The Chemistry of Methyl Vinyl Ketone. I. The Acetoethylation of Ketones

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The anions of a number of ketones react in the Michael condensation with methyl vinyl ketone to give either acetoethylated products, the normal open-chain Michael adducts (A), or mixtures of A and cyclohexanone derivatives (B), which appear to arise from A by intramolecular aldol condensations.

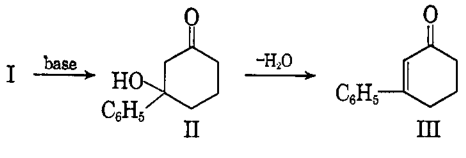
The scope and limitations of the cyanoethylation[2] and pyridylethylation[3-5] of a large variety of ketones have been studied. However, a comparable study of the reactions of ketones with methyl vinyl ketone has apparently not been reported. Although many ketones have been condensed with methyl vinyl ketone, these reactions have been usually effected as part of a synthetic scheme aimed at preparing other compounds, *e.g.*, steroid intermediates. The purpose of the present paper is to study the scope and limitations of the Michael condensation of a series of representative ketones with methyl vinyl ketone.[6]

Since these reactions, in a strictly formal sense, involve the initial introduction of an acetoethyl group, $CH_3COCH_2CH_2$, into the ketone in place of an α-hydrogen atom, it is suggested that these reactions be called acetoethylations.

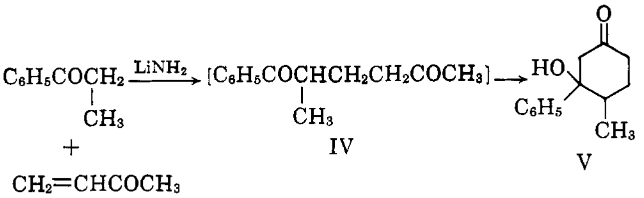
$$RCOCH_2R' + CH_2{=}CHCOCH_3 \xrightarrow{\text{base}} RCOCHR'(CH_2CH_2COCH_3)$$

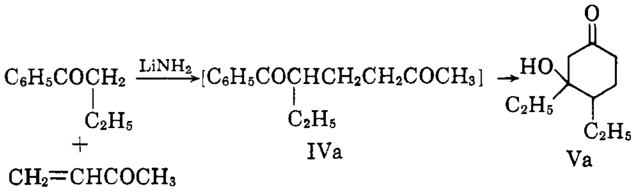
Orienting experiments were performed with acetophenone since it has only one α-carbon atom with active hydrogen atoms. Depending on reaction conditions (Table I), the expected open-chain product (I), 1-phenylhexane-1,5-dione, 3-phenyl-3-hydroxycyclohexanone (II), 3-phenylcyclohex-2-enone (III), or a mixture of I and II was obtained. It appears that II arises from I by an intramolecular aldol condensation and III arises from the dehydration of II. It is interesting to note that, although the stoichiometry of the reaction requires only 1 mole of acetophenone per mole of methyl vinyl ketone, considerably higher yields of products were obtained using a 2:2:1 molar ratio of acetophenone–base–methyl vinyl ketone (compare runs 4, 5, and 6).

$$C_6H_5COCH_3 + CH_2{=}CHCOCH_3 \xrightarrow{\text{base}} \underset{\text{I}}{C_6H_5COCH_2CH_2CH_2COCH_3}$$



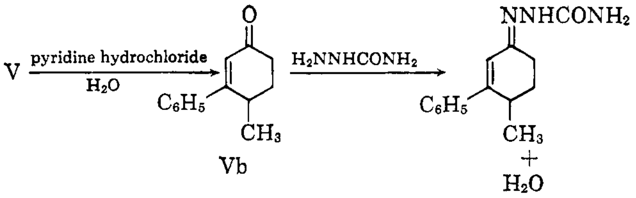
From the reactions of methyl vinyl ketone with propiophenone and *n*-butyrophenone, none of the open-chain acetoethylated products, IV and IVa, were isolated. Instead, the cyclized products, 3-phenyl-3-hydroxy-4-methylcyclohexanone (V, 52.4%) and 3-phenyl-3-hydroxy-4-ethylcyclohexanone (Va, 53%), were obtained.





The structure of V was elucidated from its infrared spectrum which showed the presence of both carbonyl and hydroxyl groups and the absence of vinyl group absorption thus ruling out the possibility that the anion of propiophenone had added across the carbonyl group of methyl vinyl ketone.

The formation of the semicarbazones of V and Va was accompanied by dehydration when these derivatives were prepared by McElvain's[7] semicarbazide hydrochloride pyridine method. In a separate experiment, it was shown that, although V is not dehydrated by pyridine alone, this dehydration was effected in 97% yield by pyridine hydrochloride.



Acetone, like acetophenone, was acetoethylated to give heptane-2,6-dione in low yield (7.4%). This 1,4-diketone had been prepared previously in 16% yield.[8] by the reaction of acetone with 4-diethylamino-2-butanone methiodide.

Methyl *n*-propyl ketone behaved like *n*-butyrophenone and gave the cyclic ketone VII in low yield (15.5%), probably *via* VI. That the initial condensation product is VI, *i.e.*, that methyl *n*-propyl ketone has been

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[1] Monsanto Chemical Co. Research Fellow, 1957-1959. This paper is based on a portion of the thesis presented by N. C. Ross to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

[2] "The Chemistry of Acrylonitrile," American Cyanamid Co., 1959, pp. 18-19 and 92-120.

[3] R. Levine and M. H. Wilt, *J. Am. Chem. Soc.*, **74**, 342 (1952).

[4] M. H. Wilt and R. Levine, *ibid.*, **75**, 1368 (1953).

[5] G. Magnus and R. Levine, *J. Org. Chem.*, **22**, 270 (1957).

[6] An excellent review of much of what has been published has been summarized by E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

[7] S. M. McElvain, "The Characterization of Organic Compounds," Rev. Ed., The Macmillan Co., New York, N. Y., 1953, p. 193.

[8] N. S. Gill, K. B. James, F. Lions, and K. T. Potts, *J. Am. Chem. Soc.*, **74**, 4923 (1952).

TABLE I

REACTIONS OF ACETOPHENONE WITH METHYL VINYL KETONE (MVK)

Moles of reactants						
Acetophenone	MVK[a]	Base	Base	Reaction time, hr.[b]	Products	% yield
0.6	0.2	0.03	Triton B[c]	2	I[d,e]	14
0.4	0.2	0.03	Triton B[c]	48	III[d,f]	8
0.4	0.2	0.08	$KOC(CH_3)_3$	2	none	
0.3	0.3	0.3	$NaNH_2$[g]	0	I	19
0.5	0.25	0.5	$NaNH_2$[g]	0	I	34
0.5	0.25	0.5	$LiNH_2$[g]	0	I	37
					II[h]	3.2

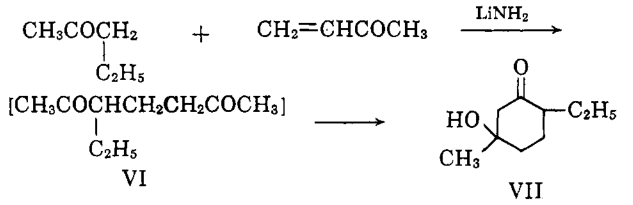
[a] MVK in 100–150 ml. of ether was added slowly to the base and acetophenone. [b] Reaction time after the addition of the MVK which required 60–80 min. [c] This is a 38% aqueous solution of benzyltrimethylammonium hydroxide. [d] Considerable amounts of polymerized MVK were also formed. [e] I is 1-phenylhexane-1,5-dione, m.p. 67.2–67.6° from petroleum ether (60–70°). *Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.77; H, 7.42. Found: C, 75.80; H, 7.50. Dioxime, m.p. 122.4–123.4° from ethanol–water. *Anal.* Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.44; H, 7.31. Found: C, 65.00; H, 6.91. [f] III is 3-phenylcyclohex-2-enone, m.p. 63.8–64.2°; F. C. Novello, E. M. Christy, and J. M. Sprague [*J. Am. Chem. Soc.*, **75,** 1330 (1953)] report 63.8–64.6°. Semicarbazone, m.p. 212–213° from 95% ethanol. [g] The alkali amides were prepared in and the reactions were run in liquid ammonia. [h] II is 3-phenyl-3-hydroxycyclohexanone, m.p. 152–153° from petroleum ether (90–100°). *Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.77; H, 7.42. Found: C, 75.73; H, 7.25. When II was treated with semicarbazide hydrochloride and pyridine, it was dehydrated and gave the semicarbazone of III, m.p. 212–213°. *Anal.* Calcd. for $C_{13}H_{15}N_3O$: C, 68.09. H, 6.59. Found: C, 67.92; H, 6.49.

TABLE II

REACTIONS OF CYCLOHEXANONE AND 2-METHYLCYCLOHEXANONE WITH METHYL VINYL KETONE

Reactants			Products, % yield	
Ketone, moles	Base, moles	MVK, moles	Hydroxydecalone	Ketooctalin
Cyclohexanone, 0.5	$LiNH_2$,[a] 0.5	0.25	XI,[b] 14.4	XII,[c] 35.0
0.4	Triton B,[d] 0.03	0.2	11.2	30.6
0.4	KOH, 0.08	0.2	2.4	38.5
2-Methylcyclohexanone, 0.5	$LiNH_2$,[a] 0.5	0.25	XIV,[e] 9.5	XV,[f] 24.7
0.4	Triton B,[d] 0.09	0.2	0	45.8
0.4	KOH, 0.03	0.2	0	55.5

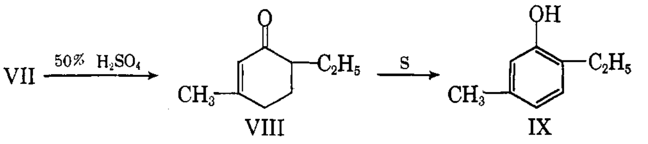
[a] This was prepared in and the reaction was run in liquid ammonia. [b] This is 9-hydroxy-2-decalone, b.p. 132–136°, m.p. 146.0–146.9°. *Anal.* Calcd. for $C_{10}H_{16}O_2$: C, 71.48; H, 9.60. Found: C, 71.60; H, 9.77. [c] This is 2-keto-$\Delta^{1,9}$-octalin, b.p. 103–104° at 2 mm. (see ref. 10). Both XI and XII gave the same semicarbazone, m.p. 206–207° (see ref. 10). [d] This is a 38% aqueous solution of benzyltrimethylammonium hydroxide. [e] This is 2-keto-9-hydroxy-10-methyldecalin, m.p. 120.8–121.4°. *Anal.* Calcd. for $C_{11}H_{18}O_2$: C, 72.50; H, 9.96. Found: C, 72.61; H, 9.77. [f] This is 2-keto-10-methyl-$\Delta^{1,9}$-octalin, b.p. 111–112° at 2.5 mm. (see ref. 10). Both XIV and XV gave the same semicarbazone, m.p. 204–205° (see ref. 10).



VI

VII

acetoethylated at its α-methylene carbon atom, has precedent in the work of Wilt and Levine[4] who showed that Michael condensations between 2-vinylpyridine and unsymmetrical dialkyl ketones occur at the more highly substituted α-carbon atoms of the ketones. The structure of VII was established with certainty by dehydrating it to 3-methyl-6-ethylcyclohex-2-enone (VIII), which was then aromatized to IX by heating it with sulfur.



VIII

IX

Methyl isopropyl ketone did not undergo the Michael condensation with methyl vinyl ketone under the reactions used in the present study.

While the acyclic ketones showed little or no (0–15.5%) tendency to add to methyl vinyl ketone, the cyclic ketones, cyclopentanone, cyclohexanone, and 2-methylcyclohexane, reacted readily to give fair to good yields of condensation products. Cyclopentanone, when converted to its anion, was acetoethylated to give 2-(3-ketobutyl)cyclopentanone in 40% yield. This same compound had been prepared earlier in 28% yield by Gill, *et al.*,[8] by the high temperature reaction of cyclopentanone with the methiodide of 4-diethylamino-2-butanone in the presence of catalytic amounts of base. Also, Bergmann and Corett[9] found that cyclopentanone reacts with methyl vinyl ketone in the presence of a basic ion-exchange resin gave a 30% yield of $\Delta^{4,5}$-perhydroindanone-3 and none of the normal acetoethylated product.

Both cyclohexanone and 2-methylcyclohexanone reacted (Table II) with methyl vinyl ketone to give the decalone derivatives, XI, XII, XIV, and XV, probably *via* the intermediates X and XIII, respectively (see Scheme I).

The 2-keto-$\Delta^{1,9}$-octalin (XII) had been obtained as the only product[10] in 17.3% yield by condensing the methiodide of 4-diethylamino-2-butanone with 2-carbethoxycyclohexanone followed by hydrolysis and decarboxylation. Similarly, the reaction of this methiodide with 2-methylcyclohexanone gave 2-keto-10-methyl-$\Delta^{1,9}$-octalin (XV) in 35–40% yield. More recently, Stork and Landesman[11] have prepared XII in 66% yield from the reaction of the pyrrolidine enamine

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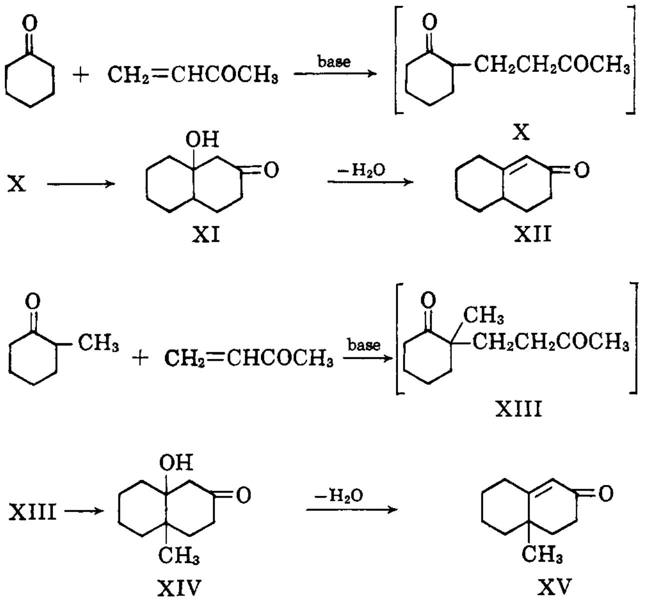
(9) E. E. Bergmann and R. Corett, *J. Org. Chem.*, **23**, 1507 (1958).

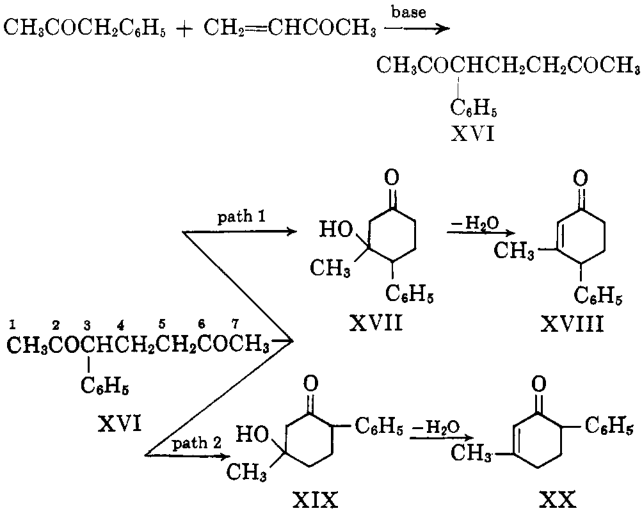
(10) E. C. DuFeu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937).

(11) G. Stork and H. K. Landesman, *J. Am. Chem. Soc.*, **78**, 5129 (1956).

SCHEME I



SCHEME II



of cyclohexanone with methyl vinyl ketone. In addition, Johnson, *et al.*,[12] treated cyclohexanone with methyl vinyl ketone in the presence of Triton B and get a 25% yield of XI which was dehydrated to XII in high yield by reaction with sodium methoxide.

Apparently, when methyl benzyl ketone was treated with methyl vinyl ketone using lithium amide, sodium amide, Triton B (38% aqueous benzyl trimethylammonium hydroxide), or ethanolic potassium hydroxide as the condensing agent, 3-phenylheptane-2,6-dione (XVI) was formed initially. However, XVI was not isolated from the reactions. In every case (Table III), intramolecular aldol condensation occurred to give substituted cyclohexanone derivatives. Thus, XVI may undergo intramolecular condensation in two ways as shown in Scheme II.

TABLE III

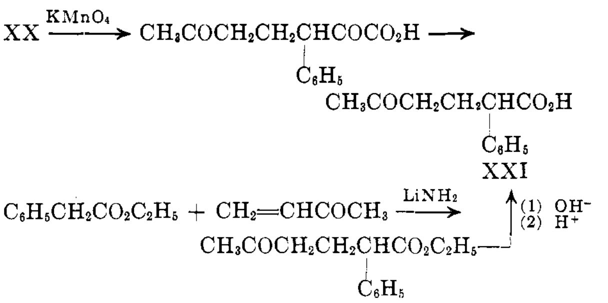
REACTIONS OF METHYL BENZYL KETONE (MBK) WITH METHYL VINYL KETONE (MVK)[a]

Reactants		
Base	Base-MBK, moles	Products, % yield
$LiNH_2$[b]	1:1	XVII,[c] 28.2 XVIII,[d] 27.7
$NaNH_2$[b]	0.14:1	XVIII,[d] 45.3 XX,[e] 10.3
Triton B[f]	0.14:1	XVIII,[d] 32.7 XX,[e] 46.5
KOH[g]	0.16:1	XX,[e] 58.2

[a] Two moles of MBK per mole of MVK were used. [b] This was prepared in and the reaction was run in liquid ammonia. [c] This is 3-methyl-3-hydroxy-4-phenylcyclohexanone, m.p. 142.4–143.0° from petroleum ether (60–70°). *Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.42; H, 7.89. Found: C, 76.83; H, 7.74. [d] This is 3-methyl-4-phenylcyclohex-2-enone, b.p. 129° at 2 mm., m.p. 39.2–40.2° from petroleum ether (30–60°). *Anal.* Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.48. Found: C, 83.90; H, 4.80. Both XVII and XVIII gave the same semicarbazone, m.p. 203–204° from 95% ethanol. *Anal.* Calcd. for $C_{14}H_{17}N_3O$: C, 69.12; H, 7.04. Found: C, 68.82; H, 7.24. [e] This is 3-methyl-6-phenylcyclohex-2-enone, m.p. 62–63° from petroleum ether (b.p. 30–60°). *Anal.* Calcd. for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.93; H, 7.93. [f] This is a 38% aqueous solution of benzyltrimethylammonium hydroxide. [g] This is a 30% ethanolic solution of potassium hydroxide.

In path 1, the "number 2" carbonyl group of XVI is attacked by the "number 7" methyl group to give 3-methyl-3-hydroxy-4-phenylcyclohexanone (XVII). Path 2 results from the attack of the "number 1" methyl group on the "number 6" carbonyl group to give 3-methyl-3-hydroxy-6-phenylcyclohexanone (XIX). Dehydration of XVII and XIX then gives 3-methyl-4-phenylcyclohex-2-enone (XVIII) and 3-methyl-6-phenylcyclohex-2-enone (XX), respectively. Three of the possible products, XVII, XVIII, and XX, have been isolated and identified. It is interesting to note that earlier, Cologne, *et al.*,[13] isolated only XX in 63% yield from the interaction of methyl benzyl ketone (4 equiv.) with methyl vinyl ketone (1 equiv.) using potassium methoxide as the condensing agent.

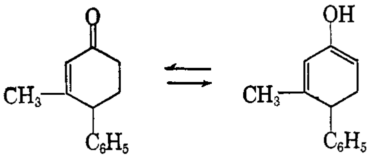
The structure of XX was established by permanganate oxidation to 2-phenyl-5-ketohexanoic acid (XXI), which was shown to be identical with the acid which was obtained by hydrolysis of the condensation product of ethyl phenylacetate with methyl vinyl ketone.



$$XX \xrightarrow{KMnO_4} CH_3COCH_2CH_2\underset{C_6H_5}{CH}COCO_2H \longrightarrow CH_3COCH_2CH_2\underset{C_6H_5}{CH}CO_2H \; (XXI)$$

$$C_6H_5CH_2CO_2C_2H_5 + CH_2{=}CHCOCH_3 \xrightarrow{LiNH_2} CH_3COCH_2CH_2\underset{C_6H_5}{CH}CO_2C_2H_5 \xrightarrow{(1)\ OH^-,\ (2)\ H^+} XXI$$

A similar oxidation was attempted without success on XVIII, the isomer of XX. However, XVIII was aromatized to XXI *via* its enol form, XVIIIa, by reaction



XVIII XVIIIa

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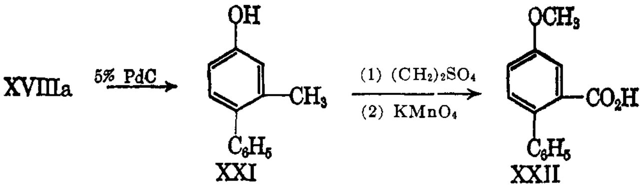
[12] W. S. Johnson, J. J. Korst, R. A. Clement, and J. Dutta, *J. Am Chem. Soc.*, **82**, 614 (1960).

[13] J. Cologne, J. Dreux, and R. Chapurlat, *Compt. rend.*, **251**, 252 (1960).

with 5% palladium on charcoal. Then, XXI was methylated and the resulting ether was oxidized to 2-carboxy-4-methoxybiphenyl (XXII), a known compound.



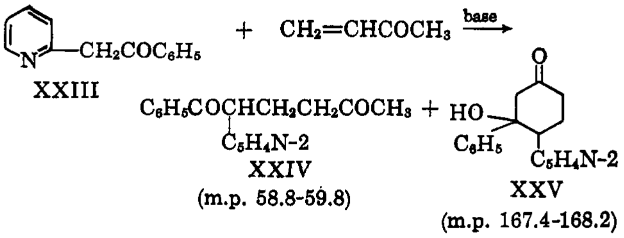
Since the 3-hydroxycyclohexanone derivatives are dehydrated during the formation of their semicarbazones, it was possible to identify XVII by showing that its semicarbazone was identical with that which was obtained from XVIII.

Finally, the reactions of the three highly reactive ketones, desoxybenzoin, 2-phenacylpyridine, and phenacylpyrazine, with methyl vinyl ketone were studied. From these reactions high yields (Table IV) of only the acetoethylated compound (in the case of phenacylpyrazine) or a mixture of the acetoethylated and the intramolecular aldol cyclohexanone derivative (in the cases of desoxybenzoin and 2-phenacylpyridine) were obtained.

That intramolecular aldol condensation did not occur in the reaction of phenacylpyrazine with methyl vinyl ketone may be due to the insolubility of the initially formed 1-phenyl-3-pyrazyl-1,5-dione in the reaction medium.

Experiments seven and eight in Table IV indicate that reaction time has a pronounced effect on the ratio of products obtained in the reaction of desoxybenzoin with methyl vinyl ketone. If the reaction is permitted to run for only 0.5 hr. after the complete addition of the reactants, nearly equivalent amounts of the open-chain compound, 1,2-diphenylhexane-1,5-dione (25.7%), and the cyclic ketone, 3,4-diphenyl-3-hydroxycyclohexanone (35%), are obtained. However, if the reaction time is increased to 1 hr., the yield of combined products is increased greatly and an 89.5% yield of the former and a 10.5% yield of the latter compound are obtained.

In the acetoethylation of 2-phenacylpyridine (XXIII) two compounds, XXIV and XXV, were obtained. In this connection, it should be pointed out that earlier 2-phenacylpyridine hydrochloride had been treated with methyl vinyl ketone and alcoholic potassium hydroxide by Beyer, *et al.*,[14] who obtained a compound, m.p. 166°. Although they did not elucidate its structure, these workers claim that they obtained XXIV. From our work there is little doubt that they prepared XXV.



Experimental[15]

The Reaction of Acetophenone with Methyl Vinyl Ketone Using Lithium Amide as the Condensing Agent.—Lithium amide (0.5 mole) was prepared from lithium[16] (3.5 g., 0.5 mole) dissolved in 400 ml. of anhydrous liquid ammonia using a reactor which consisted of a 1-l., three-neck, round-bottom flask equipped with ground glass joints and fitted with a slip-seal stirrer, an addition funnel, and a Dry Ice condenser (fitted with a drying tube filled with Drierite). The procedure which was used followed that which was employed earlier.[17]

Acetophenone (0.5 mole, 60.0 g.), in 25 ml. of anhydrous ether, was added to the rapidly stirred, gray suspension of lithium amide over a 15-min. period and then the reaction mixture was stirred for an additional 15 min. Methyl vinyl ketone (0.25 mole, 17.2 g.), in 150 ml. of anhydrous ether, was added over a 1-hr. period, and the reaction was then immediately quenched by the addition of solid ammonium chloride (0.51 mole, 27.1 g.).

After the ammonia had been displaced by ether, the reaction mixture was poured onto ice, acidified with concentrated hydrochloric acid, and extracted with several portions of ether. The combined extracts were dried over anhydrous sodium sulfate, and the solvent and unreacted acetophenone were removed. Vacuum distillation of the residue gave 18.9 g. of mixed products, b.p. 125–150° at 1 mm. This mixture solidified and was fractionally recrystallized from petroleum ether (60–70°) to give 17.4 g. (37%) of 1-phenylhexane-1,5-dione, m.p. 67.2–67.6°, and 1.5 g. (3.2%) of 3-phenyl-3-hydroxycyclohexanone, m.p. 152.0–153.0°.

The Reaction of 2-Phenacylpyridine with Methyl Vinyl Ketone Using Triton B as the Condensing Agent.—Methyl vinyl ketone (0.15 mole, 10.5 g.) in 100 ml. of ether was added over a 1-hr. period to a mixture of 2-phenacylpyridine[18] (0.8 mole, 59.1 g.) and 12 ml. of 38% aqueous solution of benzyltrimethylammonium hydroxide (Triton B) in 150 ml. of ether and 30 ml. of dioxane at 0–5°. The reaction mixture was stirred for 1 hr. at room temperature during which time a solid formed and was filtered to give 16.2 g. (40.6%) of 3-phenyl-3-hydroxy-4-(2-pyridyl)cyclohexanone, m.p. 167.4–168.2° from petroleum ether (90–100°). The filtrate was poured over ice and neutralized with concentrated hydrochloric acid to give a second solid. Filtration gave 15.2 g. (37.9%) of 1-phenyl-2-(2-pyridyl)hexane-1,5-dione, m.p. 58.8–59.8° from petroleum ether (30–60°).

The Reaction of Cyclohexanone with Methyl Vinyl Ketone Using Ethanolic Potassium Hydroxide as the Condensing Agent.—Methyl vinyl ketone (0.20 mole, 14.0 g.) in 100 ml. of ether was added over a 1-hr. period to a mixture of cyclohexanone (0.40 mole, 39.2 g.) and ethanolic potassium hydroxide (0.08 mole, 4.5 g. in 15 ml. of ethanol) in 150 ml. of ether at 0°. The reaction mixture was stirred for 1 hr. at room temperature and was then processed in the usual manner to give 18.0 g. of recovered cyclohexanone, b.p. 57–61° at 27 mm.; 11.5 g. (38.5%) of 2-keto-$\Delta^{1,9}$-octalin, b.p. 106–108° at 3.5 mm.; and 0.8 g. (2.4%) of 9-hydroxy-2-decalone, m.p. 146.0–146.6°.

Proof of Structure of 2-Ethyl-5-methyl-5-hydroxycyclohexanone. A. Dehydration of 2-Ethyl-5-methyl-5-hydroxycyclohexanone.—A mixture of 2-ethyl-5-methyl-5-hydroxycyclohexanone (0.029 mole, 4.5 g.) and 75 ml. of a 50% aqueous solution of sulfuric acid was refluxed 1 hr. The reaction mixture was cooled, poured over ice, and was then extracted with ether. After the ether extracts were dried over anhydrous sodium sulfate, the solvent was removed by distillation at atmospheric pressure. The residue consisted of 3.9 g. of what was believed to be crude 3-methyl-6-ethylcyclohex-2-enone and was used directly in the next reaction.

B. Aromatization of 3-Methyl-6-ethylcyclohex-2-enone.—A mixture of 3-methyl-6-ethylcyclohex-2-enone (0.29 mole, 3.9 g.) and sulfur (0.29 mole, 0.962 g.) was refluxed for 1 hr. The reaction mixture was extracted with ether and the ether was evaporated leaving a tarry residue. The tarry residue was taken up in petroleum ether (60–70°) from which an oil separated.

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(14) H. Beyer, W. Lassig, and G. Schudy, *Ber.*, **90**, 592 (1957).

(15) The methyl vinyl ketone which was used in this study was supplied through the courtesy of Charles Pfizer and Co., New York, N. Y.

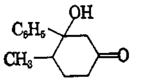
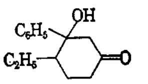
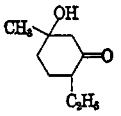
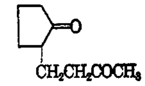
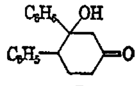
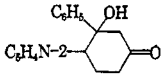
(16) The lithium which was used in this study was supplied through the courtesy of Lithium Corporation of America.

(17) M. Hamell and R. Levine, *J. Org. Chem.*, **15**, 162 (1950).

(18) N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Am. Chem. Soc.*, **73**, 4301 (1951).

Table IV

Reactions of Other Ketones with Methyl Vinyl Ketone[a]

Ketone (moles)	Base (moles)	Reaction time, hr.	Product	% yield	B.p. (mm.) or m.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Propiophenone (0.5)	$LiNH_2$[b] (0.5)	0[c]		52.4	133–134[d,e]	$C_{13}H_7O_2$	76.42	76.36	7.89	7.67
n-Butyrophenone (0.5)	$LiNH_2$[b] (0.5)	0[c]		53.0	133–134[d,f]	$C_{14}H_{19}O_2$	77.07	76.75	7.31	7.57
Acetone (0.5)	$LiNH_2$[b] (0.5)	0[c]	$CH_3CO(CH_2)_3COCH_3$	7.4	97–103 (12)[g]					
Methyl *n*-propyl (0.5)	$LiNH_2$[b] (0.5)	0[c]		15.5	120.2–120.8[h]	$C_9H_{16}O_2$	69.20	68.86	10.33	10.05
Cyclopentanone (0.5)	$LiNH_2$[b] (0.5)	0[c]		40	98–99 (2)[i–k]					
Phenacylpyrazine (0.15)	Triton B[l] (6 ml.)	1.0	$C_6H_5COCHCH_2CH_2COCH_3$ | $C_4H_3N_2$	95.0	107.6–108.0[m]	$C_{16}H_{16}N_2O_2$	71.68	71.59	6.01	5.96
Desoxybenzoin (0.275)	Triton B[l] (6 ml.)	0.5	$C_6H_5COCH(C_6H_5)CH_2CH_2COCH_3$ A	25.7	71.6–72.2[n]	$C_{18}H_{18}O_2$	81.19	81.43	6.81	7.28
			 B	35.0	208.5–209.5[o]	$C_{18}H_{18}O_2$	81.19	81.06	6.81	7.04
(0.3)	(7 ml.)	1.0	A	89.0	71.6–72.2					
			B	10.5	208.5–209.5					
2-Phenacylpyridine (0.3)	Triton B[l] (12 ml.)	1.0	$C_6H_5COCHCH_2CH_2COCH_3$ | $C_5H_4N—2$ XXIII	40.6	58.8–59.8[p]	$C_{17}H_{17}NO_2$	76.38	75.88	6.43	6.20
			 XXIV	37.9	167.4–168.2[q]	$C_{17}H_{17}NO_2$	76.38	76.46	6.43	6.74

[a] In all experiments 1 equiv. of methyl vinyl ketone was used for 2 equiv. of the ketone which was being acetoethylated.

[b] The reaction was run in a mixture of 400 ml. of liquid ammonia and 250 ml. of anhydrous ether as the solvent.

[c] The reaction was quenched with solid ammonium chloride immediately after the MVK was added.

[d] Recrystallized from petroleum ether (90–100°).

[e] By using the semicarbazide hydrochloride–pyridine method, the product gave the semicarbazone of 3-phenyl-4-methylcyclohex-2-enone, m.p. 204–205° from 95% ethanol. *Anal.* Calcd. for $C_{14}H_{17}N_3O$: C, 69.12; H, 7.04. Found: C, 69.27; H, 6.87.

[f] The product gave (see footnote *e*) the semicarbazone of 3-phenyl-4-ethylcyclohex-2-enone, m.p. 194–195° from 95% ethanol. *Anal.* Calcd. for $C_{15}H_{19}N_3O$: C, 70.02; H, 7.44. Found: C, 69.98; H, 7.49.

[g] Disemicarbazone, m.p. 212–213° from 95% ethanol [R. G. Fargher and W. H. Perkin, *J. Chem. Soc.*, **105,** 1361 (1914)].

[h] The product gave (see footnote *e*) the semicarbazone of 3-methyl-6-ethylcyclohex-2-enone, m.p. 200–201° from 95% ethanol. *Anal.* Calcd. for $C_{10}H_{17}N_3O$: C, 61.50; H, 8.78. Found: C, 61.23; H, 8.94.

[i] This compound gave a disemicarbazone, m.p. 220–221°. *Anal.* Calcd. for $C_{11}H_{20}N_6O_2$: C, 49.23; H, 7.55. Found: C, 49.41; H, 7.53.

[j] Ref. 10 reports the melting point of this desemicarbazone to be 229°.

[k] This reaction failed with Triton B as the catalyst.

[l] Triton B is a 38% aqueous solution of benzyltrimethylammonium hydroxide.

[m] This compound gave a disemicarbazone, m.p. 205–206° from 95% ethanol. *Anal.* Calcd. for $C_{18}H_{22}N_8O_2$: C, 56.52; H, 5.80. Found: C, 56.30; H, 5.45.

[n] This compound gave a dioxime, m.p. 118.8–119.8° from 95% ethanol. *Anal.* Calcd. for $C_{18}H_{20}N_2O_2$: C, 73.16; H, 6.82. Found: C, 73.43; H, 6.89.

[o] This compound (see footnote *c*) gave the semicarbazone of 3,4-diphenylcyclohex-2-enone, m.p. 218–219° from 95% ethanol. *Anal.* Calcd. for $C_{18}H_{19}N_3O$: C, 74.97; H, 5.96. Found: C, 75.12; H, 6.39.

[p] This compound gave a disemicarbazone, m.p. 212.0–212.5° from 95% ethanol. *Anal.* Calcd. for $C_{19}H_{23}N_7O_2$: C, 59.83; H, 6.08. Found: C, 59.51; H, 5.75.

[q] This compound (see footnote *e*) gave the semicarbazone of 3-phenyl-4-(2-pyridyl)cyclohex-2-enone, m.p. 215.5–216.0° from 95% ethanol. *Anal.* Calcd. for $C_{18}H_{19}N_4O$: C, 70.33; H, 6.23. Found: C, 69.99; H, 5.99.

The oil consisted of 1.0 g. (25.9%) of crude 2-ethyl-5-methylphenol.

A sample of the 2-ethyl-5-methylphenol was converted to its *p*-nitrobenzoate, m.p. 87.8–88.2° (from 95% ethanol),[19] alone and when mixed with an authentic sample.

Proof of Structure of 3-Methyl-6-phenylcyclohex-2-enone.—The reactor was charged with 3-methyl-6-phenylcyclohex-2-enone (0.025 mole, 4.7 g.) dissolved in 50 ml. of acetone. Potassium permanganate (0.072 mole, 12.0 g.) was added over a 2-hr. period holding the reaction temperature at 0° by means of an ice bath. After complete addition of the potassium permanganate, the reaction mixture was stirred for 18 hr. at room temperature. The solid which was present was removed by filtration and washed with 30 ml. of acetone. The solid was then suspended in 250 ml. of water and a solution of 30 ml. of concentrated sulfuric acid in 75 ml. of water was added slowly. Then solid sodium bisulfite was added in small portions until the reaction mixture became homogenous. The aqueous solu-

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(19) G. Baddeley, *J. Chem. Soc.*, 330 (1944).

tion was then extracted with several portions of ethyl acetate. The extracts were combined and dried over anhydrous sodium sulfate, and then the ethyl acetate was removed by atmospheric distillation. Vacuum distillation of the product residue gave 2.0 g. (59.1%) of 2-phenyl-5-ketohexanoic acid, b.p. 155–184° at 2.5 mm., m.p. 69.8–70.2° from petroleum ether alone and when mixed with an authentic sample.

Synthesis of an Authentic Sample of 2-Phenyl-5-ketohexanoic Acid.—Ethyl 2-phenyl-5-ketohexanoate was prepared from the reaction of ethyl phenylacetate and methyl vinyl ketone. The ester (0.019 mole, 4.0 g.) was added to a solution of potassium hydroxide (0.23 mole, 13.0 g.) in 50 ml. of water. The mixture was refluxed for 2 hr., poured into 100 ml. of cold water, acidified with dilute hydrochloric acid, and extracted with several portions of ether. The combined extracts were dried over anhydrous sodium sulfate and the solvent was distilled. The residue solidified and gave 4.0 g. (75.5%) of 2-phenyl-5-ketohexanoic acid, m.p. 69.2–70.5° from petroleum ether (30–60°). A mixture melting point between this acid and that which was obtained in the last experiment showed no depression.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.56; H, 6.76.

This keto acid gave a 2,4-dinitrophenylhydrazone, m.p. 167.6–168.6° from 95% ethanol.

Anal. Calcd. for $C_{18}H_{18}N_4O_6$: C, 55.95; H, 4.70. Found: C, 55.72; H, 4.42.

Attempted Oxidation of 3-Methyl-4-phenylcyclohex-2-enone.—3-Methyl-4-phenylcyclohex-2-enone (0.025 mole, 4.7 g.) was dissolved in 50 ml. of acetone at 0°. Potassium permanganate (0.095 mole, 15.0 g.) was added over a 2-hr. period maintaining the reaction temperature at 0°, and the mixture was then stirred at room temperature for 48 hr. The reaction was processed using the method described above in the oxidation of the isomeric ketone, 3-methyl-6-phenylcyclohex-2-enone, to give 3.9 g. (83%) of recovered 3-methyl-4-phenylcyclohex-2-enone, b.p. 100–103° at 0.3 mm., m.p. 39–40°.

Proof of Structure of 3-Methyl-4-phenylcyclohex-2-enone. A. Reduction of 3-Methyl-4-phenylcyclohex-2-enone.—3-Methyl-4-phenylcyclohex-2-enone (0.015 mole, 3.0 g.) and 0.6 g. of 5% palladium on charcoal were dispersed in 3.0 ml. of *p*-cymene in a 5-ml. flask connected to a reflux condenser. Using a metal bath as a heating source, the reaction mixture was refluxed at 180° for 30 hr. Nitrogen gas was used intermittently to flush out the hydrogen gas produced in the reaction. At the end of the reaction period, the mixture was cooled and the palladium catalyst was filtered. The solution was poured over ice and made basic with 50% sodium hydroxide. An organic layer separated. This consisted of *p*-cymene and unreacted 3-methyl-4-phenylcyclohex-2-enone and was discarded. The aqueous phase was made acid with hydrochloric acid and extracted with several portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate and then the ether was removed by distillation at atmospheric pressure. Vacuum distillation of the residue gave 1.6 g. (53.4%) of 4-hydroxy-2-methylbiphenyl, b.p. 112–122° at 0.6 mm.[20]

B. Reaction of 2-Methyl-4-hydroxybiphenyl with Dimethyl Sulfate.—2-Methyl-4-hydroxybiphenyl (0.0054 mole, 1.0 g.), sodium hydroxide (0.0054 mole, 0.20 g.), and dimethyl sulfate (0.0054 mole, 0.7 g.) in 8 ml. of water were heated in a boiling water bath for 0.5 hr. The reaction mixture was cooled and extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and then the ether was removed by distillation. Approximately 1.0 g. of a residue remained. This was assumed to be 2-methyl-4-methoxybiphenyl and was used directly in the next reaction.

C. Oxidation of 2-Methyl-4-methoxybiphenyl.—2-Methyl-4-methoxybiphenyl (0.005 mole, 1.0 g.) and sodium hydroxide (0.10 mole, 4.0 g.) were placed in 60 ml. of water. Potassium permanganate (0.015 mole, 2.4 g.) was added, and then the reaction mixture was stirred between 90–100° for 30 min. at which time the red color of the mixture was discharged. The reaction mixture was filtered, and the aqueous layer was acidified and extracted with ether. The ether was evaporated and a solid residue (0.5 g., 43.8%) remained of crude 4-methoxybiphenyl-2-carboxylic acid. After recrystallization from water the 2-carboxy-4-methoxybiphenyl melted at 139–141°[20] alone and when mixed with an authentic sample.

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[20] N. Chatterjee, *J. Indian Chem. Soc.*, **12**, 410 (1935).

The Chemistry of Methyl Vinyl Ketone. II. Reactions with Esters, β-Keto Esters, Malonic Ester, Amines, Tar Bases, and Inorganic Salts

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Several esters, β-keto esters, malonic ester, amines, and inorganic salts have been acetoethylated in good yields with methyl vinyl ketone. Although γ-picoline gives the expected acetoethylated product, 5-(4-pyridyl)-2-pentanone, the reaction of α-picoline with methyl vinyl ketone gives the alcohol, 3-(2-picolyl)-3-hydroxy-1-butene. A possible explanation for these anomalous results is presented.

In the first paper of this series,[2] we described the Michael condensations of a series of ketones, as the addenda, with methyl vinyl ketone as the acceptor molecule. The present report is concerned with the use of esters, β-keto esters, malonic ester, amines, tar bases, and inorganic salts as addenda.

Reactions of Methyl Vinyl Ketone (II) with Simple Esters.—The attempted acetoethylation of ethyl acetate with II using both potassium *t*-butoxide and lithium amide as the condensing agents gave none of the expected product, ethyl 5-ketohexanoate. The former reaction gave polymer and starting materials, while, in the latter reaction, ethyl acetate was self-condensed to give a 40% yield of ethyl acetoacetate.

Although the reaction of II with ethyl phenylacetate (I) using potassium *t*-butoxide as the condensing agent gave a 28.5% yield (see Table I) of the desired product, ethyl 2-phenyl-5-ketohexanoate (III), repeating this reaction with lithium amide as the condensing agent gave a mixture of III (29.5%) and 1,3-diphenyl-3-carbethoxyheptane-2,6-dione (VI, 13.8%). Apparently I self-condensed to ethyl α,γ-diphenylacetoacetate (IV), which is then acetoethylated to give VI (p. 2348).

Reactions of II with Malonic Ester and β-Keto Esters.—Malonic ester was acetoethylated to give good yields, 40.8% and 82.7%, respectively, of the expected product, ethyl 2-carbethoxy-5-ketohexanoate (VII) using Triton B and ethanolic potassium hydroxide as the condensing agents. The structure of the product

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[1] Monsanto Chemical Co. Research Fellow, 1957-1959. This paper is based on a portion of the thesis submitted by N. C. Ross to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

[2] N. C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2341 (1964).