[CONTRIBUTION NO. 753 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Reactions of Certain Ketone Anions with β-Chloropropionitrile[1]

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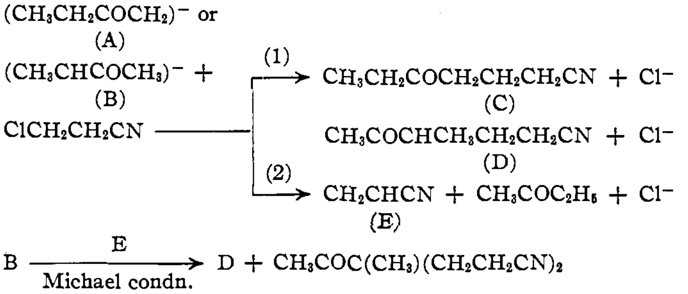
Several workers have studied extensively the reactions between a number of unsymmetrical ketones and acrylonitrile[3,4] in the presence of such basic condensing agents such as alcoholic potassium hydroxide and "Triton B."

In the present study, several ketone anions (formed by reaction of the ketones with sodium amide) have been condensed with another cyanoethylating agent, β-chloropropionitrile. When a ketone anion reacts with β-chloropropionitrile, two types of reactions may occur. The anion may be alkylated or it may react with the chloronitrile by a β-elimination process to give acrylonitrile, which may then undergo a typical Michael condensation with part of the anion by a mechanism described earlier.[5]

These two possible courses of reaction are represented by the following scheme using the anions which may be formed from methyl ethyl ketone.



$(CH_3CH_2COCH_2)^-$ or
(A)
$(CH_3CHCOCH_3)^- +$
(B)
$ClCH_2CH_2CN$

$$\xrightarrow{(1)} CH_3CH_2COCH_2CH_2CH_2CN + Cl^-$$
(C)
$$CH_3COCHCH_3CH_2CH_2CN + Cl^-$$
(D)
$$\xrightarrow{(2)} CH_2CHCN + CH_3COC_2H_5 + Cl^-$$
(E)

$$B \xrightarrow[\text{Michael condn.}]{E} D + CH_3COC(CH_3)(CH_2CH_2CN)_2$$

Apparently, the anions of unsymmetrical ketones react exclusively by the elimination-condensation mechanism since, as has been observed earlier[6] when acrylonitrile was used as the cyanoethylating agent, the reaction products have the cyanoethyl groups located on the more highly substituted (less acidic) alpha carbon atom.[7] In agreement with the concept that most alkylation reactions occur relatively slowly and elimination reactions take place rapidly,[8] it was found that when β-chloropropionitrile was added to an alcoholic solution of sodiomalonic ester (prepared by the reaction of the ester with alcoholic sodium ethoxide), the reaction mixture was neutral to moist litmus paper within a few minutes after the addition of the nitrile was completed.

The yields of the keto nitriles prepared are found in Table I. Also listed are the yields of the cyanoethylation products obtained by other workers from the direct cyanoethylation of the same ketones with acrylonitrile. It may be seen that methyl isopropyl ketone gives only a monocyanoethylated product by either the β-chloropropionitrile or acrylonitrile method. Using either method, diisopropyl ketone gives a mixture of mono- and dicyanoethylated products, while cyclohexanone gives a mixture of mono-, di- and tetracyanoethylated derivatives. While the direct cyanoethylation of diisobutyl ketone failed, its reaction with β-chloropropionitrile has resulted in the formation of both the mono- (35.4%) and the dicyanoethylated (18.8%) compounds. All the other ketones listed in the table gave a mixture of mono- and dicyanoethylated compounds by the β-chloropropionitrile method, but only dicyanoethylated products were obtained in the direct cyanoethylation with acrylonitrile.

Experimental

General Method for the Condensation of β-Chloropropionitrile with Ketone Anions.—The apparatus used in these condensations consisted of a 2000-ml. three-neck, round-bottom flask equipped with ground-glass joints, a dibutyl phthalate-sealed stirrer, an addition funnel and a reflux condenser (protected from atmospheric moisture by a drying tube filled with Drierite). Into this flask was placed about 500 ml. of anhydrous liquid ammonia. Following the method described in the literature,[9] one mole (23 g.) of sodium was added to the ammonia and converted to sodium amide. Then, 500 ml. of absolute ether was added to the flask and the reaction mixture placed on a steam-bath. When the ammonia had evaporated, as evidenced by the refluxing of the ether, the steam-bath was removed.

To the stirred suspension of sodium amide was added 1.25 moles of the appropriate ketone, dissolved in 150 ml. of absolute ether, at such a rate as to keep the ether refluxing rapidly. After adding the ketone, the mixture was stirred until refluxing stopped (ten to fifteen minutes) and then 500 ml. more of absolute ether was added. Then, 1.0 mole of β-chloropropionitrile, dissolved in 75 ml. of absolute ether, was added at such a rate as to keep the ether refluxing rapidly. After adding the nitrile (this takes about sixty minutes), the mixture was stirred for ten minutes.

The contents of the flask was poured into 250 ml. of ice and water and acidified with concentrated hydrochloric acid. The mixture was extracted with several 200-ml. portions of ether and the combined extracts dried over Drierite. After distilling the solvent, the residue was fractionated in vacuum. The monocyanoethylated products were obtained as liquids directly on distillation. The

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[1] Paper V in the series, "Condensations Effected by the Alkali Amides"; for paper IV, see Hamell and Levine, *J. Org. Chem.*, **15**, 162 (1950).

[2] This paper is based on a thesis submitted by Lloyd B. Barkley to the graduate school of the University of Pittsburgh in partial fulfillment of the requirements for the degree of Master of Science.

[3] For an excellent review on this subject, see Bruson, "Organic Reactions," Vol. **5**, Chapt. 2.

[4] Acara and Levine, THIS JOURNAL, **72**, 2864 (1950).

[5] Zellars and Levine, *J. Org. Chem.*, **13**, 911 (1948).

[6] Bruson and Riener, THIS JOURNAL, **64**, 2850 (1942).

[7] In this connection, Boekelheide (*ibid.*, **69**, 790 (1947)) has treated the anion of 2-phenylcyclohexanone with β-chloropropionitrile and obtained 2-(2-cyanoethyl)-2-phenylcyclohexanone.

[8] Hauser, Shivers and Skell, *ibid.*, **67**, 409 (1945).

[9] Levine and Hauser, *ibid.*, **66**, 1768 (1944).

TABLE I

CYANOETHYLATION PRODUCTS OF CERTAIN KETONES[a]

Ketone	Cyanoethylation products	B. p. or m. p., °C.	Mm.	Cyanoethylating agent: β-Chloropropionitrile yield, %	Cyanoethylating agent: Acrylonitrile yield, %	Formula	Analyses, %: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Methyl ethyl	Mono	115–116.5	15[b]	6.0	0[d]	$C_7H_{11}NO$					11.19	10.88
	Di	200–214	5									
		65.5–66.5[c,d]		47.2	89[d]							
Methyl *n*-propyl	Mono	109–110	7.5[e]	14.9		$C_8H_{13}NO$	69.01	69.26	9.44	9.15	10.06	10.09
	Di	190–205	5									
		108.5–109[c,d]		14.2	43[d]							
Methyl isopropyl	Mono	94–96.5	3[f]	53.5	59[f]							
	Di			0	0			69.07		9.06		10.26
Methyl isobutyl	Mono	122–124	5[g]	17.4	0[d]	$C_9H_{15}NO$	70.53	70.91	9.89	9.71	9.14	9.40
	Di	99–99.5[c,d]		15.2	20[d]							
Methyl *n*-amyl	Mono	124–126	6[h]	18.7	0[d]	$C_{10}H_{17}NO$					8.43	8.37
	Di	220–230	3.5									
		62–62.5[c,d]		40.0	50[d]							
Methyl *n*-hexyl	Mono	130–132	4[i]	18.8	0[d]	$C_{11}H_{19}NO$					7.73	7.44
	Di	210–215	2									
		46.5–47[c,d]		30.6	50[d]							
Diisopropyl	Mono	126.5–128	10[j]	55.2	40[j]							
	Di	145–155	0.6[j]	17.6	?[k]							
Diisobutyl	Mono	99–101.5	2	35.4	0[d]	$C_{12}H_{21}NO$					7.17	7.27
	Di	185–200	3.5									
		80–81[c]		18.8	0[d]	$C_{15}H_{24}N_2O$					11.28	11.22
Cyclohexanone	Mono	143–148	10[l]	16.3	10.9[d]							
	Di	223–230	2.5									
		69–70[c,d]		44.5	12.2[d]							
	Tetra	164–165[c,d]		12.2	38.6[d]							

[a] All melting points are corrected. [b] After refluxing a small amount of this compound with 10% NaOH, it gave a positive iodoform test. [c] Melting point. [d] Bruson and Riener, THIS JOURNAL, 64, 2850 (1942). [e] Saponified in 74% yield to 4-acetylhexanoic acid, b. p. 156–158° at 10 mm.; the acid gave a positive iodoform test; semicarbazone of acid, m. p. 140–141°; analysis: Calcd. for $C_9H_{17}N_3O_3$: N, 19.52; Found: N, 19.67; this acid was oxidized by alkaline sodium hypobromite solution to α-ethylglutaric acid, m. p. 58–59° (Auwers and Titherley, *Ann.*, **292**, 144 (1896)). [f] Saponified in 84.8% yield to 4-acetyl-4-methylpentanoic acid, b. p. 151–152° at 12 mm.; m. p. 46–48° (from anhydrous ether) (Campbell, *et al.*, *J. Chem. Soc.*, 1741 (1948)). [g] Saponified in 78.2% yield to 4-acetyl-5-methylhexanoic acid, b. p. 149–151° at 7 mm.; m. p. 46–46.5° (from 30–60° petroleum ether); the acid gave a positive iodoform test; semicarbazone of acid, m. p. 165.5–166°; analysis: Calcd. for $C_{10}H_{19}N_3O_3$: N, 18.83. Found: N, 18.74; the acid was oxidized with alkaline sodium hypobromite solution to α-isopropylglutaric acid, b. p. 195–203° at 10 mm.; m. p. 94–95° (Boedtker, *Bull. soc. chim.*, [4] **17**, 397 (1915). [h] Saponified in 64% yield to 4-acetyloctanoic acid, b. p. 150–151° at 2.5 mm.; the acid gave a positive iodoform test; neutral equiv. Calcd. for $C_{10}H_{18}O_3$: 186.23; Found: 187.25; semicarbazone of acid, m. p. 137–138°; analysis: Calcd. for $C_{11}H_{21}N_3O_3$: N, 17.27. Found: N, 17.41. [i] Saponified in 60% yield to 4-acetylnonanoic acid, b. p. 165–165.5° at 3.5 mm.; the acid gave a positive iodoform test; neutral equiv. Calcd. for $C_{11}H_{20}O_3$: 200.3. Found: neut. equiv., 201.1; semicarbazone of acid, m. p. 136–137°; analysis: Calcd. for $C_{12}H_{23}N_3O_3$; N, 16.3. Found: N, 16.58. [j] Bruson, U. S. Patent 2,386,736 (*C. A.*, **40**, 7234 (1946)). [k] No yield given in ref. in footnote *j*. [l] Since Bruson and Riener (ref. in footnote *d*) report b. p. of this compound is 138–142° at 10 mm., a sample was saponified to 3-(2-cyclohexanoyl)-propionic acid, m. p. 63–64° (Mannich and Koch, *Ber.*, **75B**, 804 (1942)); semicarbazone of acid, m. p. 185° (dec.) (see previous ref.).

dicyanoethylated products usually distilled as yellow viscous oils which crystallized on standing. These dicyanoethylated derivatives were recrystallized by dissolving them in absolute ethanol and cooling the solutions in a Dry Ice-acetone mixture. The product which separates as an oil crystallizes if the beaker containing the product is scratched with a glass rod while the mixture is warming to room temperature.

Proof of Structure of the Monocyanoethylated Derivatives.—The structures of these compounds were established in the following ways: (a) if the corresponding δ-keto acids were known compounds, the keto nitriles were saponified to the δ-keto acids and suitable derivatives were prepared; (b) if the δ-keto acids were new compounds, their neutral equivalents were determined and a qualitative iodoform test performed; (c) if the δ-keto acids were new compounds and the corresponding glutaric acids were known, samples of the acids were oxidized with alkaline sodium hypobromite solution and the melting points of the acids compared with those reported in the literature.

Cyanoethylation of Malonic Ester.—In a 1000-ml. three-neck flask equipped as described above was placed 4.28 moles (197.2 g., 250 ml.) of absolute ethanol. Freshly cut sodium (0.5 mole, 11.5 g.) was added and converted to sodium ethoxide. Diethyl malonate (0.515 mole, 82.5 g., 78.2 ml.) was added over a fifteen-minute period. To the sodiomalonic ester, β-chloropropionitrile (0.5 mole, 44.8 g., 39.0 ml.) was added over a ten-minute period. Five minutes after the addition of the nitrile was complete, the reaction mixture was neutral to moist litmus paper. The excess ethanol was removed on a steam-bath and the residue poured into 200 ml. of ice water and acidified with cold concentrated hydrochloric acid. The mixture was extracted with several 100-ml. portions of ether and the combined extracts dried over Drierite. The solvent was distilled and the residue fractionated in vacuum. There was obtained 30.0 g. (28.1%) of diethyl 2-cyanoethylmalonate, b. p. 144–146° at 5 mm.[10] The residue, which crystallized on cooling, gave 31.1 g. (46.7%) of diethyl bis - (2 - cyanoethyl) - malonate. Recrystallization from acetone gave white crystals, m. p. 61.5°.[10]

Acknowledgment.—The authors are grateful to the American Cyanamid Company for having contributed the β-chloropropionitrile used in this investigation.

Summary

1. Nine ketone anions (prepared from the ketones by reaction with sodium amide) have been cyanoethylated.
2. From each experiment a mixture of mono- and polycyanoethylated products has been obtained.
3. A possible course for the condensations has been suggested. The proposed mechanism assumes that two consecutive reactions occur, *i. e.*, an elimination reaction between the ketone anion and β-chloropropionitrile to give the ketone and acylonitrile, which then undergo a Michael condensation to give the cyanoethylated derivatives.

PITTSBURGH, PA. RECEIVED JANUARY 26, 1950

(10) Hesse and Bucking, *Ann.*, **563**, 31 (1949).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE]

The 1,3-Rearrangement. The Synthesis and Rearrangement of 4,4-Dimethyl-3-ethyl-2-pentanol[1a]

BY WILLIAM A. MOSHER AND JAMES C. COX, JR.[1b]

In 1933 Laughlin[2] observed the formation of 2,3,4-trimethyl-2-pentene in addition to expected products, in the copolymerization of *s*-butyl and *t*-butyl alcohols. This was regarded as such an unusual rearrangement that its discovery was not published until it had been repeatedly observed. This product can be accounted for by assuming a 1,3-rearrangement of a methyl group in the intermediate carbonium ion.

Drake, Kline and Rose[3] obtained 3,4,5,5-tetramethyl-2-hexene as one of the decenes from the acid treatment of methylisopropylcarbinol, but rejected the idea of a possible "1,3-shift" in the intermediate proposed by Whitmore. Whitmore and Mosher[4] confirmed the results of Drake, Kline and Rose.[3] Whitmore and Mosher[5] further encountered several such "1,3-shifts" in the course of their studies on the depolymerization of 3,4,5,5-tetramethyl-2-hexene and of 3,5,5-trimethyl-2-heptene.

From all cases reported, however, it has been impossible to conclude whether this rearrangement involves a single 1,3-shift or two successive 1,2-shifts, *i. e.*, the "double pinacol rearrangement" suggested by Wachter.[6]

The present investigation was undertaken with the highly-branched secondary alcohol, 4,4-dimethyl-3-ethyl-2-pentanol, which has both methyl and ethyl in rearrangeable positions.

The identification of 2,3,4-trimethyl-2-hexene as the dehydration product of this alcohol would indicate two successive 1,2-shifts. If 2,4-dimethyl-3-ethyl-2-pentene, however, resulted as the dehydration product, it would establish the rearrangement as a 1,3-shift. The possible routes that the dehydration reaction could take are represented in Fig. 1.

The dehydration of 4,4-dimethyl-3-ethyl-2-pentanol yielded 43% of 4,4-dimethyl-3-ethyl-2-pentene (I) and 57% of 2,4-dimethyl-3-ethyl-2-pentene (II). No 2,3,4-trimethyl-2-hexene (III) was found. This indicates that both normal (I) and rearranged (II) products were formed, and in the ratio of 3:4. These results indicate that the formation of the rearranged nonene (II) took place by means of a 1,3-rearrangement rather than by two successive 1,2-shifts.

The synthesis of 4,4-dimethyl-3-ethyl-2-pentanol presented difficulties, but was eventually accomplished from the lower boiling isomer of "diisobutylene," 2,4,4-trimethyl-1-pentene, proceeding through methyl neopentyl ketone and 4,4-dimethyl-3-ethylidene-2-pentanone, followed by reduction. The over-all yield was poor.

The initial step of the synthesis, the oxidation of 2,4,4-trimethyl-1-pentene to methyl neopentyl ketone, was carried out with yields up to 56% of the ketone, considerably higher than reported previously for this reaction. This yield was obtained by the slow addition of the theoretical amount of concentrated sulfuric acid to a mixture of diisobutylene and potassium dichromate solution, the reaction temperature being maintained at 30–35°. Appreciable polymer was obtained under higher temperature conditions.

Acid dichromate was found to be a more effec-

(1) (a) Presented before the Division of Organic Chemistry, American Chemical Society, Atlantic City, September 20, 1949. From a dissertation presented by James C. Cox, Jr. in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Delaware, June, 1949. (b) E. I. du Pont de Nemours and Company Post Graduate Fellow in Chemistry, 1948–1949.

(2) (a) Laughlin, Ph.D. Thesis, The Pennsylvania State College; (b) Whitmore, Laughlin, Matuszeski and Surmatis, THIS JOURNAL, **63**, 576 (1941).

(3) Drake, Kline and Rose, THIS JOURNAL, **56**, 2076 (1934).

(4) Whitmore and Mosher, *ibid.*, **63**, 1120 (1941).

(5) Whitmore and Mosher, *ibid.*, **68**, 281 (1946).

(6) Wachter, *Ind. Eng. Chem.*, **30**, 822 (1938).