[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis of Keto Acids by Chromic Anhydride Oxidation of Tertiary Alcohols

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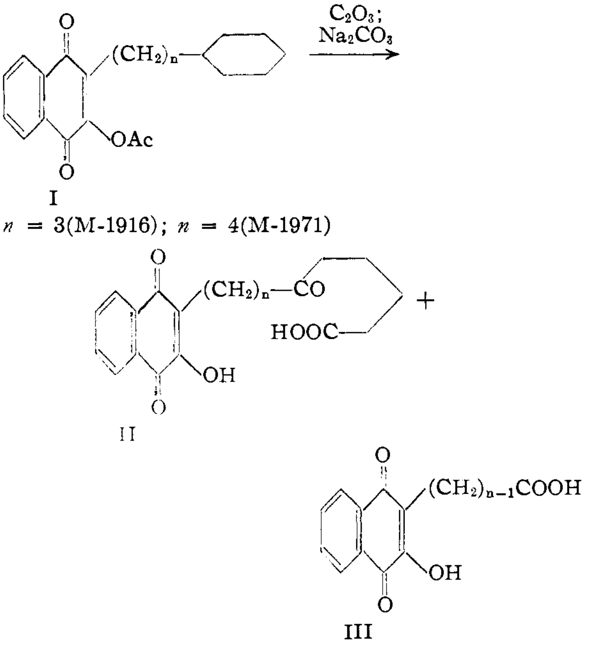
In an extension of a previous study,[2] we first investigated the action of chromic anhydride suspended in anhydrous acetic acid on two homologous acetoxynaphthoquinones having cycloalkylalkyl side chains (I). In each case oxidation at 25° for one hour gave a keto acid (II) in good yield; oxidation for a longer period results in further degradation to an acid of type III.

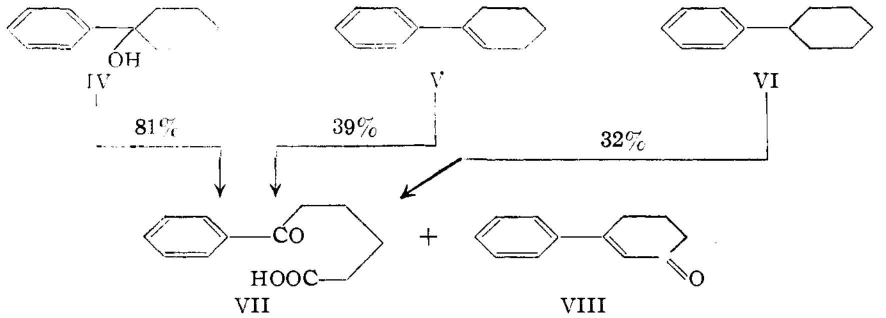


I

n = 3(M-1916); n = 4(M-1971)

II

III



IV V VI VII VIII

The smooth oxidative fission of a cycloalkyl ring observed in these and earlier[2] instances, suggested trial of the procedure of anhydrous oxidation with simpler cyclic compounds. Phenylcyclohexane was first investigated, together with the intermediate carbinol and ethylene in the Grignard synthesis from cyclohexanone. Although previous observations[2] have shown that tertiary alcohols are subject to ready oxidation, it was surprising to find that 1-phenylcyclohexanol (IV) is oxidized more rapidly and cleanly than either the saturated or unsaturated hydrocarbon. The chromic anhydride has to be added in small portions and the mixture cooled to hold the temperature to 30°, and δ-benzoylvaleric acid (VII) of high quality is obtained in good yield along with a trace of phenylcyclohexenone (VIII). Phenylcyclohexene reacts less readily and gives more of the ketone and a lower yield of acid; phenylcyclohexane also gives both products. The results suggest that although the carbinol suffers some dehydration in the course of the reaction it is largely converted to the keto acid by direct oxidative fission. Phenylcyclohexane is probably oxidized initially to the carbinol.

A number of other carbinols were found to be oxidized smoothly to keto acids, and an example of each type studied is given in the accompanying summary. The results indicate that the simple reaction sequence constitutes an efficient synthesis of keto acids supplementing the method of Cason[3] and the Friedel–Crafts procedure.[4] Both aryl and alkylcarbinols derived from various cyclic ketones can be used, and the *p*-anisyl, α-naphthyl and α-thienyl radicals are not attacked under the mild conditions required. The 9-phenanthryl radical does suffer oxidation, and another limitation is that an alkyl group having tertiary hydrogen atoms or an activated methylene group is subject to attack. Thus benzylcyclohexylcarbinol is oxidized to ben-

Components		Oxidation product	Yield, %
C_6H_5Br	Cyclopentanone	$C_6H_5CO(CH_2)_3COOH$	74.5
p-$CH_3OC_6H_4Br$	Cyclohexanone	*p*-$CH_3OC_6H_4CO(CH_2)_4COOH$	81
α-Naphthyl bromide	Cyclohexanone	α-$C_{10}H_7CO(CH_2)_4COOH$	78
α-Thienyl bromide	Cyclohexanone	α-Thienyl-$CO(CH_2)_4COOH$	60
n-$C_{18}H_{37}Br$	Cyclohexanone	*n*-$C_{18}H_{37}CO(CH_2)_4COOH$	80
C_6H_5Br	Cycloöctanone	$C_6H_5CO(CH_2)_6COOH$	85

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[1] On leave of absence from the Weizmann Institute of Science, Palestine.

[2] Fieser, THIS JOURNAL, **70**, 3237 (1948).

[3] Cason, *ibid.*, **64**, 1106 (1942); Cason and Prout, *ibid.*, **66**, 46 (1944).

[4] Papa, Schwenk and Hankin, *ibid.*, **69**, 3018 (1947).

TABLE I

CARBINOLS AND ETHYLENES

No.	Compound	Moles Halide: Mg: ketone	Yield, %	M. p. or b. p. (mm.), °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
1a	1-Phenylcyclohexanol[a]			62–63					
1b	1-Phenylcyclohexene[a]			112 (4)					
1c	Phenylcyclohexane[b]			106 (12)					
2	1-*p*-Anisyl(cyclohexanol-cyclohexene)	1:1:1.5	73	135–140 (3)	$C_{13}H_{18}O_2$ $C_{13}H_{18}O$	75.69 82.93	8.79 8.57	80.09	8.65
3	1-Benzylcyclohexanol[c]			127 (4)					
4	1-α-Naphthylcyclohexanol[d]			66–68					
5	1-Cyclohexylcyclohexanol[c]			51					
6	1,1′-Dihydroxydicyclohexyl[e]			130					
7	1-Phenylcyclopentanol[f]			121 (6)					
8	1-Isopropylcyclohexanol[g]			176 (754)					
9	1-*n*-Amylcyclohexanol[h]			96 (5)					
10	1-*n*-Dodecylcyclohexanol	1:12	74.6	152 (0.05)	$C_{18}H_{36}O$	80.52	13.45	80.28	13.40
11	1-*n*-Tetradecylcyclohexanol	1:1:2	81	168 (0.05)	$C_{20}H_{40}O$	81.03	13.59	81.03	13.42
12	1-Cetylcyclohexanol	1:1:2	80	195–200 (0.08) M. p. 35	$C_{22}H_{44}O$	81.41	13.66	81.54	13.51
13	1-*n*-Octadecylcyclohexanol	1:1:2	70	225 (0.03) M. p. 45[i]	$C_{24}H_{48}O$	81.74	13.72	81.90	13.69
14	1-Tetrahydrogeranylcyclohexanol	1:1:2	82.5	107–112 (0.02)	$C_{16}H_{32}O$	79.93	13.41	79.95	13.30
15	1-Dihydrophytylcyclohexanol	1:1:2	80	144–150 (0.1)	$C_{26}H_{52}O$	82.03	13.77	82.38	13.69
16	1-Cerylcyclohexanol[j]	1:1:2	75	235–240 (0.04) M. p. 65[k]	$C_{32}H_{64}O$	82.65	13.88	82.86	13.88
17	1-Phenyl-cycloöctanol-cycloöctene)	1:1:1	73.5	98–100 (2)	$C_{14}H_{20}O$ $C_{14}H_{18}$	82.30 90.26	9.87 9.74	88.78	9.73
18	1-Octadecylcycloöctene	1:1:1.2	70	150–155 (0.05) M. p. 78[l]	$C_{26}H_{50}$	86.00	14.00	85.57	14.50
19	1-α-Thienylcyclohexene	1:1:1.1	91.5	89–91 (0.1) M. p. 132°	$C_{10}H_{11}S$	73.32	7.39	73.12	7.37
20	1-(9′-Phenanthryl)-cyclohexene[m]								

[a] v. Auwers and Treppmann, *Ber.*, **48,** 1216 (1915). [b] Sabatier and Murat, *Compt. rend.*, **154,** 1390 (1912). [c] Sabatier and Mailhe, *ibid.*, **138,** 1322 (1904); *Ann. chim.*, [8] **10,** 547 (1907). [d] Kleene, THIS JOURNAL, **63,** 1768 (1941). [e] Gruber and Adams, *ibid.*, **57,** 2555 (1935). [f] Zelinski, *Ber.*, **58,** 2755 (1925). [g] v. Auwers and Ellinger, *Ann.*, **387,** 223 (1912). [h] Signaigo and Cramer, THIS JOURNAL, **55,** 3330 (1933). [i] Short rods from a mixture of acetone–water–ethanol; plates from acetone–water–dioxane. [j] Ceryl bromide was prepared in 80% yield by refluxing and stirring a mixture of 30 g. of ceryl alcohol, 28 g. of 48% hydrobromic acid, and 9 cc. of 96% sulfuric acid for five hours. The recrystallized bromide (acetone) melted at 57°. *Anal.* Calcd. for $C_{26}H_{53}Br$: C, 70.08; H, 11.98. Found: C, 70.32; H, 11.75. [k] Plates from alcohol–acetone. [l] Plates from acetone. [m] F. Bergmann and Szmuszkovicz, THIS JOURNAL, **69,** 1367 (1947), report an 85% yield of this compound by thermal decomposition of the Grignard reaction product at 160°. We decomposed the reaction mixture with ammonium chloride and distilled the product in high vacuum and obtained only the ethylene and no carbinol.

zoic acid; 1-isopropylcyclohexanol and the pinacol from cyclohexanone both yield adipic acid and cyclohexanone.

This synthesis, coupled with the simple Wolff–Kishner reduction procedure of Huang-Minlon[5] provides a convenient route to higher fatty acids, for example, arachidic (C_{20}), behenic (C_{22}), lignoceric (C_{24}) and cerotic acid (C_{26}).

Experimental

Oxidation of **M-1916** (I, *n* = 3).—A solution of 5 g. of the acetate (m. p. 72.5–73.5°) in 200 cc. of glacial acetic acid was stirred with 15 g. of chromic anhydride at 25° (cooling) for one hour. The mixture was diluted with water and extracted with ether; the ethereal solution was extracted with sodium carbonate and the extract acidified and extracted with ether. The dried solution on evaporation afforded in two crops a total of 3.0 g. (59%) of crystalline keto acid II (*n* = 3), m. p. 129–131°. Recrystallization from dilute methanol gave yellow leaflets, m. p. 138–139°.

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.68; H, 6.17.

The unchanged starting material recovered amounted to 1.5 g. (34%). The **methyl ester** of the keto acid crystallized from dilute methanol in long yellow rods, m. p. 99–100°.

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.37; H, 6.45.

Oxidation of **M-1971** (I, *n* = 4).—**M-1971 Acetate** was prepared from 20 g. of the quinone, 45 cc. of acetic anhydride, and 8 cc. of boron fluoride etherate (25°, overnight); the crystalline product that separated melted at 60–62° (98% yield). Crystallization from methanol raised the m. p. to 68–69°.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.40. Found: C, 74.66; H, 7.31.

Oxidation for one hour as prescribed for M-1916 acetate gave 2.5 g. (50%) of crude keto acid II (*n* = 4). Crystallization from methanol or from benzene–ligroin gave yellow pointed rods, m. p. 122–123°.

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[5] Huang-Minlon, THIS JOURNAL, **68,** 2487 (1946).

TABLE II

CrO_3-OXIDATION OF CARBINOLS AND ETHYLENES OF TABLE I

No.	Compound	Yield, %	M. p., °C.		Solvent	Form	Formula	Analyses, %			
			Crude	Pure				Calcd. C	Calcd. H	Found C	Found H
1a	δ-Benzoylvaleric acid[a]	81	73–75	77–78	Aq. MeOH	Rods					
	1-Phenylcyclohexene-1-one-3 semicarbazone[b]			222	EtOH	Rods	$C_{13}H_{15}ON_3$	68.10	6.60	67.73	6.66
2	δ-Anisoylvaleric acid[c]	80.7	124–126	127	EtOH	Plates					
	Semicarbazone			189–190	EtOH	Needl.	$C_{14}H_{19}O_4N_3$	57.34	6.78	57.45	6.76
3	Benzoic acid	50	120	121							
4	δ-(α-Naphthoyl)-valeric acid	77.8	52–54	56–57			$C_{16}H_{16}O_3$	74.97	6.29	74.71	6.48
	Semicarbazone			186–187	EtOH	Prisms	$C_{17}H_{19}O_3N_3$	65.16	6.11	65.02	6.00
5	δ-Cyclohexoylvaleric acid	78.3	49–51	54–55			$C_{12}H_{20}O_3$	67.89	9.50	68.09	9.32
	Semicarbazone			169–170	Aq. EtOH	Rods	$C_{17}H_{19}O_3N_3$	57.97	8.61	58.23	8.59
6	Cyclohexanone (3 g.) + adipic acid (0.8 g.)	89									
7	γ-Benzoylbutyric acid[d]	74.5	126–127	127	Water	Plates					
	Semicarbazone			212–213	EtOH	Needl.					
	1-Phenylcyclopentene-1-one-3 semicarbazone[e]			226–227	Aq. HOAc	Plates	$C_{12}H_{13}ON_3$	66.96	6.09	66.61	6.17
8	Cyclohexanone (2.5 g.) + adipic acid (0.3 g.)	73									
9	ε-Keto-undecanoic acid	57.3	52–53	53–54	Lig.	Rods	$C_{11}H_{20}O_3$	65.97	10.06	66.17	10.06
	Semicarbazone			126–127	Benz.	Prisms	$C_{12}H_{23}O_3N_3$	56.03	8.95	56.28	8.85
10	ε-Ketostearic acid[f]	60.7	77–79	86	MeOH	Plates	$C_{18}H_{34}O_3$	72.43	11.48	72.25	11.61
	Semicarbazone			139–140	MeOH	Rods	$C_{19}H_{37}O_3N_3$ $^1/_2H_2O$	62.64	10.44	63.05	10.40
11	ε-Ketoarachidic acid	80	72–73	89	Acetone	Plates	$C_{20}H_{38}O_3$	73.57	11.73	73.33	11.78
	Methyl ester			54–55	MeOH	Leafl.	$C_{21}H_{40}O_3$	74.06	11.84	73.99	11.76
12	ε-Ketobehenic acid	71	79–81	92–93	Acetone	Plates	$C_{22}H_{42}O_3$	74.52	11.94	74.73	11.77
13	ε-Ketolignoceric acid	80	80–82	95–96	Acetone	Prisms	$C_{24}H_{46}O_3$	75.34	12.12	75.57	11.93
	Methyl ester			82–83	MeOH	Prisms	$C_{25}H_{48}O_3$	75.70	12.20	75.55	12.12
14 15	No pure prod. isolated										
16	Start. mat. recovered										
17	7-Benzoylheptylic acid[g]	85	70–72	78–78.5	Lig.	Plates	$C_{14}H_{18}O_3$	71.77	7.74	71.79	7.82
	Semicarbazone			156–156.5	EtOH		$C_{15}H_{21}O_3N_3$	61.83	7.27	62.13	7.19
18	8-Ketohexacosanoic acid	80	94–95	97.5–98.5	Acetone	Prisms	$C_{26}H_{50}O_3$	76.04	12.27	76.13	12.23
	Methyl ester			69–70	MeOH	Plates	$C_{27}H_{52}O_3$	76.35	12.43	76.36	12.34
19	δ-2-Thenoylvaleric acid[h]	60	76–77	77.8–78	Water	Plates					
	Semicarbazone			204–204.4	EtOH	Needl.	$C_{11}H_{15}N_3O_3S$	49.05	5.01	49.20	5.55
20	9,10-Phenanthrenequinone	Quant.		207–208							

[a] Prepared by v. Auwers and Treppmann, *Ber.*, **48**, 1216 (1915), in low yield by the permanganate oxidation of phenylcyclohexene; by adipoylation of benzene, Papa, Schwenk and Hankin, THIS JOURNAL, 69, 3018 (1947); and as a secondary product in the preparation of 1,4-dibenzoylbutane, Bauer, *Ann. chim.*, [9] 1, 395 (1914). [b] Abdullah, *Chem. Zentr.*, **106**, I, 3926 (1935). [c] Plant and Tomlison, *J. Chem. Soc.*, 1092 (1935). [d] Fichter and Bauer, *Ber.*, **31**, 2001 (1898); Bauer, *Ann. chim.*, [9] 1, 367 (1914); Fuson, *et al.*, THIS JOURNAL, **56**, 235 (1934). [e] Borsche and Menz, *Ber.*, **41**, 199 (1908). [f] Lactarinic acid: Bougault and Charaux, *Compt. rend.*, **153**, 572, 880 (1911); Zellner, *Monatsh.*, **41**, 443 (1920); Robinson and Robinson, *J. Chem. Soc.*, **127**, 179 (1925). [g] Wieland and Dragendorff, *Ann.*, **473**, 83 (1929), report the m. p. 84–85°. [h] Billman and Travis, *Proc. Indiana Acad. Sci.*, **54**, 101 (1945) [*C. A.*, **40**, 1826 (1946)].

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.09; H, 6.14.

Recovered starting material amounted to 1.8 g. (41%). The **methyl ester** crystallized from benzene-ligroin in clusters of branched needles, m. p. 101–102°.

Anal. Calcd. for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.77; H, 6.69.

Another oxidation (2.5 g. of acetate) was conducted for four hours without cooling. The acidic fraction (1.2 g.) was digested twice with hot benzene and the residue (0.5 g.) crystallized from toluene. The acid obtained melted at 145–146° and its methyl ester at 131–132°; the substance was identified as the acid III ($n = 4$) by mixed melting point comparison with the known acid and its ester.[2]

Carbinols and Ethylenes

The known and new carbinols (Table I) were all prepared by the Grignard reaction and distilled; in some instances the analyses indicated that some dehydration had occurred, but the product was nevertheless suitable for oxidation. In the preparation of the higher 1-alkylcyclohexanols 10–19, the Grignard reagent was formed from 0.1 mole of halide by refluxing almost to complete disappearance of the magnesium (about two hours); the ketone (for ratio see Table I) was added in the cold (ice-water) and eventually the mixture was refluxed for three hours, and let stand overnight. Decomposition was effected with saturated ammonium chloride solution and the product purified by distillation. The yields are calculated on the basis of the halide.

Oxidation

The general procedure was as follows: 4 g. of substance was dissolved in 150 cc. of glacial acetic acid and the solution was stirred vigorously and 1 g. of chromic anhydride was added. After an induction period varying from five seconds to a few minutes, the anhydride began to dissolve, the solution darkened, and the temperature started to rise. The temperature was then controlled to 30° by ice cooling while 11 g. of chromic anhydride was added in small portions. After a total period of one hour the brown or black mixture was diluted with an equal volume of water and extracted four times with a total of 500 cc. of ether. The ethereal extract was washed four times with water and extracted with 300 cc. of water containing 15 g. of sodium hydroxide. In cases 10, 11, 12 and 13 a larger volume of 5% alkali was necessary (800–900 cc.) and the alkaline extracts were invariably cloudy. The alkaline extract was heated on the steam-bath to

TABLE III

FATTY ACIDS BY WOLFF–KISHNER REDUCTION (PER HUANG)

No.	Name	Yield of crude mat., %	M. p., °C.		Formula	Analyses, %			
						Calcd.		Found	
			Crude	Pure		C	H	C	H
11	Arachidic acid	90	70–72	74–75[6]	$C_{20}H_{40}O_2$	76.80	12.95	76.90	12.95
12	Behenic acid	91	78–79	79.9[6]	$C_{22}H_{44}O_2$	77.58	13.02	77.59	13.17
13	Lignoceric acid	93	76–78	84.1[6]	$C_{24}H_{48}O_2$	78.19	13.13	78.25	13.20
18	Cerotic acid	95	82–83	87–87.5[6]	$C_{26}H_{52}O_2$	78.72	13.22	79.59	13.42

remove the ether (except in the preparation of thenoylvaleric acid), cooled and poured into 100 cc. of 36% hydrochloric acid. The precipitated acid was collected and the filtrate continuously extracted with ether (except in cases where solubility of the acid in water was negligible). The ethereal residue was evaporated and the oil was treated with semicarbazide hydrochloride and sodium acetate. In cases 1a, 1b, 1c, 5 and 7 a crystalline semicarbazone was obtained.

In some oxidations (rarely in the case of carbinols) a troublesome scum of finely divided red solid appears in the ether extract. After the bulk of the acetic acid has been removed by washing, this scum can be eliminated and any yellow coloration of the solution discharged by brief shaking with water containing a little freshly added sodium hydrosulfite.

The results are summarized in Table II. The yields refer to the acids as initially obtained, for the crude preparations were of good quality suitable for further use. Additional notes are as follows.

No. 4: **δ-(α- and β-Naphthoyl)-valeric Acids from Naphthalene.**—Aluminum chloride (105 g.) was added to a solution of 50 g. of naphthalene in 400 cc. of nitrobenzene and then 64 g. of ethyl adipoyl chloride in 100 cc. of nitrobenzene was added during fifteen minutes at 0–5°. After four hours at 0–5° and ten hours at 25° the mixture was decomposed, the ester collected in benzene and hydrolyzed. The crude acid mixture (53 g., 63.5%) on crystallization from methanol afforded one isomer (m. p. 140°) that was purified by sublimation at 0.1 mm. (170–230°) and crystallization from methanol:

δ-(β-Naphthoyl)-valeric Acid, m. p. 144–145°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.97; H, 6.29. Found: C, 74.83; H, 6.36.

The **semicarbazone**: clusters of needles (ethyl alcohol), m. p. 210°.

Anal. Calcd. for $C_{17}H_{19}O_3N_3$: C, 65.16; H, 6.11. Found: C, 64.89; H, 6.21.

The **methyl ester**: rods (methyl alcohol), m. p. 74–75°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.38; H, 6.81.

δ-(α-Naphthoyl)-valeric acid was isolated from the methanol mother liquor. The recovered oily acid was distilled at 220–240° (4 mm.) and the oil solidified on long standing. Purification through the semicarbazone (m. p. 187°), redistillation, and crystallization gave acid melting at 56–57° and showing no depression when mixed with sample No. 4. The yield of α-acid was 3 g.

The acidic product of oxidation was sublimed at 210–230° (0.08 mm.) and afforded first a small amount of α-naphthoic acid, m. p. 159–160°. The main reaction product was then purified through the semicarbazone as above.

No. 5.—The neutral fraction afforded a disemicarbazone that crystallized from dilute acetic acid in needles, m. p. 245°. The analysis suggests that the substance is the **hydrate of the disemicarbazone of dicyclohexadiene-1,1′-dione-3,3′.**

Anal. Calcd. for $C_{14}H_{32}O_3N_6$: C, 52.16; H, 6.88. Found: C, 52.33; H, 6.66.

No. 18.—1-Octadecylcycloöctene was dissolved in the usual amount of acetic acid by warming and the solution cooled to 30° with stirring so as to obtain a fine suspension of the hydrocarbon. During the extractions care must be taken to avoid vigorous shaking or troublesome emulsions result. Extraction of the ethereal solution with alkali caused precipitation of the colloidal sodium salt; this was filtered by gravity, washed with ether, and suspended in the alkaline extract. The ether was expelled by heating and the mixture acidified.

No. 19.—The thenoylvaleric acid is somewhat sensitive to alkali (odor of hydrogen sulfide) and is best extracted with sodium carbonate.

Reduction to Higher Fatty Acids

The procedure of Huang-Minlon[5] was applied as follows. A mixture of 1 g. of keto acid, 0.8 g. of sodium hydroxide, 1 cc. of 85% hydrazine hydrate, and 5 cc. of triethylene glycol was refluxed for one hour, the inside temperature was brought to 200° by distillation, and the solution refluxed for three hours longer. The solution was cooled to about 90° and acidified; the acid solidified easily and the crude product (see Table III for m. p. and yield) afforded after three recrystallizations the pure fatty acid. The melting points of the pure samples were determined according to the method of Francis and Piper.[6]

Summary

Carbinols obtained from an alkyl or aryl Grignard reagent and cyclopentanone, cyclohexanone, or cycloöctanone are oxidized smoothly by chromic anhydride at 30° under anhydrous conditions to δ-, ε- or η-keto acids in good yield. Thirteen successful applications of the reaction are reported and limiting features are defined.

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[6] Francis and Piper, THIS JOURNAL, **61**, 577 (1939).