

48. *Synthesis of $\alpha\beta$ -Unsaturated Cyclopropyl Ketones and 3-Cyclopropylpyrazolines.*

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The synthesis of $\alpha\beta$ -unsaturated cyclopropyl ketones (I) by base-catalysed condensation of aromatic aldehydes with cyclopropyl methyl ketone is reported. Reactions of aliphatic aldehydes with cyclopropyl methyl ketone led to ketols (IV) or mixtures of ketols and unsaturated ketones. Pronounced exaltation of molar refraction is noted for compounds of type (I). 5-Aryl-3-cyclopropyl-1-phenylpyrazolines have been prepared by the reaction of the unsaturated ketones with phenylhydrazine.

THE activity of cyclopropyl methyl ketone in reactions involving carbanion formation has been used in several preparative reactions.¹ The formation of cyclopropyl styryl ketone in good yield by base-catalysed reaction of cyclopropyl methyl ketone with benzaldehyde²⁻⁴ led to the investigation of the reaction of cyclopropyl methyl ketone with

¹ Cannon and Whidden, *J. Org. Chem.*, 1952, **17**, 685; Bunce, *J. Amer. Chem. Soc.*, 1955, **77**, 6616; Meshcheryakov and Glukhovtsev, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1958, 780 (*Chem. Abs.*, 1958, **52**, 19,974).

² West, Ph.D. Thesis, Rensselaer Polytechnic Institute, 1950.

³ Smith and Rogier, *J. Amer. Chem. Soc.*, 1951, **73**, 3831, 3840.

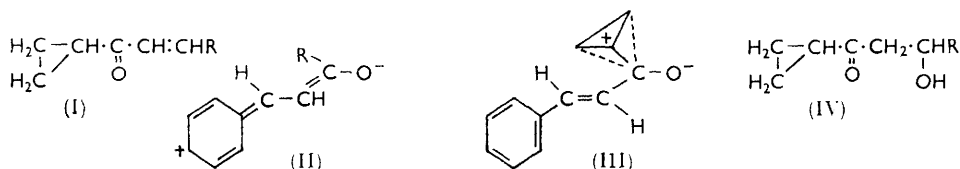
⁴ Mariella and Raube, *J. Amer. Chem. Soc.*, 1952, **74**, 521.

other carbonyl compounds. The reaction with aromatic aldehydes was found to be a generally useful synthetic method, but the reaction with aliphatic aldehydes, which we hoped would lead to synthetic intermediates of value, proved more complex.

In Table I are presented the results of a number of condensations, conducted by heating cyclopropyl methyl ketone and araldehydes with sodium hydroxide in dilute ethanol. After neutralization of the reaction mixture, the unsaturated ketones (I) were crystallized or were extracted and then distilled. The colour of these aryl-substituted unsaturated ketones ranges from pale straw colour to more intense yellow.

The infrared spectra, of Nujol mulls, confirmed these structures. For example, that for cyclopropyl 3,4-diethoxystyryl ketone showed a carbonyl absorption at 1655 cm^{-1} , ethylenic unsaturation at 1625 and 1600 cm^{-1} , and cyclopropyl at 1030 and 890 cm^{-1} . 1-Cyclopropyl-5-phenylpenta-3,5-dien-1-one had carbonyl absorption at 1675 cm^{-1} , ethylenic unsaturation at 1620, 1610, and 1598 cm^{-1} , and cyclopropyl absorption at 1010 and 895 cm^{-1} .

The reaction failed, under mild conditions, with salicylaldehyde, *p*-hydroxybenzaldehyde, acetophenone, and benzophenone. Higher temperatures and more concentrated sodium hydroxide solutions did not cause reaction of these ketones, except to induce self-condensation of the acetophenone.



The unusually high exaltations in the molar refraction of these ketones invites comment. Mariella and Raube⁴ noted the high exaltations of styryl ketones, attributed to the contributions of such forms as (II). The exaltations which they found for the styryl ketones in which R (of II) = alkyl (Prⁿ, 3·9; Prⁱ, 4·3; Buⁱ, 4·3) may be compared with the exaltations of benzylideneacetone (R = Me) 2·8,⁵ cinnamaldehyde (R = H) 0·5,⁴ ethyl cinnamate (R = OEt) 2·1,⁶ and cinnamoyl chloride (R = Cl) 4·9.⁷ It seems clear that groups R which can participate in resonance as electron donors in conjugation with carbonyl can increase the polarizability and hence the exaltation even in the cross-conjugated system.

The comparatively large effect of cyclopropyl in increasing exaltation in such a system by the contribution of structures such as (III) is consistent with the exaltation in molar refraction noted for conjugation of cyclopropane with ethylenic unsaturation^{8,9} and with carbonyl,⁹ and with the bathochromic shifts observed in ultraviolet and infrared spectra when cyclopropyl groups are conjugated with carbonyl, ethylenic, or phenyl groups.^{3,10} It must be contrasted with the similarity of the spectra of cyclopropyl phenyl ketone and acetophenone, which Mariella and Raube⁴ cite as showing little cross-conjugative effect of cyclopropyl.

While aromatic aldehydes gave good yields, in general, of unsaturated ketones, the reactions of aliphatic aldehydes with cyclopropyl methyl ketone were complicated by self-condensations of the former and incomplete dehydration of the ketols (IV) to unsaturated ketones. The reaction of butyraldehyde was modelled on the condensation of mesityl oxide with butyraldehyde,¹¹ and, like that, gave 18% of the self-condensation product of

⁵ von Auwers, *Ber.*, 1912, **45**, 2764.

⁶ Eisenlohr, "Spektrochemie Organischer Verbindungen," Enke, Stuttgart, 1912, pp. 124, 130.

⁷ von Auwers and Schmidt, *Ber.*, 1913, **43**, 457.

⁸ Van Volkenburgh, Greenlee, Derfer, and Boord, *J. Amer. Chem. Soc.*, 1949, **71**, 172 and 3595.

⁹ Slabey, *J. Amer. Chem. Soc.*, 1954, **76**, 3603.

¹⁰ Eastman, *J. Amer. Chem. Soc.*, 1954, **76**, 4115; Cannon, Santilli, and Shenian, *ibid.*, 1959, **81**, 1660; Kierstead, Linstead, and Weedon, *J.*, 1952, 3610, 1953, 1799; Mohrbacher and Cromwell, *J. Amer. Chem. Soc.*, 1957, **79**, 401.

¹¹ Powell and Wasserman, *J. Amer. Chem. Soc.*, 1957, **79**, 1934.

butyraldehyde, as well as 28% of 1-cyclopropyl-3-hydroxyhexan-1-one (IV; R = Pr^u). The infrared spectrum indicated hydroxyl absorption at 3440, carbonyl at 1700, and cyclopropyl at 1025 and 900 cm.⁻¹.

The reaction of isobutyraldehyde with cyclopropyl methyl ketone has been reported³ to give mixtures of ketol and unsaturated ketone; our results are in qualitative agreement although boiling points and refractive indices differ markedly.

The reaction with formaldehyde also gave a mixture of ketol and cyclopropyl vinyl ketone; the latter, unstable, has been prepared¹² by a Hofmann degradation. The attempted distillation of this mixture gave liquids whose infrared spectra indicated the presence of hydroxyl (3560—3420 cm.⁻¹), of unconjugated (1725 cm.⁻¹) and conjugated carbonyl (1665 cm.⁻¹), and cyclopropyl (1015 cm.⁻¹).

Acetaldehyde gave no identifiable condensation product with cyclopropyl methyl ketone; the corresponding reaction of chloral proved to be complex. The solid ketol, formed in small amounts, has hydroxyl absorption at 3410 cm.⁻¹, carbonyl at 1695 cm.⁻¹ and cyclopropyl at 1020 and 910 cm.⁻¹. There was also formed a large amount of a steam-volatile liquid which appears to be a mixture containing cyclopropyl methyl ketone or a compound hydrolysable to it, since it formed cyclopropyl methyl ketone 2,4-dinitrophenylhydrazone.

Reaction of the unsaturated ketones with phenylhydrazine in acetic acid, by the procedure of Raiford and Peterson,¹³ led to pyrazolines in good yield. The physical properties are reported in Table 2; all exhibited infrared absorptions at ~1140 and 1390 cm.⁻¹ which have been reported¹⁴ for other pyrazolines, and none had absorption in the 3300—3400 cm.⁻¹ region characteristic of N-H stretching frequencies.

EXPERIMENTAL

Microanalyses are by Spang Microanalytical Laboratory, Ann Arbor, Michigan; Drs. Weiler and Strauss, Oxford, England; and Clark Microanalytical Laboratory, Urbana, Illinois. M. p.s are corrected.¹⁵

Condensation of Cyclopropyl Methyl Ketone with Aromatic Aldehydes.—In a typical preparation, cyclopropyl methyl ketone (8.4 g., 0.10 mole), b. p. 111—112°, and the aromatic aldehyde (0.10 mole) were stirred in ethanol (7 ml.), and 20% aqueous sodium hydroxide solution (7 ml.) was added during 30 min. After 3 hours' heating at 40°, the mixture was cooled and neutralized with dilute hydrochloric acid. The crystalline ketones were recovered by filtration, washed with ethanol and water, and recrystallized from 95% ethanol or ethanol-water. The liquid products separated on neutralization as oils which were extracted with ether. The extracts were washed, dried (Na₂SO₄), and distilled at reduced pressure. The unsaturated ketones whose properties are listed in Table 1 all decolorise 2% aqueous potassium permanganate solution. The semicarbazones, prepared in the usual manner, recrystallized from ethanol-water.

1-Cyclopropyl-3-3'-isoquinolylpropen-1-one.—To isoquinoline-3-carboxaldehyde (0.9 g., 0.0057 mole) in 95% ethanol (1 ml.) and cyclopropyl methyl ketone (0.5 g., 0.006 mole) was added, with stirring and cooling, 5% sodium hydroxide solution (1.5 ml.). After being stirred for 11 hr. at room temperature, the solution was neutralized with acetic acid, extracted with ether, and dried (Na₂SO₄). The extract was concentrated to give an oil (0.83 g., 65%). Treatment of a portion of this oil with ethanolic picric acid gave a picrate having m. p. 207—208° after several recrystallizations from 95% ethanol. Decomposition of the picrate with lithium hydroxide gave the impure solid 1-cyclopropyl-3-3'-isoquinolylpropen-1-one, m. p. 89—95°, whose infrared spectrum in a Nujol mull showed carbonyl absorption at 1655 cm.⁻¹ and cyclopropyl at 1000—1020 cm.⁻¹. A small amount of a 2,4-dinitrophenylhydrazone was prepared, having m. p. 185—190°.

¹² Smith and Showell, *J. Org. Chem.*, 1952, **17**, 839.

¹³ Raiford and Peterson, *J. Org. Chem.*, 1936, **1**, 544.

¹⁴ Cromwell, Miller, Johnson, Frank, and Wallace, *J. Amer. Chem. Soc.*, 1949, **71**, 3337.

¹⁵ Bunce, *Analyt. Chem.*, 1953, **25**, 825.

Condensation of Cyclopropyl Methyl Ketone with Butyraldehyde.—A solution of potassium hydroxide (2 g.) in water (2 ml.), dioxan (50 ml.), and cyclopropyl methyl ketone (42 g., 0.5 mole) was stirred while butyraldehyde (25.2 g., 0.35 mole) was added in 30 min. The mixture was stirred for an additional 30 min., and after neutralization with acetic acid was concentrated *in vacuo* and distilled to give: (1) 2-ethylhex-2-enal, b. p. 68—74°/17 mm. (7.3 g., 16.6%)

TABLE I.
 $\alpha\beta$ -Unsaturated cyclopropyl ketones (I).

No.	R	Yield (%)	M. p.	B. p./mm.	n_D^{20}	d_4^{20}	$\Delta[\text{MR}]_D$ (obs. — cal.)
1	Phenyl *	72	52.8—53.0°		1.5877 †	1.039 ‡	4.3 §
2	<i>p</i> -Nitrophenyl	33	118.0—118.5				
3	<i>o</i> -Methoxyphenyl	62		123—126°/0.5	1.6147	1.105	6.2
4	<i>o</i> -Ethoxyphenyl	74		151—155°/1.5	1.5968	1.072	6.6
5	3,4-Diethoxyphenyl ¶	78	91.3—92.0				
6	1-Naphthyl	48		153—155°/0.5	1.6660	1.122	7.2
7	Styryl **	66	106.0—107.5				
8	3-Isoquinolyl	65	89—95				

* Ref. 2—4. † n_D^{55} . ‡ d_4^{55} . § At 55°. Ref. 4 gives 5.26 at 20°. ¶ Found: C, 73.8; H, 7.8. $\text{C}_{16}\text{H}_{20}\text{O}_3$ requires C, 73.8; H, 7.7%. ** Found: C, 84.8; H, 7.25. $\text{C}_{11}\text{H}_{14}\text{O}$ requires C, 84.8; H, 7.1%; cf. Mariella and Raube, *J. Org. Chem.*, 1953, **18**, 282.

Semicarbazones.

No.	M. p.	Found (%)			Formula	Required (%)		
		C	H	N		C	H	N
1	172.8—173.3°	67.8	6.5	—	$\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}$	68.1	6.6	—
2	216—216.5	—	—	20.3	$\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_3$	—	—	20.4
3	175—176	64.2	6.8	16.2	$\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_2$	64.8	6.6	16.2
4	117.6—118.6	—	—	13.3	<i>a</i>	—	—	13.2
	132.8—133.5	65.5	7.1	15.7	$\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_2$	65.9	7.0	15.4
6	187—188	72.6	6.4	—	$\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}$	73.1	6.1	—
8(b)	207—208	56.0	3.6	—	$\text{C}_{21}\text{H}_{16}\text{N}_4\text{O}_8$	55.75	3.6	—

(a) Monoethanolate, converted into the unsolvated form in 24 hr. over P_2O_5 . (b) Picrate.

(lit.,¹¹ b. p. 62—63°/14 mm.) [2,4-dinitrophenylhydrazone, m. p. 144—145° (lit.,¹¹ m. p. 122—123°) (Found: C, 55.1; H, 5.7; N, 18.2. Calc. for $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_4$: C, 54.9; H, 5.9; N, 18.3%)]; (2) 1-cyclopropyl-3-hydroxyhexan-1-one, b. p. 120—122°/17 mm. (15.0 g., 27.5%) [*oxime*, m. p. 83.5—84.5° (Found: C, 63.2; H, 9.8. $\text{C}_9\text{H}_{17}\text{NO}_2$ requires C, 63.1; H, 10.0%)]; and (3) a thick dark residue (1.8 g.).

Condensation of Cyclopropyl Methyl Ketone with Isobutyraldehyde.—A solution of cyclopropyl methyl ketone (30.3 g., 0.36 mole) and 13% alcoholic potassium hydroxide (10 ml.) was stirred at 40° while isobutyraldehyde (10.8 g., 0.15 mole) was added dropwise during 30 min. Stirring was continued for 1 hr. and glacial acetic acid was added to neutralize the mixture. The mixture was extracted with ether, and the extract was washed with water and dried (Na_2SO_4). The solvent was removed and, after recovery of some cyclopropyl methyl ketone, distillation at reduced pressure gave fractions, (A) b. p. 71—74.5°/8—9 mm. (2 g.), n_D^{20} 1.4670, and (B), b. p. 74—75°/3.7—3.9 mm. (2.8 g.), n_D^{20} 1.4802, and a residue (3.7 g.), n_D^{20} 1.4922. Both fractions A and B gave a 2,4-dinitrophenylhydrazone, m. p. 159.1—160.2° (reported³ for 1-cyclopropyl-4-methylpent-2-en-1-one 2,4-dinitrophenylhydrazone, m. p. 159.5—160°).

Both fractions A and B decolorized 2% aqueous potassium permanganate, and B gave a positive ceric nitrate test. The infrared spectrum of A included a weak hydroxyl absorption at 3440 cm^{-1} , carbonyl bands of about equal intensity at 1700 and 1640 cm^{-1} , and cyclopropyl absorptions at 1025 and 900 cm^{-1} . Fraction B had strong hydroxyl absorption at 3450 cm^{-1} , the carbonyl band at 1700 cm^{-1} strong and that at 1640 cm^{-1} weak, and cyclopropyl absorption at 1022 and 900 cm^{-1} .

Condensation of Cyclopropyl Methyl Ketone with Formaldehyde.—To paraformaldehyde (5 g., 0.17 mole) and cyclopropyl methyl ketone (28 g., 0.33 mole), 0.2% alcoholic potassium hydroxide solution (10 ml.) was added and the mixture was heated on the steam-bath for 8 hr. More potassium hydroxide solution (100 ml.) was added in ~15-ml. portions during this time. Then quinol (0.1 g.) was added and the mixture was stored in the cold. Distillation *in vacuo*

gave, after removal of alcohol and unchanged cyclopropyl methyl ketone, a liquid, b. p. 82—87°/12 mm. (6.15 g.) (Found: C, 66.6; H, 9.0. Calc. for C_6H_8O : C, 75.0; H, 8.3. Calc. for $C_6H_{10}O_2$: C, 63.1; H, 8.8. Calc. for a 7 : 3 mixture of ketol-ketone: C, 66.7; H, 8.7%).

This material did not form an oxime; it gave a 2,4-dinitrophenylhydrazine which was extremely difficult to recrystallize and mainly gave tars. A small amount with m. p. 173.6—176.6° was obtained (Found: C, 51.1; H, 4.2. $C_{12}H_{12}N_4O_4$ requires C, 52.2; H, 4.4%).

In another run, the product, b. p. 110—115°/22 mm., was divided into two portions. The first was mixed with dibutyl phthalate and quinol and distilled to give a liquid, b. p. 72—75°/3.7—3.9 mm., n_D^{20} 1.4992. The other portion was added to a mixture of dibutyl phthalate, iodine, and quinol at 185° and distilled *in vacuo*. Redistillation gave a liquid, b. p. 71—75°/5 mm., n_D^{20} 1.5042. Both materials obtained by these treatments readily polymerized to a thick viscous material.

Condensation of Cyclopropyl Methyl Ketone with Chloral.—A mixture of cyclopropyl methyl ketone (8.4 g., 0.1 mole), chloral hydrate (16.5 g., 0.1 mole), and glacial acetic acid (25 ml.) was heated on the steam-bath for 10 hr. After then being kept for several days, the mixture was steam-distilled and the material in the distillate was extracted with ether and dried ($CaCl_2$). Distillation gave a liquid, b. p. 80—85°/278—288 mm. (15.4 g.), which has not been identified. This liquid decolorized a 2% potassium permanganate solution and gave a 2,4-dinitrophenylhydrazine which appeared to be a mixture. After the residue from the steam-distillation had been kept for several days, a small amount of solid was found in it. This solid was separated and crystallized from warm water (charcoal), to give a white solid, m. p. 89.2—89.8° (0.06 g.), probably 4,4,4-trichloro-1-cyclopropyl-3-hydroxybutan-1-one (Found: C, 36.1; H, 4.0. $C_7H_9Cl_3O_2$ requires C, 36.3; H, 3.9%).

5-Aryl-3-cyclopropyl-1-phenylpyrazolines.—In a typical preparation, cyclopropyl styryl ketone (5.0 g., 0.029 mole), phenylhydrazine (3.2 g., 0.029 mole), and glacial acetic acid (25 ml.) were heated under reflux for 1 hr. On cooling to 0°, the pyrazoline crystallized and was then separated and recrystallized several times from ethanol. All the pyrazolines obtained, which are listed in Table 2, gave a blue colour with ferric chloride in alcohol (Knorr pyrazoline base test). Purified samples of several of the pyrazolines (the phenyl, and particularly the alkoxyphenyl derivatives) were unstable on long storage.

TABLE 2.

5-Aryl-3-cyclopropyl-1-phenyl-2-pyrazolines.

Aryl	Yield (%)	M. p.	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
Ph	69	96.3—96.8°	—	—	10.2	$C_{18}H_{12}N_2$	—	—	10.7
<i>p</i> -NO ₂ -C ₆ H ₄	57	132.8—133.4	—	—	13.7	$C_{18}H_{17}N_2O_2$	—	—	13.7
CHPh:CH	57	103—105	82.9	7.0	—	$C_{20}H_{20}N_2$	83.3	7.0	—
1-C ₁₀ H ₇	100	138.2—139.5	—	—	8.9	$C_{22}H_{20}N_2$	—	—	9.0
<i>o</i> -MeO-C ₆ H ₄	80	74.6—75.1	78.9	7.35	9.25	$C_{18}H_{20}N_2O$	78.05	6.9	9.6
<i>o</i> -EtO-C ₆ H ₄	23	104.0—104.3	78.8	7.25	9.1	$C_{20}H_{22}N_2O$	78.4	7.2	9.1
3,4-(EtO) ₂ C ₆ H ₃ ...	74	88.5—89.5	75.4	7.5	—	$C_{22}H_{26}N_2O_2$	75.4	7.5	—

3-Cyclopropyl-5-3'-isoquinolyl-1-phenylpyrazoline.—Crude 1-cyclopropyl-3-3'-isoquinolylpropen-1-one (0.5 g., 2.2 mmoles), phenylhydrazine (0.25 g., 2.3 mmoles), and glacial acetic acid (3.5 ml.) were refluxed for 1 hr. After cooling, the solution was concentrated *in vacuo* to a gummy residue. Treatment of this gum with picric acid gave a bright red *picrate*, m. p. 186—188° (Found: C, 59.5; H, 4.1. $C_{27}H_{22}N_6O_7$ requires C, 59.8; H, 4.1%).

We express our appreciation to Professor R. C. Elderfield and the Department of Chemistry of the University of Michigan for providing laboratory space and facilities (to F. D. P.) for a portion of this work.

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[Received, July 23rd, 1962.]