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ACYLATION STUDIES. I. METHYL CYCLOPROPYL KETONE

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Previous studies (1) of the acid-catalyzed acylation of unsymmetrical ketones, in which the condensation may occur at either the methyl or a methylene or methinyl group, have been restricted to aliphatic[2] ketones. An investigation of the acylation of unsymmetrical ketones containing various alicyclic rings is in progress in this laboratory. The results with methyl cyclopropyl ketone, in which the methinyl group is a member of the strained cyclopropane ring, are reported in this paper.

The ketone was acylated with both acetic and propionic anhydrides in the presence of boron trifluoride. When separation of the products with 1% sodium hydroxide (1a) was attempted, the methyl derivatives VI and VIA were obtained in yields of 57% and 18.9% respectively, but none of the methinyl derivatives could be isolated. This is in contrast to the acetylation of the analogous methyl isopropyl ketone, which under similar conditions gives a product which is 68% methinyl derivative (1a).

Formation of the enol of the ketone is considered to be a prerequisite for acid-catalyzed condensation (1a). Thus, it would appear that the enol involving the methinyl hydrogen of methyl cyclopropyl ketone is not formed under the reaction conditions employed. It should be noted that attempts to prepare cyclopropanone have failed but that the hydrate and the methyl hemiacetal, in which the strain of an oxygen atom doubly bonded to a carbon atom of the cyclopropane ring is avoided, are known (2).

Since the angle of a carbon-oxygen-carbon bond is approximately 111° (3), the strain in cyclopropanone and the enol prerequisite for acid-catalyzed acylation at the methinyl carbon of methyl cyclopropyl ketone must be similar. This strain may be responsible for the absence of the methinyl derivatives.

Certain base-catalyzed reactions (Chart I) were carried out in order that the products might be available for this and another study. It is a consequence of the mechanism (4, 5) for base-catalyzed Claisen reactions that only the methyl derivative would be expected from the acylation of methyl cyclopropyl ketone in the presence of bases such as sodium ethoxide and sodium amide. That each product was the expected methyl derivative was shown by a red enol test which is characteristic of methyl derivatives (6) and one or more of the following: formation of a copper enolate, reaction with hydrazines to form pyrazoles, or alkylation with an alkyl halide.

Hydrolysis of the 1-phenylpyrazole (V) resulted in a monocarboxylic acid which, as expected, was unaffected by permanganate oxidation. Attempts to

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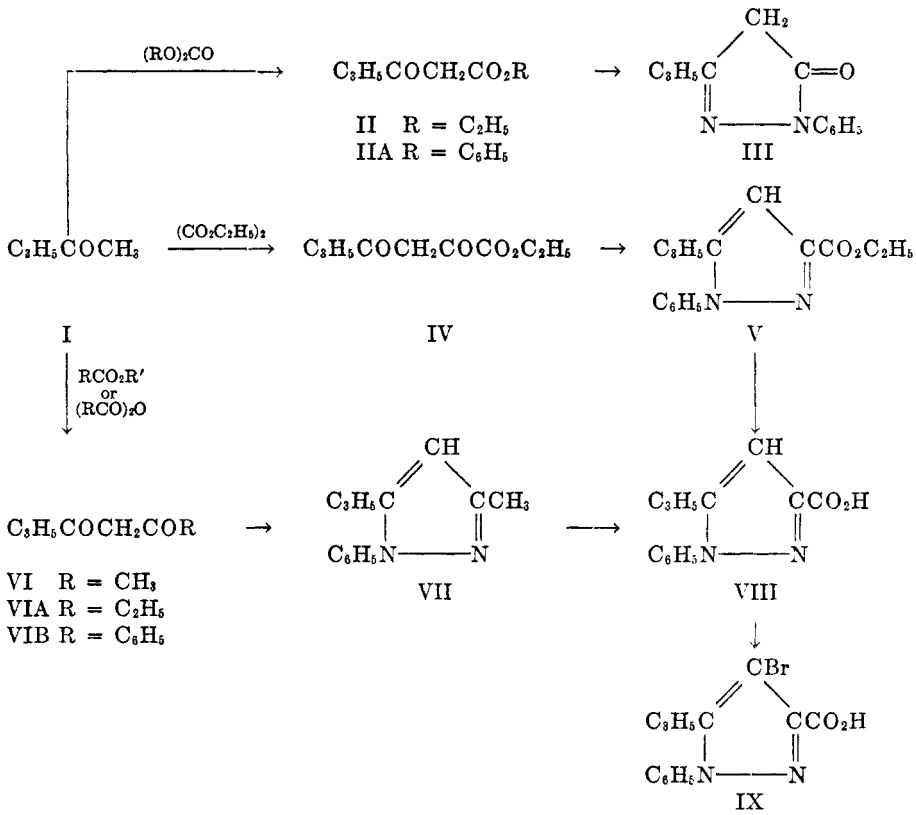
[2] 2-Methylcyclohexanone has been studied (1a) but, as the authors point out, it should react as a typical aliphatic ketone.

open the cyclopropane ring were unsuccessful. Cleavages with hydrobromic acid (7, 8) failed; the original acid was recovered in each case. Treatment of the acid with bromine in acetic acid gave a product containing only one bromine atom. The similar behavior of 2-cyclopropylpyridine has been ascribed (9) to the elimination of hydrogen bromide after opening of the ring by bromine. This results in an allylic bromide. However, our bromination product was recovered unchanged from alkaline permanganate oxidation, did not form a precipitate

CHART I[3]



with either alcoholic silver nitrate or sodium iodide in acetone, and its infrared spectra had an absorption band at 9.9 μ which is characteristic for the cyclo-

[3] Structures were written for the pyrazole derivatives on the assumption that the initial reaction of phenylhydrazine with the diketone VI was at the more reactive carbonyl group adjacent to the methyl group. Such is the case, for example, with benzoylacetone; Knorr and Duden, *Ber.*, **26**, 111 (1893). However, this is not to be construed as unequivocal assignment of structure, for each pyrazole may have the isomeric structure in which the positions of the 3- and 5-substituents are reversed. These alternate positions are indicated in parentheses in the nomenclature employed in this paper.

For an example in which both isomeric pyrazoles are obtained from an unsymmetrical 1,3-diketone, see Tracy and Elderfield, *J. Org. Chem.*, **6**, 70 (1941).

propane ring (10). This behavior indicates that the cyclopropane ring remained intact during the reaction with bromine. Since the substitution of bromine under similar conditions at the 4-position of the pyrazole ring has been reported (11), the bromination product is believed to be 1-phenyl-4-bromo-5(3?)-cyclopropylpyrazole-3(5?)-carboxylic acid (IX). Methyl 2-phenyl-3-benzoyl-1,1-cyclopropanedicarboxylate is similarly resistant to halogens (12).

The similarity in the boiling points of the diethyl oxalate condensation products obtained in the present work and by Chelintsev (13) suggested that they were the same. Chelintsev, however, assigned the structure II to his product, perhaps on the assumption that loss of carbon monoxide had occurred. To test such an assumption, IV was heated until evolution of gas occurred (175–200°). The only product isolated in sufficient quantity to characterize was methyl cyclopropyl ketone (54% yield). Pyrolysis of II also resulted in the formation of the ketone. Formation of a ketone by the loss of carbon dioxide and ethylene has been observed for certain other ethyl β-ketoesters (14), and it explains the failure to isolate any quantity of II from the pyrolysis of IV. Consequently, it seems likely that Chelintsev's product was IV and not II as reported.

EXPERIMENTAL[3, 4]

Materials. Samples of diphenyl carbonate and methyl cyclopropyl ketone were kindly furnished by the U. S. Industrial Chemicals, Inc. Most of the ketone used was prepared from α-acetylbutyrolactone (15). Sodium amide was purchased from the Farchan Research Laboratories, Cleveland, Ohio. The reactants were dried with a suitable agent, fractionated, and the portion boiling over a one-degree range used.

ACID-CATALYZED ACYLATIONS

The procedure of Hauser and Adams (1a) was used. Removal of the diketones by steam-distillation was unsatisfactory. Instead, the reaction mixtures were added to the sodium acetate solution and were heated with rapid stirring on a steam-bath for 45 minutes. The mixtures were then allowed to stand overnight at room temperature. The dark brown oily layers were separated, and the aqueous layers were extracted with ether. Attempted separation of methyl and methinyl derivatives with 1% sodium hydroxide gave no methinyl derivative from either product. From 192 g. (1.88 moles) of acetic anhydride and 79 g. (0.94 mole) of the ketone, 67.5 g., yield 57%, of the methyl derivative VI was separated. From 232 g. (1.78 moles) of propionic anhydride and 75.2 g. (0.89 mole) of the ketone, there was separated 23.6 g. (18.9%) of the methyl derivative VIA, b.p. 78–79°/8 mm., n_D^{25} 1.4900.

Considerable non-distillable high-boiling material was obtained from the propionic anhydride condensation. When this was heated at atmospheric pressure, dense white fumes were evolved and a liquid finally distilled. Fractionation of this gave an additional 8 g. of the methyl derivative VIA.

Benzoylation with benzoic anhydride under similar conditions gave only unreacted benzoic anhydride and ketone and some benzoic acid.

Acetylation using boron trifluoride-etherate (16) gave insufficient product to be isolated, although a small quantity of the copper salt of VI was obtained.

BASE-CATALYZED ACYLATIONS

The condensations using sodium amide as the catalyst were effected by the usual procedure (4), except that the sodium amide was not prepared in the reaction flask but was

[4] All melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Boiling points are uncorrected.

added as the free-flowing powder. Previously described procedures (17) were used for the diethyl oxalate condensations. The results of the condensations are summarized in Tables I and II. The preparation of derivatives of the reaction products follow.

TABLE I

BASE-CATALYZED ACYLATIONS OF METHYL CYCLOPROPYL KETONE

ESTER	CONDENSING AGENT	RATIO OF REACTANTS[a]	TEMP., °C.	TIME, HOURS	PRODUCT	YIELD, %	B.P., °C./MM.	n_D^{25}
Diethyl carbonate[b]	$NaNH_2$	A	35	2.5[c]	Ethyl β-cyclopropyl-β-ketopropionate (II)	55	90–95/4	1.4542
Diphenyl carbonate	Na	B	0–5	4[d]	Phenyl β-cyclopropyl-β-ketopropionate (IIA)	10[e]	105–110/10	1.5059
Diphenyl carbonate	$NaNH_2$	C	35	1.5[d]	Compound IIA	60[f]	105–110/10	1.5059
Diethyl oxalate	$NaOC_2H_5$	B	25	15	Ethyl γ-cyclopropyl-α, γ-diketobutyrate (IV)	78	124.5–125.5/6 138–142/15	1.5048
Ethyl acetate[g]	$NaNH_2$	C	0	1[d]	1-Cyclopropyl-1,3-butanedione (VI)	38[h]	55–58/5 68–70/12	1.4924
Ethyl acetate	$NaNH_2$	A	35	2[c]	Compound VI	75[i]	55–58/5	1.4924
Ethyl benzoate	$NaNH_2$	A	35	2[d]	1-Cyclopropyl-3-phenyl-1,3-propanedione (VIB)	68[j]	153–156/4[k]	1.5655
Phenyl benzoate	$NaNH_2$	D	35	2[d]	Compound VIB	17[l]	153–156/4	1.5655
Phenyl benzoate	Na	B	0–5	2[d]	Compound VIB	40	153–156/4	1.5655

[a] From 0.5 to 1 mole of ketone was used in each reaction. The molar ratios of the ester, ketone, and condensing agent respectively are: A = 2:1:2, B = 1:1:1, C = 1:1:2, D = 1.5:1:2. [b] Using sodium ethoxide with continuous removal of ethanol [Wallingford, Homeyer, and Jones, *J. Am. Soc. Chem.*, **63**, 2252 (1941)] no product was obtained. [c] Stirred an additional 3–4 hours at room temperature. [d] Stood an additional 16–18 hours at room temperature. [e] Yield based on crude product. [f] Yield based on crude product. Decomposition occurred during fractionation; final yield of pure product was 20%. [g] No solvent was used; see Claisen, *Ber.* **38**, 695 (1905). [h] Yield based on β-diketone obtained by acidification of the copper salt. [i] Reaction at room temperature for less than 3 or more than 18 hours resulted in 38–40% yields. [j] Benzamide also obtained. [k] M.p. 36–37°. [l] Dibenzamide also obtained.

a. Derivatives of II and IIA. Ethyl α-butyl-β-cyclopropyl-β-ketopropionate was obtained by alkylating (18) 23.4 g. (0.15 mole) of II using 24 g. (0.17 mole) of dry *n*-butyl bromide and 3.4 g. (0.15 g.-atom) of sodium. There was obtained 15 g. (44%) of product, b.p. 125–128°/11–12 mm., n_D^{25} 1.4484.

Anal. Calc'd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50.
Found: C, 67.97; H, 9.67.

TABLE II

ANALYSES OF ACYLATION PRODUCTS AND THEIR COPPER SALTS

COMPOUND	FORMULA	ANALYSES				M.P., °C.	COPPER SALT YIELD, %	FORMULA	ANALYSES[a]	
		C		H					Copper	
		Calc'd	Found	Calc'd	Found				Calc'd	Found
Ethyl β-cyclopropyl-β-ketopropionate (II)	$C_8H_{12}O_3$	61.52	61.78	7.75	7.76	134–135	80	$C_{16}H_{22}CuO_6$	17.00	16.94
Phenyl β-cyclopropyl-β-ketopropionate (IIA)	$C_{12}H_{12}O_3$	70.57	70.29	5.93	5.47		[b]			
Ethyl γ-cyclopropyl-α,γ-diketobutyrate (IV)	$C_9H_{12}O_4$	58.68	58.52	6.57	6.71	149–151	95	$C_{18}H_{22}CuO_8$	14.78	14.72
1-Cyclopropyl-1,3-butanedione (VI)	$C_7H_{10}O_2$	66.67	66.89	7.99	8.21	193–194	80	$C_{14}H_{18}CuO_4$	20.25	20.15
1-Cyclopropyl-1,3-pentanedione (VIA)	$C_8H_{12}O_2$	68.54	68.42	8.63	8.61	168–169	82	$C_{16}H_{22}CuO_4$	18.65	18.42
1-Cyclopropyl-3-phenyl-1,3-propanedione (VIB)	$C_{12}H_{12}O_2$	76.57	76.71	6.43	6.12	188–189	97	$C_{24}H_{22}CuO_4$	14.51	14.38

[a] Copper was determined gravimetrically as CuO remaining after combustion of the sample with 2 drops of dilute nitric acid in a crucible.

[b] A copper salt appeared to form, but it could not be crystallized.

Hydrolysis (19) of the above ester yielded caproic acid, which was further characterized by its *p*-bromophenacyl ester (20).

The *2,4-dinitrophenylhydrazone* of II was prepared by adding 30 ml. of 2,4-dinitrophenylhydrazine reagent (21) to 1 g. of II. A red gummy solid separated which crystallized after standing in the refrigerator. Two recrystallizations from methanol gave 1 g. (60%) of solid, m.p. 85°.

Anal. Calc'd for $C_{14}H_{16}N_4O_6$: C, 49.98; H, 4.79; N, 16.66.

Found: C, 50.30; H, 4.78; N, 16.58.

1-Phenyl-3-cyclopropyl-5-pyrazolone (III). To a solution of 7.8 g. (0.05 mole) of II in 25 ml. of glacial acetic acid, there was added 5.4 g. (0.05 mole) of phenylhydrazine. The mixture was heated under reflux for five hours. It was poured onto cracked ice, and a yellow-white solid separated. After four recrystallizations from absolute ethanol, white III, m.p. 111–114°, was obtained.

Anal.[5] Calc'd for $C_{12}H_{12}N_2O$: C, 71.97; H, 6.04; N, 13.99.

Found: C, 71.91; H, 6.15; N, 14.17.

Similar treatment of IIA gave a white solid, m.p. 111–113°, whose m.p. was not depressed when mixed with the above pyrazolone.

b. Derivatives of IV. Ethyl 1-phenyl-5(3?)-cyclopropylpyrazole-3(5?)-carboxylate (V). The general procedure of Claisen and Roosen (22) was used. From 37 g. (0.2 mole) of IV in 75 ml. of glacial acetic acid and 22 g. (0.2 mole) of phenylhydrazine, there was obtained after two recrystallizations (95% ethanol) 48 g. (95%) of yellow-white crystals, m.p. 59–60°.

Anal. Calc'd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29.

Found: C, 70.37; H, 6.28.

1-Phenyl-5(3?)-cyclopropylpyrazole-3(5?)-carboxylic acid (VIII) was obtained by refluxing 10 g. (0.04 mole) of V with 35 ml. of a 5% solution of sodium hydroxide in water-ethanol (1:1) for three hours. After removal of the alcohol, the residue was dissolved in 20 ml. of water and acidified with 15% hydrochloric acid. The precipitate was recrystallized twice from benzene, and 8.5 g. (92%) of white VIII, m.p. 137–139°, was obtained.

Anal. Calc'd for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.30; Neut. equiv., 228.3.

Found: C, 68.32; H, 5.21; Neut. equiv., 230.9, 231.0.

Oxidation with aqueous permanganate resulted in the recovery of unchanged VIII.

1-Phenyl-5(3?)-cyclopropyl-4-bromopyrazole-3(5?)-carboxylic acid (IX). A solution of 2 g. of VIII in 40 ml. of glacial acetic acid was warmed to 60° on a water-bath, 1.2 ml. of bromine in 4 ml. of glacial acetic acid was added, and the temperature of the reaction mixture was maintained at 80–85° for 20 minutes. Hydrogen bromide was liberated. The reaction mixture was poured onto 150 g. of cracked ice, and a finely divided yellow solid, m.p. 174–176°, was collected. It was recrystallized twice from ethanol-water, m.p. 176–178°.

Anal. Calc'd for $C_{13}H_{11}BrN_2O_2$: C, 50.83; H, 3.61.

Found: C, 50.72; H, 3.57.

Oxidation with alkaline permanganate resulted in the recovery of unreacted IX. Tests for active bromine with sodium iodide in acetone (23) and with alcoholic silver nitrate (24) were both negative.

IX was mulled in mineral oil and its spectra obtained with a Perkin-Elmer Model 12-A single beam infrared spectrophotometer using sodium chloride optics. A fairly strong band appeared at 9.9μ.

Pyrolysis. Compound IV (35 g., 0.137 mole) was heated at 175–200° for four hours. Gas evolution occurred and a colorless liquid refluxed gently. At the end of this time the temperature steadily dropped, gas evolution decreased, and the contents of the flask increased in viscosity and color. Distillation of the reaction mixture gave 6.0 g. of a liquid, b.p. 108–111°, which was identified as methyl cyclopropyl ketone, yield 54%. Continuation of the distillation under reduced pressure gave a few drops of a light yellow liquid, b.p. 110–115°/15 mm., which may have been II. There remained in the flask 8 g. of carbonaceous residue.

[5] This analysis by Oakwold Laboratories.

c. Derivatives of VI. A solution of 18.9 g. (0.15 mole) of VI and 16.5 g. (0.15 mole) of phenylhydrazine in 56 ml. of glacial acetic acid was allowed to react as above in the preparation of V from IV. The resultant oil (presumably impure VII) could not be crystallized. The acid-free oil (35 g.) was refluxed with 12 g. of potassium hydroxide and 60 g. of potassium permanganate in 700 ml. of water for 19 hours. The reaction mixture was worked up in the usual manner, and 2.3 g. of a white solid, m.p. 138–139° after two recrystallizations from benzene, was obtained. When mixed with VIII obtained from V, the m.p. was not depressed.

3(5?)-Methyl-5(3?)-cyclopropylpyrazole was obtained by refluxing a mixture of 2 g. (0.016 mole) of VI and 1.5 ml. of 85% hydrazine hydrate in 2 ml. of glacial acetic acid for 15 minutes. The reaction mixture was poured onto cracked ice, and a thick oil separated and crystallized on cooling. It weighed 1.6 g., yield 82%, m.p. 36–42°. After recrystallization from 50% ethanol it melted at 43–45°.

Anal. Calc'd for $C_7H_{10}N_2$: C, 68.81; H, 8.25.

Found: C, 68.60; H, 8.39.

The *copper salts* (Table II) were obtained in the usual way (4) from methanol solutions of the products.

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SUMMARY

Acylation of methyl cyclopropyl ketone with acetic and propionic anhydrides resulted in the formation of the methyl derivatives exclusively. Additional methyl derivatives of the ketone, obtained by base-catalyzed acylation, are described.

The cyclopropane ring in 1-phenyl-5(3?)-cyclopropylpyrazole-3(5?)-carboxylic acid is unaffected by hydrogen bromide or bromine.

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