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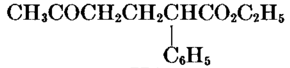
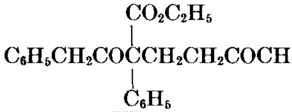
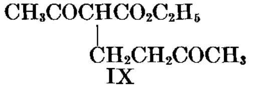
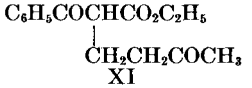
[1] Monsanto Chemical Co. Research Fellow, 1957–1959. This paper is based on a portion of the thesis submitted by N. C. Ross to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

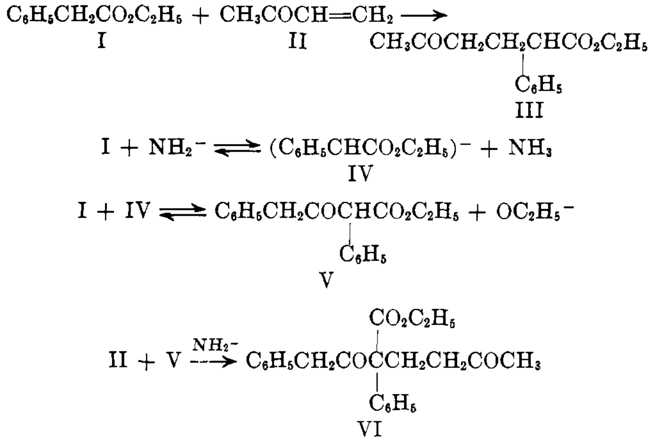
[2] N. C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2341 (1964).

TABLE I

REACTIONS OF VARIOUS SUBSTRATES WITH METHYL VINYL KETONE[a]

Substrate (moles)	Base (moles)	Product	% yield	B.p. (mm.) or m.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
$C_6H_5CH_2CO_2C_2H_5$ (0.2)	KOC_4H_9-*t* (0.054)	 $CH_3COCH_2CH_2\underset{C_6H_5}{\underset{\vert}{C}H}CO_2C_2H_5$ III	28.5	113 (0.38)	$C_{14}H_{18}O_3$[b]	71.65	71.62	7.73	7.78
(0.5)	$LiNH_2$ (0.5)	III	29.5	157–163 (1.7)					
		 $C_6H_5CH_2CO\overset{CO_2C_2H_5}{\overset{\vert}{\underset{\underset{C_6H_5}{\vert}}{C}}}CH_2CH_2COCH_3$ VI	13.8	125.2–126.0	$C_{22}H_{24}O_4$	74.97	74.69	6.87	7.08
$CH_2(CO_2C_2H_5)_2$ (0.4)	Triton B[c] (5 ml.)	$CH(CO_2C_2H_5)_2(CH_2CH_2COCH_3)$ VII	40.8	119–120 (1.8)					
(0.4)	KOH[d] (0.1)	VII	82.7		$C_{11}H_{18}O_5$	57.30	56.99	7.88	7.65
$CH_3COCH_2CO_2C_2H_5$ (0.4)	Triton B[c] (5 ml.)	 $CH_3CO\underset{CH_2CH_2COCH_3}{\underset{\vert}{C}H}CO_2C_2H_5$ IX	48.2	126–128 (4)[e]					
(0.5)	KOH[d] (0.13)	IX	90.7						
$C_6H_5COCH_2CO_2C_2H_5$ (0.4)	Triton B[c] (5 ml.)	 $C_6H_5CO\underset{CH_2CH_2COCH_3}{\underset{\vert}{C}H}CO_2C_2H_5$ XI	86.3	181–183 (3)	$C_{15}H_{18}O_4$	68.70	68.54	6.92	6.71
n-$C_3H_7NH_2$ (0.4)	*f*	$(n\text{-}C_3H_7NH_2CH_2CH_2COCH_3)^+\ HC_2O_4^-$ XIV	94.2	149.4–149.8 dec.[g]	$C_9H_{17}NO_5$	49.30	48.90	7.83	8.03
$C_6H_{11}NH_2$[h] (0.4)	*f*	$(C_6H_{11}NH_2CH_2CH_2COCH_3)^+\ Cl^-$ XV	94.5	131.0–132.0[i]	$C_{10}H_{19}ClNO$	58.37	58.07	9.80	9.49
t-$C_4H_9NH_2$ (0.4)	*f*	$(t\text{-}C_4H_9NH_2CH_2CH_2COCH_3)^+Cl^-$ XVI	62.3	123.8–124.8[j]	$C_8H_{18}ClNO$	53.40	53.05	9.60	9.74
$C_6H_5NH_2$ (0.6)	*f*	$C_6H_5NHCH_2CH_2COCH_3$ XIII	69.0	113–116 35.2–35.8 (1.5)[k]					
$(C_2H_5)_2NH$ (0.8)	*f*	$(C_2H_5)_2NCH_2CH_2COCH_3$ XVII	92.5	69–71 (12)[l]					
C_4H_9NO[m] (0.4)	*f*	$C_4H_8ONCH_2CH_2COCH_3$ XVIII	89.3	85–87 (2)[n]					
$C_5H_4NCH_3$-2[o] (0.5)	$NaNH_2$ (0.5)	$(C_5H_4NCH_2\text{-}2)C(OH)(CH_3)(CH{=}CH_2)$ XXIII	22.2	79.5 (1.8)[p]	$C_{10}H_{13}NO$	73.59	73.24	7.84	7.94
	C_6H_5Li (0.5)	XXIII	61.5						
$C_5H_4NCH_3$-4[q] (0.5)	$NaNH_2$ (0.5)	$(C_5H_4NCH_2\text{-}4)CH_2CH_2COCH_3$ XIX	24.7	112–114 (2)[r]					
Na_2S (0.4)		$CH_3COCH_2CH_2SH$ XXVII	28.8	77 (30)[s]	C_4H_8OS	45.20	45.31	7.75	7.65
		$(CH_3COCH_2CH_2)_2S$ XXVIII	29.9	102–107 (1)[t]					
KCN (0.2)	CH_3CO_2H (0.2)	$CH_3COCH_2CH_2CN$ XXIX	39.6	112–113 (15)[u]					

[a] In all experiments 1 equiv. of methyl vinyl ketone was used for 2 equiv. of the substrate. [b] 2,4-Dinitrophenylhydrazone, m.p. 88–89° from 95% ethanol. *Anal.* Calcd. for $C_{22}H_{22}N_4O_6$: C, 57.96; H, 5.48. Found: C, 57.79; H, 5.55. [c] This is a 38% aqueous solution of benzyltrimethylammonium hydroxide. [d] Dissolved in 20 ml. of 95% ethanol. [e] See ref. 5. [f] No added catalyst. [g] Picrate of 4-*n*-propylamino-2-butanone, m.p. 158.4–159.4°, from 95% ethanol. *Anal.* Calcd. for $C_{13}H_{18}N_4O_8$: C, 43.57; H, 5.06. Found: C, 43.38; H, 5.37. [h] This is cyclohexylamine. [i] Benzenesulfonamide of 4-cyclohexylamino-2-butanone, m.p. 106.6–107.4°. *Anal.* Calcd. for $C_{16}H_{23}NO_3S$: C, 62.10; H, 7.51. Found: C, 61.80; H, 7.32. Hydrogen oxalate of 4-*t*-butylamino-2-butanone, m.p. 125.6–125.8°. *Anal.* Calcd. for $C_{10}H_{19}NO_5$: C, 51.48; H, 8.21. Found: C, 51.15; H, 8.01. [k] Semicarbazone, m.p. 163–164° [A. T. Babazan and N. P. Gambaryan, *Izv. Akad. Nauk. Arm., SSR*, **3**, 563 (1950); *Chem. Abstr.*, **47**, 3266 (1953)]. Also see ref. 7. [l] See ref. 9. [m] This is morpholine. [n] Picrate, m.p. 112.6–113.6° (see ref. 10). [o] This is 2-picoline. [p] Picrate, m.p. 143.8–144.8° from 95% ethanol. *Anal.* Calcd. for $C_{16}H_{16}N_4O_8$: C, 48.99; H, 4.11. Found: C, 48.69; H, 4.30. Picrate of 5-(2-pyridyl) 2-pentanone, m.p. 106° (see ref. 13). [q] This is 4-picoline. [r] See ref. 11. [s] 2,4-Dinitrophenylhydrazone, m.p. 129.2–129.8° from 95% ethanol. *Anal.* Calcd. for $C_{10}H_{12}N_4O_4S$: C, 42.24; H, 4.26. Found: C, 41.94; H, 4.09. [t] Disemicarbazone, m.p. 226–227° from 95% ethanol (see ref. 19). [u] 2,4-Dinitrophenylhydrazone, m.p. 146.0–146.8° from 95% ethanol (see ref. 14).



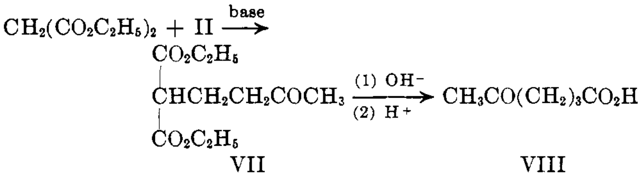
$$\underset{\text{I}}{C_6H_5CH_2CO_2C_2H_5} + \underset{\text{II}}{CH_3COCH{=}CH_2} \longrightarrow \underset{\text{III}}{CH_3COCH_2CH_2\underset{C_6H_5}{C}HCO_2C_2H_5}$$

$$\text{I} + NH_2^- \rightleftharpoons \underset{\text{IV}}{(C_6H_5CHCO_2C_2H_5)^-} + NH_3$$

$$\text{I} + \text{IV} \rightleftharpoons \underset{\text{V}}{C_6H_5CH_2CO\underset{C_6H_5}{C}HCO_2C_2H_5} + OC_2H_5^-$$

$$\text{II} + \text{V} \xrightarrow{NH_2^-} \underset{\text{VI}}{C_6H_5CH_2CO\overset{CO_2C_2H_5}{\underset{C_6H_5}{C}}CH_2CH_2COCH_3}$$

was established by hydrolysis and subsequent decarboxylation to the known 5-ketohexanoic acid (VIII) in 41.6% yield. Prior to our work, Tsuruta[3] effected the acetoethylation of dimethylmalonate in unreported yield using a catalytic amount of sodium methoxide as the condensing agent. Also, Kress[4] diacetoethylated malonic ester in 85% yield by the interaction of the ester (1 equiv.) with II (2 equiv.) in the presence of Triton B.

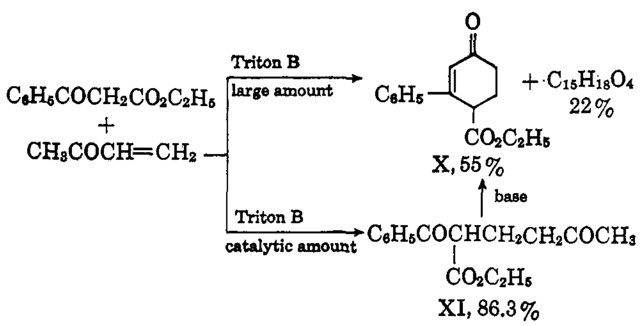


$$CH_2(CO_2C_2H_5)_2 + \text{II} \xrightarrow{\text{base}} \underset{\text{VII}}{\overset{CO_2C_2H_5}{\underset{CO_2C_2H_5}{C}}HCH_2CH_2COCH_3} \xrightarrow[\text{(2) H}^+]{\text{(1) OH}^-} \underset{\text{VIII}}{CH_3CO(CH_2)_3CO_2H}$$

Ethyl acetoacetate also condenses with II to give good to high yields of 3-carbethoxyheptane-2,6-dione (IX) when either Triton B (48.2%) or ethanolic potassium hydroxide (90.7%) is used as the condensing base. This compound has also been prepared similarly by Henecka[5] in 85–88% yield except that sodium methoxide was used as the condensing agent.

Walker[6] has reported that the reaction of essentially equivalents of ethyl benzoylacetate and II in the presence of a large amount of Triton B gave a 55% yield of 3-phenyl-4-carbethoxycyclohex-2-enone (X) and 22% yield of a compound, $C_{15}H_{18}O_4$, whose structure was not elucidated. In the present study, it was found that none of X was obtained when ethyl benzoylacetate (2 equiv.) was allowed to react with II (1 equiv.) in the presence of a catalytic amount of Triton B. Instead, the normal acetoethylated product, 1-phenyl-2-carbethoxyhexane-1,5-dione (XI), was obtained in 86.3% yield. It is quite likely that, in Walker's reaction, XI was formed initially and that in the presence of the large amount of Triton B it underwent intramolecular aldol condensation followed by dehydration to give X. The structure of XI was established by cleaving it with alkali to give the expected products, benzoic acid and 5-ketohexanoic acid (XII) (see col. 2, top).

Reactions of II with Amines.—With the exception of a few aromatic amines,[7,8] the addition of primary amines to II appears not to have been reported. The amines are apparently sufficiently basic so that they add to II without any added catalyst.



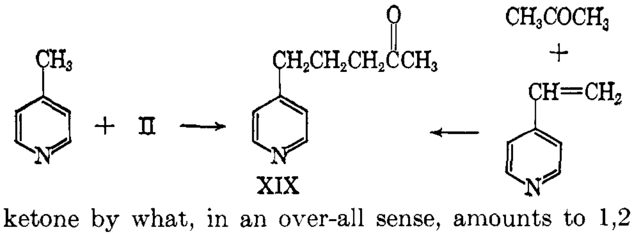
$$\text{XI} \xrightarrow[\text{(2) H}^+]{\text{(1) OH}^-} C_6H_5CO_2H + \underset{\text{XII}}{CH_3COCH_2CH_2CH_2CO_2H} + C_2H_5OH$$

Although Murata and Arai[7] reported that a 2-week reaction period is necessary to acetoethylate aniline in 78% yield, in the present study a 69% yield of 4-anilino-2-butanone (XIII) was isolated after a reaction time of only 20 hr. This ketoamine decomposes upon distillation but it was purified and stored as a white, crystalline solid.

Three primary alkylamines added readily to II: Since the products are unstable as the free bases, they were isolated and purified as their hydrogenoxalates or hydrochlorides. Thus, 4-*n*-propylamino-2-butanone hydrogen oxalate (XIV, 94.2%), 4-cyclohexylamino-2-butanone hydrochloride (XV, 94.5%), and 4-*t*-butylamino-2-butanone hydrochloride (XVI, 62.3%) were prepared.

Diethylamine and II gave 4-diethylamino-2-butanone (XVII) in 92.5% yield as compared with a 66% yield by the Mannich reaction.[9] Similarly, the acetoethylation of morpholine gave N-(3-ketobutyl)morpholine (XVIII) in 89.3% yield as compared with a 73% yield by the Mannich reaction.[10]

Reactions of II with Tar Bases—2-Picoline and 4-picoline, both of which have acidic hydrogen atoms in their methyl groups, have been condensed with II. The sodium derivative of 4-picoline was acetoethylated to give 5-(4-pyridyl)-2-pentanone (XIX, 24.7%) which had been prepared previously[11] in 5% yield by the condensation of acetone with 4-vinylpyridine. By contrast, the sodium derivative of 2-picoline does not undergo Michael addition to II but reacts with this ketone by what, in an over-all sense, amounts to 1,2-addition to give the tertiary alcohol, 3-(2-picolyl)-3-hydroxy-1-butene (XX), in 22.2% yield. The yield of XX is increased to 61.5% when 2-picolyllithium (prepared from 2-picoline and phenyllithium) is used in place of 2-picolylsodium.



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[3] T. Tsuruta, *Bull. Inst. Chem. Res. Kyoto Univ.*, **31**, 190 (1953); *Chem. Abstr.*, **49**, 6183 (1955).

[4] B. H. Kress, U. S. Pat. 2,540,267; *Chem. Abstr.*, **45**, 5720 (1951).

[5] H. Henecka, *Ber.*, **81**, 179 (1948).

[6] G. N. Walker, *J. Am. Chem. Soc.*, **77**, 3664 (1955).

[7] N. Murata and H. Arai, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **56**, 809 (1953).

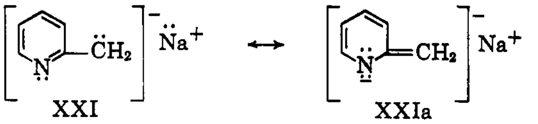
[8] H. Hopff and H. Spong, German Patent, 840,546 (June 3, 1952); *Chem. Abstr.*, **47**, 1739 (1953).

[9] E. C. du Feu, F. J. McQuillan, and R. Robinson, *J. Chem. Soc.*, 53 (1937).

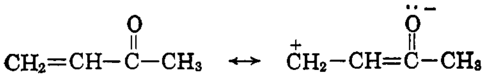
[10] R. H. Harradence and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1938); *Chem. Abstr.*, **37**, 5855 (1943).

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

A possible scheme to explain the difference in the nature of the products which are obtained from the reactions of 2- and 4-picoline with II is shown in eq. 1–4.



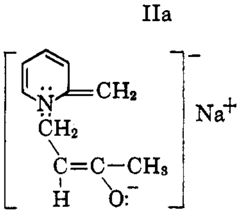
XXI XXIa (1)



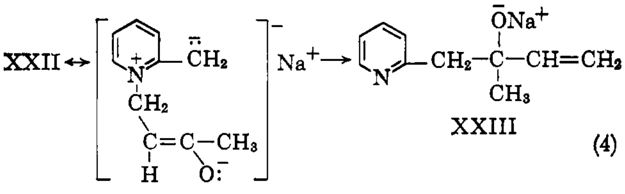
$$CH_2{=}CH{-}\overset{O}{\overset{\|}{C}}{-}CH_3 \leftrightarrow \overset{+}{C}H_2{-}CH{=}\overset{\ddot{O}^-}{\overset{|}{C}}{-}CH_3 \quad (2)$$

II IIa

IIa + XXIa ⟶



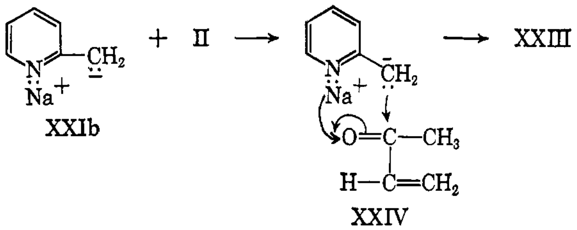
XXII (3)



XXIIa XXIII (4)

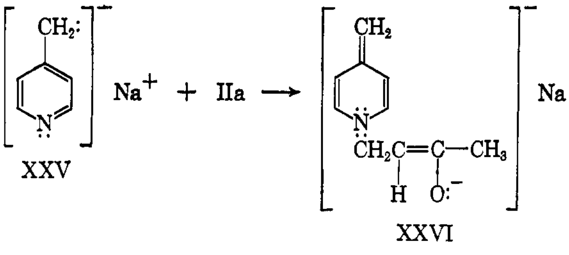
It is envisioned that the contributing resonance structure XXIa reacts with IIa by forming a carbon to nitrogen bond to give XXII (eq. 3). Then, XXIIa (one of the resonance forms of XXII) undergoes intramolecular reaction with the formation of a carbon to carbon bond and rupture of a carbon to nitrogen bond. The over-all result is the formation of XXIII, the sodium salt of 3-(2-picolyl)-3-hydroxy-1-butene.

An alternate route can be imagined for the formation of XXIII. If XXI is envisioned as having the extreme structure XXIb with the sodium ion electrostatically bonded to nitrogen, then XXIb may react with II by forming a carbon to carbon bond to give XXIII *via* the six-membered transition state (XXIV).



XXIb XXIV

While 4-picolylsodium (XXV) can also react with IIa by forming a carbon to nitrogen bond to give XXVI, which is analogous to XXII, subsequent rearrangement of XXVI cannot occur to give the 4-pyridyl isomer of XXIII. Compound XXVI can only revert to IIa and XXV, which then undergo a normal Michael condensation to give XIX.



XXV XXVI

That the tertiary alcohol was obtained in the 2-picoline reaction rather the isomeric acetoethylated product, 5-(2-pyridyl)-2-pentanone, was shown by a comparison of the physical properties of the alcohol with those of an authentic sample of the ketone.[12,13]

Reactions of II with Inorganic Salts.—Finally, two salts containing highly nucleophilic groups, *viz.*, sodium sulfide and potassium cyanide, were added to II. The reaction of sodium sulfide, with II in aqueous solution gave two products, 4-mercapto-2-butanone (XXVII, 28.8%) and bis(3-ketobutyl) sulfide (XXVIII, 29.9%). These results, which were obtained by using 2 equiv. of sodium sulfide per equivalent of II in an attempt to make XXVII the only or major product, appear to indicate that the initially formed ketomercaptan reacts more rapidly with more II to give the thio ether than the sodium sulfide reacts with II to give the mercaptan.

$$Na_2S + II \longrightarrow \underset{XXVII}{CH_3COCH_2CH_2SH} + \underset{XXVIII}{(CH_3COCH_2CH_2)_2S}$$

In order to have potassium cyanide react with II it was found necessary to produce hydrogen cyanide. This was done by liberating the hydrogen cyanide *in situ* by adding the potassium cyanide slowly to an ethanolic solution of II and glacial acetic acid. In this way a 39.6% yield of γ-ketovaleronitrile (XXIX) was obtained. The present one-step route to this

$$KCN + II \xrightarrow{CH_3CO_2H} \underset{XXIX}{CH_3COCH_2CH_2CN}$$

ketonitrile is superior to that in the literature[14] which involves the cyanoethylation of nitroethane to 4-nitrobutylcyanide in 29% yield followed by hydrolysis to the desired product in unreported yield.

Experimental[15]

Reaction of Ethyl Phenylacetate with II Using Lithium Amide as the Condensing Agent.—Lithium amide (0.5 mole), ethyl phenylacetate (0.5 mole), and II (0.25 mole) were allowed to react as described earlier[2] for the acetoethylation of acetophenone. The reaction mixture was poured onto ice and was extracted (basic extract) with several portions of ether. The aqueous phase was then acidified with dilute hydrochloric acid and was extracted (acidic extract) with several portions of ether. Both extracts were dried over anhydrous sodium sulfate and the solvent was distilled. Vacuum distillation of the residue from the basic extract gave 42.3 g. (51.6%) of recovered ethyl phenylacetate, b.p. 70–75° at 1.7 mm.; 17. g. (29.5%) of ethyl 2-phenyl-5-ketohexanoate (III), b.p. 113° at 0.38 mm.; 8.0 g. (13.8%) of 1,3-diphenyl-3-carbethoxyheptane-2,6-dione (VI), b.p. 157–163° at 1.7 mm. (m.p. 125.2–126.0° from 95% ethanol); and 13.0 g. of a tarry, nondistillable residue. The diketo ester gave a bis-2,4-dinitrophenylhydrazone, m.p. 192–193° (from 95% ethanol).

Anal. Calcd. for $C_{34}H_{32}N_8O_{10}$: C, 57.29; H, 4.53. Found: C, 57.41; H, 4.57.

Distillation of the residue from the acidic extract gave 4.0 g. (5.9%) of phenylacetic acid, m.p. 76–77° alone and when mixed with an authentic sample.

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(12) W. E. Doering and R. A. N. Weil, *J. Am. Chem. Soc.*, **69**, 2461 (1947).

(13) R. Levine and M. H. Wilt, *ibid.*, **74**, 342 (1952).

(14) G. D. Buckley, T. J. Elliott, F. G. Hunt, and A. Lowe, *J. Chem. Soc.*, 1505 (1947).

(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.

Reaction of Diethyl Malonate with II Using Ethanolic Potassium Hydroxide as the Condensing Agent.—II (0.2 mole, 14.0 g.), in 100 ml. of ether, was added over 90 min. to a mixture of diethyl malonate (0.4 mole, 64.0 g.) and potassium hydroxide (0.10 mole, 5.2 g. in 20 ml. of 95% ethanol) in 150 ml. of ether at 15°. The reaction mixture was stirred for an additional 2 hr. at room temperature, poured onto ice, acidified with dilute hydrochloric acid, and processed to give 33.3 g. of recovered diethyl malonate, b.p. 108–113° at 20 mm., and 38.1 g. (82.7%) of ethyl 2-carbethoxy-5-ketohexanoate (VII), b.p. 119–120° at 1.8 mm. A sample of VII (0.05 mole, 11.5 g.) was added slowly to a refluxing solution of potassium hydroxide (0.19 mole, 10.6 g.) in 15 ml. of water and the mixture was refluxed for 2 hr. Then an additional 15 ml. of water was added and 11 ml. of liquid was distilled to remove the ethanol. The mixture was cooled and concentrated sulfuric acid (0.18 mole, 17.6 g. in 24 ml. of water) was added slowly. The mixture was refluxed for an additional 3 hr. It was then cooled and extracted with ether. The ether extracts were dried and the solvent was removed by distillation at atmospheric pressure. Vacuum distillation of the residue gave 2.7 g. (41.6%) of 5-ketohexanoic acid (VIII), b.p. 132–133° at 4 mm.[16]; semicarbazone, m.p. 172.6–173.4°.[16]

Reaction of Ethyl Benzoylacetate with II Using Triton B as the Condensing Agent.—II (0.2 mole, 14.0 g. in 100 ml. of dioxane) was added over 90 min. to a mixture of ethyl benzoylacetate (0.4 mole, 76.4 g.) and 5 ml. of Triton B (38% aqueous solution) in 150 ml. of dioxane at 30°. The reaction mixture was stirred for an additional hour at room temperature and was then processed in the regular manner to give 33.4 g. of recovered ethyl benzoylacetate, b.p. 126–131° at 3 mm., and 45.1 g. (86.3%) of 1-phenyl-2-carbethoxyhexane-1,5-dione (XI), b.p. 181–183° at 3 mm. A sample of XI (0.05 mole, 13.1 g.) was added slowly to a solution of potassium hydroxide (0.25 mole, 14.0 g. in 15.0 ml. of water), and the mixture was refluxed for 2 hr. The mixture was poured over ice and acidified with dilute hydrochloric acid. Benzoic acid (3.0 g., 49.2%, m.p. 121–122° alone and when mixed with an authentic sample) was filtered and the filtrate was then extracted with ether. After drying the ether extracts and removing the solvent, the residue was distilled to give an additional 0.8 g. (18.1%) of benzoic acid (b.p. 128–138° at 5 mm., m.p. 121–122°) and 0.9 g. (13.2%) of 5-ketohexanoic acid (XII), b.p. 138–140° at 5 mm.[16]; semicarbazone,[16] m.p. 173–174°.

Reaction of *n*-Propylamine with II.—II (0.2 mole, 14.0 g. in 50 ml. of anhydrous ether) was added over a 40-min. period to *n*-propylamine (0.4 mole, 23.6 g. in 100 ml. of anhydrous ether) at 0–5°. The reaction mixture was stirred for an additional 2 hr. at room temperature and then the ether and unchanged *n*-propylamine were removed at 100 mm. The residue was diluted with 250 ml. of anhydrous ether and then oxalic acid dihydrate (0.2 mole, 18.0 g.) was added, and the hydrogenoxalate salt which precipitated was filtered to give 40.7 g. (94.2%) of 4-*n*-propylamino-2-butanone hydrogenoxalate (XIV), m.p. 149.4–149.8° dec.

The picrate of 4-*n*-propylamino-2-butanone was prepared as follows. The hydrogenoxalate was decomposed with 50% aqueous sodium hydroxide solution. The free 4-*n*-propylamino-2-butanone was extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and the ether was removed. The residual 4-*n*-propylamino-2-butanone was treated with a saturated ethanolic solution of picric acid to give its picrate, m.p. 158.4–159.4° from 95% ethanol.

Reaction of Cyclohexylamine with II.—II (0.2 mole, 14.0 g. in 50 ml. of anhydrous ether) was added over a 30-min. period to a solution of cyclohexylamine (0.4 mole, 29.7 g. in 100 ml. of anhydrous ether) at 0°. The reaction was stirred for an additional 90 min. at room temperature, and the ether and most of the unchanged cyclohexylamine were removed by distillation at 100 mm. The residue was diluted with 150 ml. of anhydrous ether and was saturated with dry hydrogen chloride to give 49.2 g. of a mixture of amine hydrochlorides. A benzene–petroleum ether (30–60°) mixture dissolved the hydrochloride of 4-cyclohexylamino-2-butanone (XV), while the hydrochloride of cyclohexylamine was not soluble. Filtration gave 10.1 g. (18.7%) of cyclohexylamine hydrochloride, m.p. 203–204°.[17] Evaporation of the benzene–petroleum ether solution gave 39.1 g. (94.5%) of XV, m.p. 131.0–132.0°.

The benzenesulfonamide of XV, m.p. 106.6–107.4°, was prepared as follows. An ether solution of the amine was obtained by decomposing its hydrochloride with 50% aqueous sodium hydroxide solution and extracting the mixture with ether. The ether was evaporated and the benzenesulfonamide was made according to the method of Shriner and Fuson.[18]

Reaction of Morpholine with II.—II (0.2 mole, 14.0 g. in 50 ml. of ether) was added over 60 min. to morpholine (0.4 mole, 34.8 g. in 100 ml. of ether) at 0–5°. The reaction was stirred for an additional 2 hr. at room temperature and the ether was distilled at atmospheric pressure. Vacuum distillation of the residue gave 28.0 g. (89.3%) of N-3-ketobutylmorpholine (XVIII), b.p. 85–87° at 2 mm.[10]; picrate, m.p. 112.6–113.6° from 95% ethanol.[10]

Reaction of 2-Picoline with II Using Phenyllithium as the Condensing Agent.—Phenyllithium (0.5 mole) was prepared in 400 ml. of anhydrous ether. 2-Picoline (0.5 mole, 46.6 g. in 25 ml. of anhydrous ether) was added over a 20-min. period after which the mixture was refluxed an additional 0.5 hr. The mixture was cooled to 0–2° with an an external ice–salt bath, and methyl vinyl ketone (0.25 mole, 17.2 g. in 100 ml. of anhydrous ether) was added over a 50-min. period. The reaction mixture was permitted to warm to room temperature (15 min.) and then the reaction was quenched by pouring it over ice. The reaction was processed to give 27.2 g. of recovered 2-picoline, b.p. 35–55° at 50 mm.; 24.9 g. (61.5%) of 3-(2-picolyl)-3-hydroxybutene (XXIII), b.p. 83–86° at 2.2 mm.; and 9.2 g. of a tarry, nondistillable residue. The infrared spectrum of XXIII showed the presence of a hydroxyl group and an olefinic bond and the absence of carbonyl absorption which would be present if the compound were 5-(2-pyridyl)-2-pentanone.

Reaction of 4-Picoline with II Using Sodium Amide as the Condensing Agent.—4-Picoline (0.5 mole, 46.6 g. in 25 ml. of anhydrous ether) was added to a rapidly stirred sodium amide suspension (0.5 mole in 600 ml. of anhydrous liquid ammonia) over a 20-min. period. The mixture was stirred for an additional 15 min. and then II (0.25 mole, 17.2 g. in 150 ml. of anhydrous ether) was added over a 1-hr. period, immediately after which the reaction was quenched with excess ammonium chloride (0.51 mole, 27.1 g.). The ammonia was replaced by ether and the mixture was poured over ice. Then the mixture was acidified with 100 ml. of hydrochloric acid and extracted with ether. Both the acid and basic extracts were dried over anhydrous sodium sulfate and the ether was removed at atmospheric pressure. Less than 1 g. of residue was obtained from the acid extract. Vacuum distillation of the basic product residue gave 22.4 g. of recovered 4-picoline, b.p. 50–66° at 50 mm., and 10.0 g. (24.7%) of 5-(4-pyridyl)-2-pentanone (XIX), b.p. 112–114° at 2 mm.[11]; picrate, m.p. 113–115° from 95% ethanol, alone and when mixed with an authentic sample.[11]

Reaction of Sodium Sulfide with II.—II (0.2 mole, 14.0 g.) was added over a 40-min. period to a solution of sodium sulfide ($Na_2S \cdot 9H_2O$) (0.4 mole, 96.1 g. in 100 ml. of water) with the temperature controlled between 10° and 20°. The reaction mixture was stirred for an additional 3 hr. at room temperature. It was poured over ice, neutralized with hydrochloric acid, and extracted with ether. The dried (anhydrous sodium sulfate) ether extracts were distilled at atmospheric pressure to remove the solvent. Vacuum distillation of the residue gave 6.0 g. (28.8%) of 4-mercapto-2-butanone (XXVII), b.p. 35–36° at 2 mm. and 77° at 30 mm.; and 5.2 g. (29.9%) of bis(3-ketobutyl) sulfide (XXVIII), b.p. 102–107° at 1 mm.[19]; disemicarbazone, m.p. 226–227° from 95% ethanol.[19]

Reaction of Potassium Cyanide with II.—Potassium cyanide (0.2 mole, 13.0 g. in 75 ml. of water) was added over 30 min. to a solution of II (0.2 mole, 14.0 g.) and glacial acetic acid (0.2 mole, 12.0 g.) in 200 ml. of ethanol with the temperature held at 35°. The reaction mixture was stirred at room temperature for 3 hr., and then 150 ml. of a mixture of water and ethanol was distilled. The reaction mixture was then processed in the normal manner to give 7.6 g. (39.6%) of γ-ketovaleronitrile (XXIX), b.p. 112–113° at 15 mm.[14]; 2,4-dinitrophenylhydrazone, m.p. 146.0–146.8° from 95% ethanol.[14]

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