e)[b] M$^+$ (m/e)	(M—CH$_3$)$^+$[c]	(M—COCH$_3$)$^+$[d]	(M—COCH$_3$—CO)$^+$	C$_5$H$_2$X$^+$	C$_5$H$_3^+$	CH$_3$CO$^+$[e]	Other Peaks (m/e)
3-Fluoro-2-hydroxy-	154(45)	139(100)[f]	111(14)	83(23)	81(7)	63(11)	[g]	140(8) 82(5) 62(6) 57(20) 53(7) 51(7) 50(7)
3-Fluoro-4-hydroxy-	154(36)	139(100)[f]	111(33)	83(26)	81(5)	63(12)	43(28)	140(8) 82(6) 62(6) 57(24) 53(5) 51(8) 50(5) 39(7)
5-Fluoro-2-hydroxy-	154(52)	139(100)[f]	111(20)	83(29)	81(6)	63(9)	43(42)	140(8) 82(6) 57(22) 51(6) 50(5) 39(7)
3,5-Dichloro-2-hydroxy-	204(38)	189(100)	161(1)	133(19)	97(20)	63(20)	43(150)[f]	190(9) 125(5) 123(5) 77(5) 75(8) 74(7) 73(13)
	206(24)	191(66)	163(1)	135(13)	99(8)			62(21) 61(16) 53(11) 51(8) 50(8) 39(5)
		193(11)						
5-Ethyl-2-hydroxy-	164(38)	149(100)[f]	121(5)	...	...	63(9)	43(18)	150(10) 131(20) 91(11) 78(5) 77(19) 68(8) 53(10) 51(13) 50(6)

[a] Scans start at m/e 25, data presented from m/e 39. [b] Intensity given as per cent of M—CH$_3$ peak in parenthesis except for 3,5-dichloro-2-hydroxyacetophenone; all peaks with intensities greater than 5% of the base peak are shown. [c] Path C. [d] Path B. [e] Path A. [f] Base Peak. [g] Scan started at m/e 48.

Table II. Mass Spectra of 2-Ethylphenols

2-Ethylphenol	Ion Fragment (m/e)[a] M$^+$	(M—CH$_3$)$^+$	(M—C$_2$H$_5$)$^+$	(M—X)$^+$[b]	C$_7$H$_7^+$	C$_7$H$_6$X$^+$	C$_6$H$_5^+$	C$_6$H$_4$X$^+$[b]	C$_5$H$_3^+$	Others
6-Fluoro-	140(40)	125(100)		121(2)		109(8)	77(10)	95(10)	63(6)	126(8) 97(14) 96(8) 83(7) 75(5) 57(10) 51(11) 50(7)
4-Fluoro-	140(40)	125(100)		121(2)		109(8)	77(10)	95(10)	63(6)	126(8) 97(14) 96(8) 83(7) 75(5) 57(10) 51(11) 50(7)
6-Chloro-	156(35)	141(100)		121(20)	91(11)		77(29)		63(14)	142(8) 103(8) 75(5) 65(8) 62(6) 53(7) 51(22) 50(10)
	158(11)	143(33)								
4-Chloro-	156(49)	141(100)		121(23)	91(14)		77(42)		63(17)	142(8) 122(6) 103(6) 78(9) 75(8) 74(5) 73(6) 65(10)
	158(16)	143(34)								62(8) 61(5) 53(8) 52(6) 51(24) 50(13)
4,6-Dichloro-	190(50)	175(100)		155(28)		125(7)		111(18)	63(21)	179(10) 157(9) 112(2) 91(14) 89(11) 77(10) 75(20) 74(10)
	192(32)	177(65)								73(10) 62(14) 61(10) 53(11) 51(17) 50(16)
4-Bromo-	200(81)	185(100)		121(29)	91(25)		77(39)		63(30)	120(8) 106(9) 105(5) 103(17) 102(14) 79(7) 78(43) 75(9)
	202(80)	187(97)								74(9) 65(18) 64(7) 62(15) 61(8) 53(15) 52(13) 50(26)
4,6-Dibromo-	278(48)	263(53)		199(14)	91(32)		77(15)	155(5)	63(32)	281(9) 159(12) 156(12) 120(28) 102(10) 92(9) 90(10) 89(14)
	280(89)	265(100)		201(14)				157(5)		81(7) 79(9) 76(12) 75(19) 74(15) 65(17) 62(23) 61(13)
	282(45)	267(51)								53(22) 51(30) 50(29)
4-Methyl-[c]	136(40)	121(100)	107(9)		91(20)		77(20)		63(6)	135(5) 122(9) 65(7) 53(8) 52(5) 50(7)
4,5-Dimethyl-	150(39)	135(100)	121(7)		91(17)		77(10)		63(5)	136(11) 105(5) 79(6) 65(6) 53(7) 5(10)
4-Ethyl-	150(19)	135(100)	121(18)		91(16)		77(13)		63(5)	136(10) 107(5) 105(3) 103(4) 65(6) 53(6) 51(10)
Thymol[d]	150(28)	135(100)	121(15)		91(18)		77(10)		63(4)	136(11) 117(9) 115(10) 79(5) 65(6) 53(8) 51(8)

[a] All M—4 fragments less than 1%; intensity given as per cent of base peak in parenthesis; all ions greater than 7% of base peak are shown starting at m/e 50, except for 4,6-dichloro-2-ethylphenol, where ions greater than 9% of the base peak are shown. [b] X = F, Cl, Br. [c] Reference (*11*). [d] Reference (*10*).

92° C. at 0.2 mm.). 4,6-Dibromo-2-ethylphenol was prepared in the same way, using additional bromine (b.p. 112° C. at 2.3 mm., lit. (8) b.p. 121° to 122° C. at 3.5 mm.).

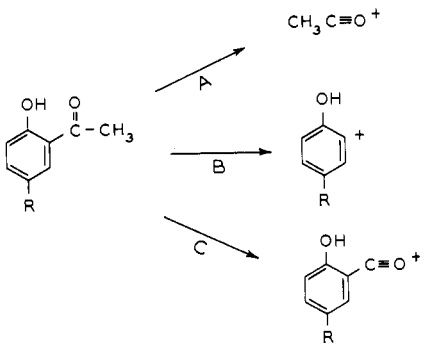
The chloro-2-ethylphenols were prepared by adding dropwise a solution of 162 grams (1.2 mole) of sulfuryl chloride in 200 ml. of chloroform to a cold agitated solution of 122 grams (1.0 mole) of 2-ethylphenol in 300 ml. of chloroform. After refluxing for one hour, excess chloroform and sulfuryl chloride were removed under vacuum and the product separated into two main fractions. The first fraction was the previously unreported 6-chloro-2-ethylphenol (b.p. 80° to 87° C. at 0.5 mm., 54.8 grams, 35% yield). Anal. calcd. for C_8H_9ClO: C, 61.35; H, 5.81; Cl, 22.64. Found: C, 61.36; H, 5.68; Cl, 22.6. The infrared showed bands in the hydrogen deformation region at 735(s), 770(s), and 840(s) $cm.^{-1}$. Other bands appear at 3540(s), 2980(m), 2940(w), 2880(w), 1620(m), 1500(shoulder/m), 1470(s), 1330(s), 1240(s), 1210(s), 1170(s), 1090(m), 975(m), and 630(s) $cm.^{-1}$. The second fraction was 4-chloro-2-ethylphenol (2) (b.p. 106° to 115° C. at 0.5 mm., 68.5 grams, 44% yield).

4,6-Dichloro-2-ethylphenol also was prepared in 82% yield by this method, using two moles of sulfuryl chloride per mole of 2-ethylphenol. The product was identical with that prepared from 3,5-dichloro-2-hydroxyacetophenone.

RESULTS AND DISCUSSION

Infrared spectra of the 2-ethylphenols agree with those of other 2,4-disubstituted phenols (25), with additional bands at 710 (4-fluoro-), 650 (4-chloro-), and 630 $cm.^{-1}$ (4-bromo-) for compounds bearing the indicated substituents.

Mass Spectra. The 2-hydroxyacetophenones fragment by three paths. In Paths A and B, the carbon-carbon bond between the acetyl group and the ring in the molecular ion breaks. In Path C, the molecular ion loses a methyl radical. This path generally gives rise to the base peak. At first glance, the spectrum of 3,5-dichloro-2-hydroxyacetophenone (Table I) appears different from the other spectra, since m/e 43 (CH_3CO^+), the product of A, is the base peak. On closer examination, the ion current due



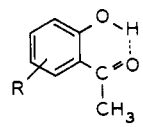
to ion $(M—CH_3)^+$ (Path C), which is in fact the sum of three peaks, is indeed greater than ion m/e 43. Path C gives rise, therefore, to the greatest ion current for all of these compounds, but not necessarily the base peak. The ion product from Path B, $(M—COCH_3)^+$, is less abundant than the initial products from either of the other two processes. However, this ion, especially in the spectra of the halogenated compounds, loses CO quite readily, giving ion $(M—COCH_3—CO)^+$.

The halogenated hydroxyacetophenones reported here show little or no loss of halogen from the molecular ion $(M—X)^+$. The $(M—CH_3—X)^+$ ions are also negligible, less than 1% of the base ion. The halogen atoms are largely retained, even in the small ion fragment, $C_5H_2X^+$. Similar behavior was observed in halogenated benzofurans on electron impact (17).

Mass spectra of the 2-ethylphenols are shown in Table II. In every case, a strong parent ion is observed with a base peak corresponding to the fragment ion $(M—CH_3)^+$. Initial loss of halogen is observed from the chlorine and bromine substituted compounds, but not the fluorine compounds. Among the smaller fragments are intense peaks corresponding to $C_7H_7^+$ (or $C_7H_6X^+$) and $C_6H_5^+$. In a few cases, the latter ion is either replaced or accompanied by a $C_6H_4X^+$ ion.

2-Ethylphenols cyclize thermally to benzofurans (18). Although numerous pyrolyses have been related to electron impact-induced fragmentation (5, 6, 14, 15), there is little or no $(M—4)^+$ ion corresponding to the benzofuran ion observed in these mass spectra. Even with an inlet temperature up to 350° C., no evidence for any $(M—4)^+$ ion was observed.

NMR Spectra. The assignments of the 2-hydroxyacetophenones shown in Table III are based on the assumption that the relative positions of the hydroxyl group and the substituent group in the 2-hydroxyacetophenones are the same as in the starting phenols. The low-field chemical shifts of the hydroxyl protons of these compounds probably result from intramolecular hydrogen bonding with the keto group. The hydroxyl proton signals in the 2-ethylphenols, where intramolecular hydrogen bonding is prohibited, are at much higher field (Table IV).

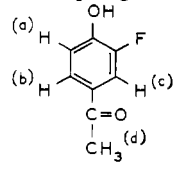


In all of these spectra in non-hydroxyl exchanging solvents, the hydroxyl proton was coupled with a meta-oriented aromatic proton. The position of the aromatic proton in 3-fluoro-2-hydroxyacetophenone was unambiguous, since it was ortho to the fluorine atom. When the hydroxyl proton in 5-fluoro-2-hydroxyacetophenone was exchanged in methanol, the shape of the proton resonance para to the acetyl group changed from doublets to singlets. Other lines in the spectrum were not affected. The absence of hydroxyl proton coupling in 2-hydroxy-4-methoxyacetophenone, where the aryl position for coupling is blocked, supports this assignment.

A coupling in the spectra of the fluorinated compounds was observed between the methyl protons and an aromatic proton adjacent to the acetyl group. Stronger couplings of this type would be expected between adjacent groups.

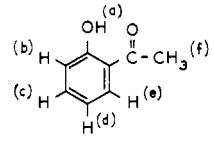
The spectrum of 3,5-dichloro-2-hydroxyacetophenone was less straightforward. The assignment given for this compound has the following features: the chemical shifts agree with the other compounds; a coupling exists between the hydroxyl proton and a proton para to the acetyl group, J_{ac}; and the methyl group is coupled with a proton ortho to the acetyl group, J_{ef}. The relative values of the chemical shifts of the aromatic protons in this compound agree with the relative values calculated from substituent shielding values (3).

The second product isolated from the Fries rearrangement of 2-fluorophenyl acetate was identified as 3-fluoro-4-hydroxyacetophenone from NMR data obtained from both proton and fluorine spectra. This compound was like the 2-ethylphenols, which exchanged so easily in deuterochloroform that the hydroxyl proton coupling could not be observed. The methyl proton resonance was much sharper than the other hydroxyacetophenones, indicating no sizable coupling with the ring protons.



δ_a	7.03 p.p.m.	$J_{a,b}$	8.50 c.p.s.
δ_b	7.65 p.p.m.	$J_{a,c}$	0.21 c.p.s.
δ_c	7.62 p.p.m.	$J_{a,F}$	8.60 c.p.s.
δ_d	2.5 p.p.m.	$J_{b,c}$	2.09 c.p.s.
		$J_{b,F}$	−0.92 c.p.s.
		$J_{c,F}$	12.0 c.p.s.

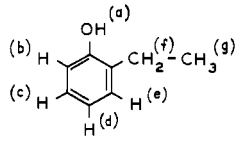
Table III. NMR Spectral Data of Substituted 2-Hydroxyacetophenones in $CDCl_3$



	δ_a	δ_b	δ_c	δ_d	δ_e	δ_f	J_{ab}	J_{ac}	J_{bc}	J_{bd}	J_{be}	J_{cd}	J_{ce}	J_{de}	J_{ef}[b]
3,5-Dichloro-[a]	12.65	...	7.50	...	7.60	2.64	...	0.56	...	...	...	...	2.49	...	0.15
3-Fluoro-	12.25	...	7.26	6.82	7.51	2.62	0.4	0.60	10.68	4.58	1.24	8.05	1.50	8.19	0.15
5-Fluoro-	11.95	6.91	7.18	...	7.38	2.60	0	0.32	9.17	4.58	0.39	7.83	3.09	8.87	0.15
5-Ethyl-[c]	12.30	6.94	7.38	...	7.58	2.59	...	0.25	9.1	...	...	...	2.2	...	...
4-Methoxy-[d]	12.73	6.30	...	6.32	7.49	2.45	...	...	...	2.41	0.36	...	...	9.01	[e]

[a] Assignment made so as to be consistent with the 3-fluoro- and 5-fluoro-2-hydroxyacetophenones. [b] Estimated from line width of appropriate resonances, determined by the computer program. [c] δ_{CH_2} = 2.62, δ_{C-CH_3} = 1.30; coupling between CH_2 and the ring protons is observed, but unresolved. [d] Aldrich Chemical Company; δ_{CH_3O} = 3.75; sample run in $CDCl_3$-acetone-d_6. Agrees with values reported previously (*16*): δ_b 6.209, δ_d 6.280, δ_e 7.464, $J_{b,d}$ 2.52, $J_{b,e}$ 0.38, $J_{d,e}$ 8.81 (in carbon disulfide). [e] $J_{ef} \leq 0.1$ Hz.

Table IV. NMR Spectral Data of Substituted 2-Ethylphenols



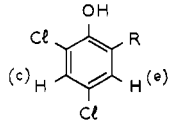
	Solvent	δ_a	δ_b	δ_c	δ_d	δ_e	δ_f	δ_g	J_{ae}	J_{bc}	J_{bd}	J_{be}	J_{cd}	J_{ce}	J_{cf}	J_{de}	J_{ef}	J_{fg}
4-Chloro-	Neat	5.88	6.58	6.89	...	7.02	2.51	1.09	[a]	8.2	...	0.6	...	2.5	...	...	...	7.5
6-Chloro-	CCl_4	5.5	...	7.05	6.66	6.92	2.67	1.19	0.5	...	...	...	7.5	2.2	0.3	7.5	0.5	7.5
4,6-Dichloro-	$CDCl_3$	5.58	...	7.1	...	6.98	2.62	1.17	0.4	...	...	...	...	2.4	0.4	...	0.6	7.5
4-Bromo-	CCl_4	5.26	6.50	7.07	...	7.16	2.55	1.18	[a]	8.0	...	...	...	...	...	...	...	7.5
4,6-Dibromo-	$CDCl_3$	5.51	...	7.40	...	7.18	2.64	1.28	0.60	...	...	...	...	2.3	0.4	...	0.6	7.5
4-Fluoro-	$CDCl_3$	5.48	[b]	[b]	...	[b]	2.58	1.18	...	...	...	...	...	...	...	...	...	7.5
6-Fluoro-	$CDCl_3$	5.25	...	[c]	[c]	[c]	2.72	1.22	...	...	...	...	...	...	...	...	...	7.5
4-Ethyl-	$CDCl_3$	5.28	6.67	6.88	...	6.98	2.60[d]	1.18	[a]	8.0	...		...	2.0	...	...	...	7.5
4-Methyl-[e]	$CDCl_3/C_6D_6$	5.21	6.58	6.88	...	6.97	2.55	1.15	[a]	8.0	...	...	...	2.0	...	...	...	7.5
4,5-Dimethyl-[f]	C_6D_6	4.70	6.28	...	...	6.81	2.56	1.18	...	...	...	...	...	...	...	...	...	7.5
4-Deutero-[g]	$CDCl_3/C_6D_6$	...	6.84	[h]	...	[h]	2.67	1.18	...	8.0	...	...	...	...	...	...	...	7.5

[a] Exchanged. [b] δ_b, δ_c, and δ_e unresolved at 6.6–6.9 p.p.m. [c] δ_c, δ_d and δ_e unresolvable at 7.5–6.0 p.p.m. [d] Two groups, second δ_f 2.54 p.p.m. [e] $\delta_{4\text{-}CH_3}$ = 2.17 p.p.m. [f] $\delta_{4\text{-}CH_3}$ = 2.02, $\delta_{5\text{-}CH_3}$ = 2.02. [g] Methyl ether, δ_{CH_3} = 3.6 p.p.m. [h] δ_c and δ_e = 7.1 p.p.m.

The NMR spectral data of the substituted 2-ethylphenols are given in Table IV. Three assumptions are inherent in these assignments: compounds prepared from 2-hydroxyacetophenones are unchanged in their positional relationships; compounds prepared by halogenating 2-ethylphenol retain the ortho relationship of the hydroxyl and ethyl groups; electrophilic addition of halogen to the ring will occur in the ortho and para positions because of the directive effect of the hydroxyl group.

In these compounds, the hydroxyl proton was coupled with a meta-oriented aromatic proton. In these same compounds, the methylene protons of the 2-ethyl group were coupled to each of two aromatic protons located ortho and para to the ethyl group. Assignment of these resonances was made on the assumption that the stronger coupling would be with the ortho proton, which also happens to be coupled with the hydroxyl group. This places the hydroxyl-aromatic proton coupling on the opposite side of the ring from that observed for the 2-hydroxyacetophenones. The relative chemical shifts of the aromatic protons in 4,6-dichloro-2-ethylphenol agrees with the values calculated by the method of Ballantine and Pillinger (*3*).

The observed and calculated values of δ_c and δ_e reverse in going from 3,5-dichloro-2-hydroxyacetophenone ($\delta_c < \delta_e$) to 4,6-dichloro-2-ethylphenol ($\delta_c > \delta_e$).



R	C_2H_5		CH_3CO	
	δ_c	δ_e	δ_c	δ_e
Calcd.	7.3	7.2	7.5	8.0
Obsd.	7.10	6.98	7.50	7.60

The assignment of the spectrum of 4,5-dimethyl-2-ethylphenol is consistent with chemical shifts of other substituted 2-ethylphenols.

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RECEIVED for review August 21, 1968. Accepted March 17, 1969.

Convenient Syntheses of Cyclopropanecarboxylic Acid, Ethyl Cyclopropanecarboxylate, Cyclopropanecarbonitrile, and Nitrocyclopropane

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Simplified procedures for the preparation of four monosubstituted cyclopropanes by 1,3-dehydrohalogenation are reported. Ethyl cyclopropanecarboxylate and cyclopropanecarbonitrile were prepared from ethyl 4-bromobutyrate and 4-iodobutyronitrile, respectively, employing sodium hydride as the base. Cyclopropanecarboxylic acid was prepared by hydrolysis of ethyl cyclopropanecarboxylate. Nitrocyclopropane was obtained from 1-iodo-3-nitropropane and aqueous sodium carbonate.

THE 1,3-DEHYDROHALOGENATION of various compounds is one of the best methods of preparing substituted cyclopropanes. Sodium hydride has been used previously as a base to prepare bicyclobutanes (*3, 15*) and cyclopropanes (*8, 12*) in high yields. This easily handled base and a simple apparatus have been employed here to give good yields of cyclopropanecarboxylic acid, ethyl cyclopropanecarboxylate, and cyclopropanecarbonitrile. In addition, a short scheme for preparing nitrocyclopropane is reported.

The synthesis of ethyl cyclopropanecarboxylate is a two-step scheme starting with γ-butyrolactone. The lactone is converted to ethyl 4-bromobutyrate (*9*) and then to the product with sodium hydride, in an over-all 76% yield. Sodium hydride is easier to handle, the work-up is easier, and the yields are higher than with other bases (*10, 13*). The ester can be hydrolyzed to provide a high-yield route to cyclopropanecarboxylic acid. This over-all three-step synthesis gives a 68% yield, as compared with 33% for the two steps of the most frequently used preparation (*11*).

The synthesis of cyclopropanecarbonitrile is a three-step synthetic scheme starting with 1-bromo-3-chloropropane. This halide is converted to 4-chlorobutyronitrile (*1*), then to 4-iodobutyronitrile, and finally to the product with sodium hydride. Although the over-all yield is less than the *Organic Syntheses* preparation (*14*), the present method employs a very simple apparatus and a more readily handled base.

Nitrocyclopropane has been prepared by a three-step synthetic scheme, starting with readily available 1-bromo-3-chloropropane. The halide is converted to 1-chloro-3-nitropropane, then to 1-iodo-3-nitropropane, and finally to the product with aqueous sodium carbonate (*2*). The major method for preparation has been the vapor phase nitration of cyclopropane, which is not an easy laboratory method (*7*).

An attempt was also made to prepare cyclopropylbenzene by a two-step scheme. The first step was the conversion of 3-phenyl-1-propanol to 1-iodo-3-phenylpropane, with phosphorus and iodine. However, only very small amounts of cyclopropylbenzene were isolated in the reaction of the iodide with sodium hydride in ether or refluxing benzene. No further attempts were made, in view of the established methods in the literature (*5, 6*).

EXPERIMENTAL

Ethyl Cyclopropanecarboxylate. To a 3-liter flask were added 67.2 grams (40.3 grams, 1.7 moles of sodium hydride) of a 60% sodium hydride dispersion in mineral oil (Metal Hydrides, Inc., Beverly, Mass.) and 300 ml. of anhydrous ether. This mixture was stirred magnetically for one hour and the ether removed by decantation. This process removed the mineral oil from the sodium hydride. To the washed hydride was added 1000 ml. of fresh anhydrous ether. The mixture was stirred magnetically as 195 grams (1.00 mole) of ethyl 4-bromobutyrate (*9*) was added. A reflux condenser and drying tube were added. There was an immediate evolution of hydrogen. The resulting slurry was stirred for 36 hours, after which time the reaction was essentially complete, as indicated by gas chromatography (Beckman GC-2, 6-foot silicone, Beckman 17449). The reaction mixture was suction-filtered through a coarse sintered glass filter and then through a fine one to remove