$\lambda_{max}^{pH\,13}$ 259 mμ (ϵ 15,700); it moved as a single spot with R_f 0.21 in solvent TE (R_f 0.80 for 4).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.8; H, 5.22; N, 27.9. Found: C, 48.0; H, 5.28; N, 28.1.

9-(3-Deoxy-β-D-*threo*-pentofuranosyl)adenine (6).—By the procedure used for preparing **8**, 1.00 g of the 3-benzylthio nucleoside **1** was converted, after 8 hr reaction time, to afford 0.45 g (67%) of **6**, mp 190–194°, homogeneous by chromatography. One recrystallization from methanol afforded 0.30 (50%) of **6**, mp 195–196°, identical with the analytical sample, obtained by another recrystallization from methanol of **6**: mp 195–196°; $[\alpha]_{589}^{22}$ −27° (c 1, DMF); $\lambda_{max}^{pH\,1}$ 258 mμ (ϵ 14,600), $\lambda_{max}^{pH\,7}$ 260 mμ (ϵ 15,800), $\lambda_{max}^{pH\,13}$ 260 mμ (ϵ 15,100); it moved as one spot in solvents G, A, and B, with R_{Ad} 0.62, 0.71, and 1.15, respectively. It had R_f 0.68 in solvent TF (**1** had R_f 0.81).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.8; H, 5.22; N, 27.9. Found: C, 47.9; H, 4.94; N, 27.9.

The ratio of sponge nickel catalyst to substrate used above was 15. Satisfactory results were obtained with the ratio of 10. Reduction of the ratio to 5 resulted in incomplete desulfurization under identical conditions. In a later run using 0.20 g of **1** with a catalyst ratio of 10, aliquots were removed at intervals and examined by chromatography. Desulfurization was complete

in about 2 hr. When an oil bath was used as the heat source, the desulfurization was not complete after 8 hr. When an oil bath was the heat source, and 2,2'-azobisisobutyronitrile was added as a free-radical source, the reaction was only one-third complete after 3.5 hr.

Two desulfurizations at 50–75° for 2.5 hr, comparing the effect of an infrared lamp and an ultraviolet lamp (using quartz apparatus), showed that the infrared lamp reaction was about 50% complete; the other one was about 25% complete, according to qualitative results by thin layer chromatography.

Two desulfurizations at 100° using an infrared lamp for heat and a catalyst–substrate ratio of 20 demonstrated that the 3-benzylthio nucleoside **1** was completely desulfurized after 2 hr, but the 3-ethylthio nucleoside **2** was only about 67% reduced after 8 hr.

Cleavage of β-Ketonic Esters by the Action of Metal Iodides. I. The Reactions with Acetoacetic Ester and Its Mono- and Dimethyl Derivatives

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Acetoacetic ester and its α-methylated derivatives were found to undergo decomposition under the influence of metal iodides, notably iodides of sodium and calcium, at temperatures ranging from 130 to 170°. The key products with acetoacetic ester and its mono- and dimethylated derivatives so far identified were carbon dioxide, acetone and its homologs, ethyl iodide, ethyl alcohol, and the ethyl ester of acetic acid and its homologs. The production of a ketone and ethyl acetate or its homolog from a β-ketonic ester revealed that ketonic cleavage and acid cleavage had taken place simultaneously, although the former pathway predominated. With the use of calcium iodide and in the presence of a hydroxylic solvent, the reaction of an α-substituted β-ketonic ester afforded the corresponding ketone in a yield as high as 65%. The reaction is useful for the production of ketones from β-ketonic esters, particularly those that are resistant to ketonic cleavage by ordinary means. The action of sodium iodide and that of calcium iodide differed from each other in several respects. Mechanisms are formulated that account for the difference. The effects of hydroxylic solvents are discussed.

In a series of investigations on the reaction between disodiosuccinosuccinic ester and ethyl iodoacetate[1,2] the senior author and his collaborators found that evolution of carbon dioxide and production of volatile substances comprising ethyl alcohol and ethyl iodide took place when the reaction mixture was held at a temperature slightly above 150°. The main products consisted of two geometric isomers of diethyl 1,4-dicarbethoxycyclohexane-2,5-dione-1,4-bis(acetate). These latter substances, when heated with sodium iodide at 150–160°, decomposed with evolution of carbon dioxide. With sodium bromide in place of sodium iodide, the reaction took place only with difficulty. With sodium chloride, the reaction did not occur at all.

To test whether the decomposition under the influence of sodium iodide might be specific for β-ketonic esters with a carbalkoxy group joined to a tertiary α-carbon atom, a number of β-ketonic esters, including acetoacetic ester and its mono- and dimethyl derivatives, were investigated. The reaction with unsubstituted acetoacetic ester took place more readily than that with its mono- and dimethyl derivatives.

More extensive investigations have since been undertaken on the reactions of these β-ketonic esters toward sodium iodide under varying conditions. In one set of experiments acetoacetic ester was heated with an equimolar amount of sodium iodide. At 150°, there was a copious evolution of carbon dioxide and the distillate proved to be mainly acetone (24% yield), ethyl alcohol, ethyl acetate, and ethyl iodide. Water, ethyl ether, methyl *n*-propyl ketone, and mesityl oxide were found in minor amounts.

The production of acetone and carbon dioxide from acetoacetic ester showed that ketonic cleavage had taken place, and the formation of ethyl iodide was suggestive of mechanisms 1–3. The decarboxylation

$$CH_3COCH_2COOEt + I^- \longrightarrow CH_3COCH_2COO^- + EtI \quad (1)$$
$$I$$

$$CH_3COCH_2COO^- \longrightarrow (CH_3COCH_2)^- + CO_2 \quad (2)$$
$$I II$$

$$(CH_3COCH_2)^- + CH_3COCH_2COOEt \longrightarrow$$
$$II$$

$$CH_3COCH_3 + (CH_3COCHCOOEt)^- \quad (3)$$
$$III$$

(1) D. Y. Chang, N. Hsieh, and T. C. Liu, *J. Chinese Chem. Soc.*, **2**, 71 (1955).

(2) D. Y. Chang, T. C. Liu, Y. T. Wei, W. S. Kung, and W. K. Sun, *ibid.*, **7**, 41 (1960).

of acetoacetate ion and similar ions has been well demonstrated by the work of Pederson.[3]
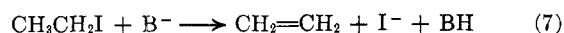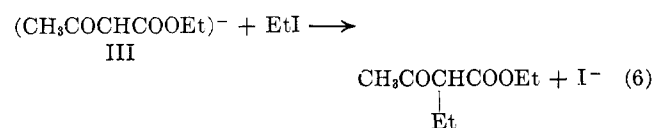
Ethyl alcohol (0.52 mole per mole of acetoacetic ester) was produced in amounts exceeding those of acetone. Its formation is presumed to result from a Claisen-type condensation (eq 4).
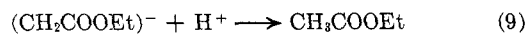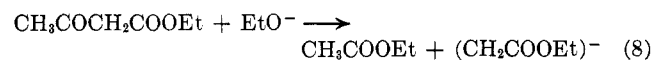
$$CH_3COCH_2COOEt + (CH_3COCH_2)^- \longrightarrow$$
$$II$$
$$CH_3COCH_2COCH_2COCH_3 + EtO^- \quad (4)$$
$$IV$$
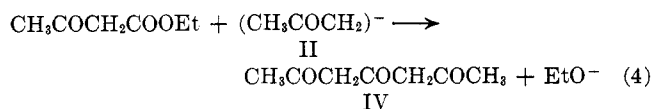
The amounts of ethyl iodide, carbon dioxide, and acetone produced in the reaction of acetoacetic ester were 0.032, 0.41, and 0.24 mole, respectively, per mole of ester. The rather low yield of acetone compared with that of carbon dioxide might be attributed to the partial consumption of the enolate ion (II) in bringing about condensation reactions such as eq 4 and, to a much less extent, to the condensation of the enolate ion and acetone to form mesityl oxide and related products as shown in eq 5. Presumably a major part

$$CH_3COCH_3 + (CH_3COCH_2)^- \longrightarrow$$
$$(CH_3)_2C=CHCOCH_3 + OH^- \quad (5)$$
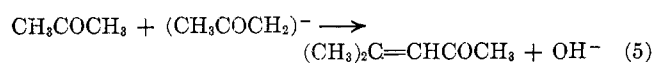
of the ethyl iodide reacted with the enolate ions such as III to afford ethylated acetoacetic ester or its condensation products, regenerating iodide ion, as shown in eq 6. This view on the fate of ethyl iodide

$$(CH_3COCHCOOEt)^- + EtI \longrightarrow$$
$$III$$
$$CH_3COCHCOOEt + I^- \quad (6)$$
$$|$$
$$Et$$

$$CH_3CH_2I + B^- \longrightarrow CH_2=CH_2 + I^- + BH \quad (7)$$

is supported by the isolation of a small amount of methyl n-propyl ketone which could have resulted from the decarboxylation of a part of the ethylated acetoacetic ester. To a lesser extent, some of the ethyl iodide could have reacted with ethoxide ion to form diethyl ether, whose presence in the distillate was detected, or ethylene. The production of ethyl acetate reveals that acid cleavage has also taken place (eq 8 and 9).

$$CH_3COCH_2COOEt + EtO^- \longrightarrow$$
$$CH_3COOEt + (CH_2COOEt)^- \quad (8)$$

$$(CH_2COOEt)^- + H^+ \longrightarrow CH_3COOEt \quad (9)$$

With methyl acetoacetic ester, the reaction was very similar to that with the unsubstituted ester, except that it was much slower. The reaction with dimethylacetoacetic ester was slower still. These results were as expected, since the electron-releasing methyl group on the α-carbon atom would impart a higher electron density on the carbethoxyl group, handicapping the approach of iodide ion.

In another series of experiments, hydroxylic solvents including ethylene glycol and phenol were used, with a view that the enolate ion would abstract a proton from the solvent molecule instead of from the β-ketonic ester, and increase the yield of ketone. The presence of either solvent facilitated decomposition of acetoacetic ester and its methylated derivatives, and resulted in the increased yields of both the corresponding ketone and ester.

We found that incorporation of a small amount of calcium chloride into the reaction mixture consisting of acetoacetic ester and sodium iodide, greatly facilitated the reaction. Experiments in which sodium iodide was replaced by anhydrous calcium iodide were conducted. Regardless of whether the β-ketonic ester was alkylated on its α-carbon atom or not, the reaction generally took place at 120°, proceeded with rapidity and vigor at temperatures ranging from 130 to 150°, and ceased within 2 hr. In contrast, the reaction using sodium iodide often took more than 10 hr to complete. Greater amounts of volatile substances identical with those produced in a similar reaction using sodium iodide, were obtained. There was an increase in the yield of the corresponding ketone, and a decrease in the amount of carbon dioxide. On the other hand, while the yield of ethyl alcohol was considerably decreased, far greater amounts of ethyl iodide was formed. The yield of the latter substance based on the β-ketonic ester used often attained 50% or more. Moreover, the reaction of β-ketonic ester with calcium iodide, either alone or in the presence of ethylene glycol, produced appreciable amounts of ethylene according to the reaction represented by eq 7.

Potassium iodide did not seem to bring about decomposition of acetoacetic ester appreciably, while magnesium iodide produced an effect about the same as that of calcium iodide. These differences in reactivity seemed to depend primarily on the different degree of covalency of the cation–halide ion bond. Among metal iodides investigated, the covalent character of bonds fall in the decreasing sequence, Mg–I > Ca–I > Na–I > K–I. From results of present investigations, conclusions may be drawn that the less the ionic character of the metal halide bond, the greater the reactivity of the halide in the cleavage reaction. Furthermore, the solubility of the iodide (and other halides) increases with covalent character. This also may be important factor in determining the reactivity of the iodide. The same explanation applies to the differences between the sodium halides (iodide, bromide, chloride) mentioned.

When acetoacetic ester or its methylated derivative was added to anhydrous calcium iodide, the latter dissolved with evolution of heat, forming an intensely yellow solution which gave well-defined crystals on cooling. These changes clearly indicated the formation of calcium complexes or chelates whose composition and structure remain to be determined. Whether or not the formation of these complexes or chelates facilitated the cleavage reaction, in a way similar to the Al^{3+}-catalyzed decarboxylation of oxalosuccinic ester and oxaloacetic ester[4] demands further investigation. What seemed most likely was that the enolate ion of a β-ketonic ester (or its condensation products) such as III might be stabilized by combining with the calcium ion to form a chelate such as V, which would not readily enter alkylation reaction as the free enolate ion did, resulting in the diminution of the consumption of ethyl iodide. This may account for the production of much ethyl iodide in the reactions involving the use of calcium iodide.

(3) (a) K. J. Pederson, J. Am. Chem. Soc., 51, 2098 (1929); (b) ibid., 58, 240 (1936).

(4) A. Kronberg, S. Ochoa, and A. H. Mehler, J. Biol. Chem., 174, 159 (1948).
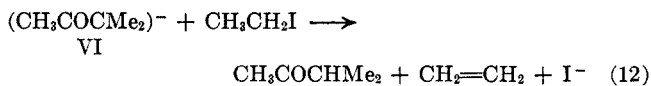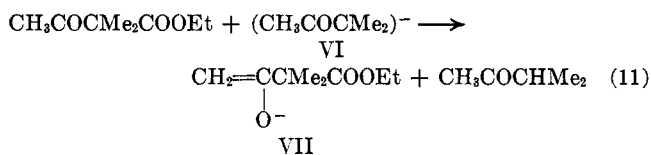
Table I

VOLATILE PRODUCTS FROM THE DECOMPOSITION OF ACETOACETIC ESTER AND ITS METHYLATED DERIVATIVES
UNDER VARYING CONDITIONS

Expt no.	β-Ketonic ester[a]	Metal halide[b]	Solvent[c]	Reacn temp, °C	Reacn time, hr	Amt of condensate, g	Yield of products, mole/mole of β-ketonic ester								
								—Ketone[d]—		—C_2H_5I[d,e]—		—C_2H_5OH[d]—		—Ester[d-f]—	
							CO_2	1	2	1	2	1	2	1	2
						CH_3COCH_3									
1	CH_3COCH_2COOEt	NaI	None	150–160	7	26.3	0.41	0.24	0.20	0.032	0.036	0.52	0.55	0.022	0.030
2	CH_3COCH_2COOEt	NaI	Ethylene glycol	150–160	4	36.5	0.52	0.32	0.34	0.010	0.014	0.90	0.84	0.031	0.022
3	CH_3COCH_2COOEt	NaI	Phenol	150–160	4	30.6	0.50	0.30	...	0.035	...	0.65	...	0.031	...
4	CH_3COCH_2COOEt	CaI_2	None	130–150	2	70.0	0.35	0.36	0.36	0.52	0.56	0.29	0.24	0.087	...
5	CH_3COCH_2COOEt	CaI_2	Ethylene glycol	130–150	2	65.0	0.56	0.52	0.57	0.26	0.28	0.49	0.42	0.15	...
6	CH_3COCH_2COOEt	CaI_2	Phenol	130–150	2	64.0	0.29	0.35	0.37	0.57	0.52	0.20	0.25	0.14	...
						$CH_3COCH_2CH_3$									
7	$CH_3COCHMeCOOEt$	NaI	None	160–170	15	14	0.21	0.15	...	0.024	...	0.17	...	0.008	...
8	$CH_3COCHMeCOOEt$	NaI	Ethylene glycol	160–170	8	33.7	0.43	0.33	...	0.007	...	0.74	...	0.044	...
9	$CH_3COCHMeCOOEt$	NaI	Phenol	160–170	8	23.2	0.32	0.14	...	0.0006	...	0.50	...	0.074	...
10	$CH_3COCHMeCOOEt$	CaI_2	None	130–150	2	55.5	0.28	0.42	0.38	0.36	0.40	0.11	0.10	0.12	...
11	$CH_3COCHMeCOOEt$	CaI_2	Ethylene glycol	130–150	2	58	0.60	0.52	...	0.20	...	0.37	...	0.18	...
12	$CH_3COCHMeCOOEt$	CaI_2	Phenol	130–150	2	77.5	0.43	0.45	0.38	0.57	0.60	0.23	0.17	0.11	...
						$CH_3COCH(CH_3)_2$									
13	CH_3COCMe_2COOEt	NaI	None	160–170	18	7	0.22	0.06	...	0.0006	...	0.014	...	0.01	...
14	CH_3COCMe_2COOEt	NaI	Ethylene glycol	160–170	12	36.1	0.53	0.32	...	0.015	...	0.35	...	0.14	...
15	CH_3COCMe_2COOEt	NaI	Phenol	160–170	12	8	0.17	0.072	...	0.0004	...	0.18	...	0.014	...
16	CH_3COCMe_2COOEt	CaI_2	None	130–150	2	67.5	0.26	0.48	...	0.29	...	0.23	...	0.19	...
17	CH_3COCMe_2COOEt	CaI_2	Ethylene glycol	130–150	2	78.2	0.45	0.65	0.61	0.30	0.40	0.38	0.45	0.17	...
18	CH_3COCMe_2COOEt	CaI_2	Phenol	130–150	2	90.5	0.57	0.56	0.48	0.56	0.44	0.37	0.28	0.15	...

[a] One-half mole of the β-ketonic ester was used in each experiment. [b] One-half gram formula weight of NaI was used in reactions with sodium iodide; one-fourth gram formula weight of CaI_2 was used for reactions with calcium iodide. [c] One-half mole of the solvent was used. [d] The figures under column 1 are results of chemical analysis, and those under column 2 are estimated from gas chromatography. [e] In the gas chromatographs of condensates containing large amounts of ethyl iodide, peaks of ethyl acetate were entirely covered by those of ethyl iodide. [f] In reactions with acetoacetic ester, only ethyl acetate was produced, while in reactions with methylacetoacetic ester and dimethylacetoacetic ester, ethyl propionate and ethyl isobutyrate, respectively, were produced in addition to ethyl acetate.

$$(CH_3COCHCOOEt)^- + \tfrac{1}{2}Ca^{2+} \longrightarrow$$
III

$$(10)$$
V
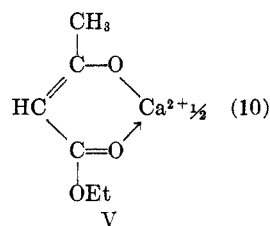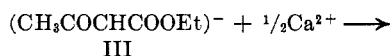
In the reaction with dimethylacetoacetic ester in the absence of a hydroxylic solvent, the formation of methyl isopropyl ketone from its enolate ion (VI) may be represented by eq 11. Additionally, the elimination reaction of ethyl iodide brought about by the enolate ion (VI) also affords methyl isopropyl ketone.

$$CH_3COCMe_2COOEt + (CH_3COCMe_2)^- \longrightarrow$$
VI

$$CH_2{=}CCMe_2COOEt + CH_3COCHMe_2 \quad (11)$$
$$\underset{O^-}{|}$$
VII

$$(CH_3COCMe_2)^- + CH_3CH_2I \longrightarrow$$
VI

$$CH_3COCHMe_2 + CH_2{=}CH_2 + I^- \quad (12)$$

Interestingly, in the decomposition of acetoacetic ester or its α-methylated derivative in the presence of calcium iodide, with or without solvent, the yield of carbon dioxide was considerably less than that of the respective ketone. This discrepancy may be due to consumption of a part of carbon dioxide in forming calcium ethylcarbonate as shown in eq 13. This view

$$C_2H_5OCa_{1/2} + CO_2 \longrightarrow C_2H_5OCO_2Ca_{1/2} \quad (13)$$

is supported by the fact that the residue of the reaction, on treatment with dilute mineral acid, gave rise to a copious evolution of carbon dioxide.

Table I summarizes relative amounts of volatile products from the reactions of the β-ketonic esters under varying conditions. The results of chemical analysis are in good agreement with those estimated from gas chromatography. Minor products such as diether ether, ethylene oxide, and acetaldehyde were identified by gas chromatography only. Investigations on products remaining in the residues are being carried on.

Discussion

Decomposition of acetoacetic ester and its α-methylated derivatives in the presence of metal iodides has been extended, in a series of preliminary experiments, to a number of β-ketonic esters including diacetylsuccinic ester, cyclopentanone–carboxylic ester and its derivatives, and succinosuccinic ester and its derivatives. All of these substances reacted in a similar way, affording, among other products, carbon dioxide, ethyl iodide, and corresponding ketones. A conclusion can be drawn, therefore, that decomposition under the influence of metal iodides is characteristic of β-ketonic esters in general. In the present investigation, decomposition of acetoacetic ester and its α-methylated derivatives by action of sodium or calcium iodide afforded, with few exceptions, the corresponding ketone in yields generally exceeding 30%. The action of calcium iodide on dimethylacetoacetic ester in the presence of ethylene glycol gave methyl isopropyl ketone in a yield as high as 65%. A reaction of this kind was previously unknown. Not only does it represent a new method of cleaving β-ketonic esters, but it may also be useful in synthesis, where the cleavage of a β-ketonic ester is sluggish to the action of hydrolyzing agents, or the β-ketonic acid is resistant to decarboxylation. For example, we found that the α-benzyl derivative of cyclopentanonecarboxylic ester

reacted sluggishly with hydrolyzing agents in aqueous solutions. In the presence of calcium iodide and without use of any solvent, it underwent ready decarboxylation, with the production of 2-benzylcyclopentan-1-one.

It has been observed that presence of a hydroxylic solvent not only increased the yield of the corresponding ketone, but also facilitated the reaction. Possibly, the solubility of sodium iodide in the hydroxylic solvent produced the latter effect.

The striking fact associated with the use of calcium iodide was that decomposition of α-methylated acetoacetic esters proceeded with the same vigor as that of the unsubstituted ester.

The presence of water in the distillates from the decomposition of β-ketonic esters, in which all the reactants including the metal iodides had been carefully dehydrated, was demonstrated by Karl Fischer method of aquametric analysis. In addition, mesityl oxide was identified from the higher boiling fraction of the distillates from the decomposition of acetoacetic ester (eq 5). This, together with further condensation processes that might arise, may account for the production of water.

In using ethylene glycol as solvent, ester interchange occurred in the first phase of the reaction. The reaction with acetoacetic ester gave ethyl alcohol and ethylene glycol monoacetoacetate. This was shown by the fact that, as soon as the reaction started, large amounts of ethyl alcohol distilled over, when only a small amount of carbon dioxide was evolving. Since ethylene glycol and acetoacetic ester do not react to any appreciable extent at temperatures around 150–160° in the absence of sodium iodide, the ester interchange should be brought about by the intermediary of certain decomposition product of acetoacetic ester. It may be presumed that the enolate ion of acetone first formed according to eq 2 abstracted a proton from ethylene glycol to form β-hydroxy ethoxide ion, which in turn reacted with acetoacetic ester (or its derivative) as shown in eq 14. The ethylene glycol mono-

$$CH_3COCH_2COOEt + HOCH_2CH_2O^- \longrightarrow$$
$$CH_3COCH_2COOCH_2CH_2OH + EtO^- \quad (14)$$

acetoacetate thus formed underwent decomposition, with the production of the enolate ion of acetone, carbon dioxide, and ethylene iodohydrin. Although the latter substance was not isolated, there were found ethylene glycol monoethyl ether (ethoxyethanol), ethylene oxide, and acetaldehyde which were undoubtedly formed from iodohydrin. The production of these substances supports the occurrence of the ester interchange in the first phase of the reaction and accounts for the relatively low yield of ethyl iodide (see Table I).

The data in Table I indicate that the use of ethylene glycol as solvent increases yield of the corresponding ketone. The use of calcium iodide in place of sodium iodide, while bringing about better yields of the corresponding ketone generally, shows a more marked effect in the reactions of α-substituted β-ketonic esters than in the reactions of the unsubstituted esters.

Experimental Section

(1) **Action of Sodium Iodide on Ethyl Acetoacetate in the Absence of a Solvent.**—Sixty-five grams (0.5 mole) of ethyl acetoacetate, 75 g (0.5 mole) of pulverized, anhydrous sodium iodide, and a Teflon-coated stirring bar were placed in a 500-ml flask fitted with a capillary tube to lead dried air through the reaction flask and a bent outlet tube connected to a vertical, Friedrichs condenser. A 150-ml filter flask was attached as a receiver. Two weighed potash bulbs containing 50% potassium hydroxide were connected in series. A second filter flask was attached to the collection train and led to an aspirator. The reaction flask was heated with an oil bath. Ice–water was circulated through the condenser. The receiver was cooled with ice and salt, and the potash bulbs were cooled in a cold-water bath.

Stirring and heating were started. The temperature was kept at 150–160° most of the time, and finally was increased to 170°. Smooth evolution of carbon dioxide and distillation of volatile products occurred. Reaction ceased at the end of 7 hr. A light suction was applied during the last few hours to drive out volatile products. Nearly exhausted potash bulbs were replaced by weighed, freshly filled ones. The amount of carbon dioxide collected was 9.0 g. Condensate, usually amounting to 25–27 g, was fractionated over a small efficient column, and the fraction boiling below 85°, and for the most part boiling constantly at 63°, was collected and weighed, and its density was determined. The distillate (22–24 g) was used for the quantitative estimation of acetone, ethyl acetate, ethyl iodide, and ethyl alcohol by chemical means and for gas chromatography.

For isolation and identification of these and other minor products, condensates from several runs were combined and fractionated, and the following fractions were collected: (a) up to 75°, (b) 75–80°, (c) 80–100°, and (d) 100–140°. A portion of fraction a was treated with a saturated solution of sodium chloride. The oil that separated was collected, first washed with concentrated sulfuric acid, then with water, dried, and distilled. The distillate passing over at 72° was identified as ethyl iodide by converting into ethyl 3,5-dinitrobenzoate (mp 83°) by treatment with silver 3,5-dinitrobenzoate. The salt solution was distilled, and from the low-boiling distillate acetone was isolated, and subsequently purified by the bisulfite compound method. It was identified by its conversion into the corresponding 2,4-dinitrophenylhydrazone, mp 126°. Another portion of fraction a was allowed to stand with silver hydroxide for several days, then treated with ethyl alcohol, and filtered to remove silver iodide. The filtrate was refluxed with an excess of sodium hydroxide, and subsequently evaporated to dryness. The dry residue was pulverized, mixed with concentrated sulfuric acid, and distilled. The liquid that distilled over around 110° was identified as acetic acid by conversion into the corresponding toluidide, mp 147°. This, together with the fact that fraction b gave a ferric hydroxamate test, indicated the presence of ethyl acetate in the original condensate. Fraction b was mixed with twice its volume of water and saturated with sodium chloride. The saline solution was filtered through a wet filter and the filtrate was distilled. To the distillate was added solid potassium carbonate. The upper layer was taken, dehydrated with anhydrous cupric sulfate, and distilled. The liquid that distilled over had bp 78°. It was identified as ethyl alcohol by conversion into the corresponding 3,5-dinitrobenzoate, mp 83°. Fraction c was treated with 2,4-dinitrophenylhydrazine. The light orange crystals that separated were repeatedly recrystallized from methanol. The purified product (mp 143°) was identified as the 2,4-dinitrophenylhydrazone of methyl n-propyl ketone. Fraction d was again fractionated. The 130–140° fraction on treatment with 2,4-dinitrophenylhydrazone reagent afforded carmine-red crystals, which on repeated crystallization from methanol gave a pure product (mp 200°) identified as mesityl oxide 2,4-dinitrophenylhydrazone. Identification of all substances mentioned above was confirmed by comparison with respective authentic samples.

For the determination of acetone, about 1 g of the distillate (boiling below 85°) was accurately weighed, treated with a solution of hydroxylamine hydrochloride of known concentration, allowed to stand for 10 min, and then titrated with standard alkali, using methyl red as indicator. Ethyl iodide was estimated by first allowing an aliquot of the distillate to react with an excess of alcoholic silver nitrate of known concentration, followed by back titration with standard potassium thiocyanate, using rhodamine 6G as indiator. Water was estimated by titrating an aliquot of the distillate with Karl Fischer reagent. Another aliquot was taken for the determination of active hydrogen by Zerewitinoff's method. The result, on comparing with the

water content, gave the alcohol content in the distillate. In some experiments, the alcohol content in the distillate was checked by acetylation method. The ethyl acetate in the distillate was estimated by determining the saponification equivalent of the fraction boiling below 85°, from which ethyl iodide had been removed by treatment with silver hydroxide. The yields are shown in Table I.

The results indicated above were checked with gas chromatography of which manipulation will be described elsewhere.

In one run of the reaction, the receiver for the condensate was not strongly cooled, and the gas issuing from the last potash bulb was passed through a solution of tetranitromethane over the entire period. The latter solution became yellow, indicating the presence of unsaturated hydrocarbon, most probably ethylene.

(2) Action of Sodium Iodide on Ethyl Acetoacetate in the Presence of Ethylene Glycol.—The reaction was carried out in the same way as expt 1, except that 31 g (0.5 mole) of ethylene glycol was also introduced in the reaction flask. The condensate (36–38 g) was fractionated, to give the following fractions: (a) up to 85°, (b) 85–100°, and (c) 100–140°. Aliquots were taken from fraction a for the estimation of water, acetone, ethyl iodide, and ethyl alcohol. From fraction b was identified methyl n-propyl ketone in the form of its 2,4-dinitrophenylhydrazone. Fraction c gave a small amount of ethoxyethyl alcohol, identified by conversion into the 3,5-dinitrobenzoate (mp 75°) and compared with an authentic sample. Fraction a was gas chromatographed.

(3) Action of Sodium Iodide on Ethyl Acetoacetate in the Presence of Phenol.—The reaction was performed in the same way as in the foregoing experiment, except that ethylene glycol was replaced by 47 g (0.5 mole) of phenol. The condensate was redistilled from a column and the portion distilling over below 85° was collected and analyzed in the same way as expt 1. Diethyl ether was also detected as a minor component by gas chromatography.

(4) Action of Calcium Iodide on Ethyl Acetoacetate in the Absence of a Solvent.—Into a 500-ml, flat-bottomed flask, fitted with a cork bearing an inlet tube connected to a hydrogen cylinder, and an outlet tube connected to a downward condenser for distillation, was introduced 92 g (0.25 mole) of hydrated calcium iodide. A moderate stream of hydrogen was introduced. The flask was wrapped with asbestos paper and strongly heated in a sand bath until no more water vapor passed over. The heater was then removed, the flask was allowed to cool to room temperature, and the stream of hydrogen was cut off. The flask was disconnected and well stoppered. Acetoacetic ester (65 g, 0.5 mole) and a Teflon-coated bar were introduced into the flask containing the dehydrated salt. The latter gradually dissolved with evolution of heat. Well-defined crystals separated when the solution was cooled. The flask was fitted with an inlet and an outlet tube leading to Friedrichs condenser and collection train, as described in expt 1. Heating and stirring were started. During the later stages, serious foaming occurred which could be readily suppressed by introducing a few milliliters of anisole.

The freshly collected, well-cooled condensate (70 g), when stored in a well-stoppered flask and allowed to warm to room temperature, would build up pressure inside the flask, often causing the stopper to bounce off. Undoubtedly this was due to evolution of ethylene originally dissolved in the condensate. In another run tests for ethylene in the gaseous products by tetranitromethane and by alkaline potassium permanganate were positive. The condensate was fractionated to give a distillate that boiled below 85° and that was analyzed as before.

(5) Action of Calcium Iodide on Ethyl Acetoacetate in the Presence of Ethylene Glycol.—The reaction was carried out in the same way as in the foregoing experiment, except that 31 g (0.5 mole) of ethylene glycol was also introduced into the reaction flask.

The condensate (66.5 g) was found to contain an appreciable amount of dissolved ethylene and 1.2 g of water. It was fractionated to give a distillate boiling below 85°, which was analyzed in the usual way. Residue resulting from the distillation of the condensate, on careful fractionation, afforded 7 g of ethoxyethyl alcohol boiling at 135°, identified by converting to its 3,5-dinitrobenzoate, mp 75°.

In another run, a small amount of a mixture of highly volatile products was collected in a strongly cooled receiver inserted between the main receiver and the first potash bulb. Gas

chromatography of this condensate revealed the presence of diethyl ether and traces of ethylene oxide and acetaldehyde.

(6) Action of Calcium Iodide on Ethyl Acetoacetate in the Presence of Phenol.—The reaction was carried out in the same way as in the foregoing experiment, except that 47 g (0.5 mole) of phenol was used in place of ethylene glycol.

(7) Action of Sodium Iodide on Ethyl Methylacetoacetate in the Absence of a Solvent.—The reaction was conducted in the same way as expt 1, except that ethyl acetoacetate was replaced by 72 g (0.5 mole) of ethyl methylacetoacetate. Fractionation of the condensate (14 g) revealed that components formed azeotropic mixtures, notably that boiling constantly at 68°. The fraction boiling below 95° contained ethyl iodide, ethyl alcohol, and methyl ketone, the latter being identified in the form of its 2,4-dinitrophenylhydrazone. Ferric hydroxamic acid test revealed the presence of ester. Determination of saponification equivalent gave the ester content, 0.04 mole. This should include both ethyl propionate and ethyl acetate.

(8) Action of Sodium Iodide on Ethyl Methylacetoacetate in the Presence of Ethylene Glycol.—The reaction was conducted in the same way as expt 2, except that acetoacetic ester was replaced by 72 g (0.5 mole) of methylacetoacetic ester. The condensate (33.7 g) was fractionated, the fraction boiling below 95° being collected for analysis of volatile products and isolation of methyl ethyl ketone. The fractionated distillate was treated with silver oxide to remove ethyl iodide and shaken successively with saturated sodium chloride solution to remove alcohol. The organic layer was dehydrated over anhydrous sodium sulphate and fractionated. The liquid boiling at 80° was identified as methyl ethyl ketone, by conversion into its 2,4-dinitrophenylhydrazone, mp 116°.

(9) Action of Sodium Iodide on Ethyl Methylacetoacetate in the Presence of Phenol.—The reaction was carried out in a manner similar to expt 3, except that ethyl acetoacetate was replaced by 72 g (0.5 mole) of ethyl methylacetoacetate. The condensate (23.2 g) was redistilled to give fraction boiling below 95° which was analyzed by the usual procedure. Distillate remaining was refluxed with sodium hydroxide. The resulting mixture was evaporated to dryness, treated with dilute sulfuric acid, and then extracted with ether. From the ether extract was obtained a small amount of propionic acid, identified by conversion to its p-toluidide, mp 126°.

(10) Action of Calcium Iodide on Ethyl Methylacetoacetate in the Absence of a Solvent.—The reaction was carried out in the same manner as expt 4, except that ethyl acetoacetate was replaced by 0.72 g (0.5 mole) of ethyl methylacetoacetate. Partial dissolution of calcium iodide in the ester occurred, with evolution of heat. Ethylene was detected from the gas issuing from the last potash bulb. The condensate (55.5 g) was redistilled to give fraction boiling below 95°, which was analyzed in the normal manner.

(11) Action of Calcium Iodide on Ethyl Methylacetoacetate in the Presence of Ethylene Glycol.—The reaction was carried out in a manner similar to expt 5 except that 72 g (0.5 mole) of methylacetoacetic ester was used in place of acetoacetic ester. At 140–150°, the reaction proceeded vigorously, with rapid gas evolution and formation of a fine, white precipitate in the reaction mixture. Ethylene was detected in the effluent gas. The condensate (58 g) contained small amounts of diethyl ether and ethylene oxide. This was redistilled to give a distillate boiling below 95°, which was then analyzed by the normal procedure. The remaining distillate was refluxed with sodium hydroxide. Acidification give propionic acid, which was purified and identified by conversion to its p-toluidide, mp 126°.

(12) Action of Calcium Iodide on Ethyl Methylacetoacetate in the Presence of Phenol.—The reaction was conducted in the same manner as expt 6, except 72 g (0.5 mole) of ethylmethyl-acetoacetate was used in place of ethyl acetoacetate. The condensate (77.5 g) was fractionated and the fraction boiling below 95° analyzed by the usual procedure.

(13) Action of Sodium Iodide on Ethyl Dimethylacetoacetate in the Absence of a Solvent.—The reaction was conducted in the same way as expt 1, except that 79 g (0.5 mole) of ethyl dimethyl-acetoacetate was used in place of ethyl acetoacetate. The condensate (7.0 g) was distilled to give a fraction boiling below 105°, which was found to contain ethyl iodide, ethyl alcohol, and methyl isopropyl ketone, the latter being identified the form of its 2,4-dinitrophenylhydrazone.

(14) Action of Sodium Iodide on Ethyl Dimethylacetoacetate in the Presence of Ethylene Glycol.—The reaction was carried

out similarly to expt 2, except 79 g (0.5 mole) of ethyl dimethyl-acetoacetate was used in place of ethyl acetoacetate. At 160–170°, the reaction was proceeding more vigorously than in the foregoing experiment; it ceased after 12 hr. The condensate (36.1 g) was distilled and the fraction boiling below 105° was collected and analyzed as usual. The remaining portion of the distillate, from which ethyl iodide had been removed by treatment with silver hydroxide, was saponified by refluxing with sodium hydroxide. The aqueous solution was acidified with sulfuric acid and distilled. The liquid collected (bp 154°) was identified as isobutyric acid by conversion to its p-toluidide, mp 107°.

(15) **Action of Sodium Iodide on Ethyl Dimethylacetoacetate in the Presence of Phenol.**—The reaction was conducted similarly to expt 3, except that 79 g (0.5 mole) of dimethylacetoacetic ester was used in place of acetoacetic ester. The condensate (3.73 g) was fractionated and analyzed as usual.

(16) **Action of Calcium Iodide on Ethyl Dimethylacetoacetate in the Absence of a Solvent.**—The procedure was the same as that described in expt 4, except that 70 g (0.5 mole) of dimethyl-acetoacetic ester was used in place of acetoacetic ester. When the reactants were mixed, partial dissolution of calcium iodide occurred with evolution of heat. The reaction took place readily at 130° and was proceeding vigorously at 140–150°. Ethylene was detected in the effluent gas. The condensate (67. 5 g) was redistilled and analyzed by usual procedure.

(17) **Action of Calcium Iodide on Ethyl Dimethylacetoacetate in the Presence of Ethylene Glycol.**—The procedure was the same as that in expt 5, except that 79 g (0.5 mole) of ethyl dimethyl-acetoacetate was used in place of ethyl acetoacetate. When the reactants were mixed, dissolution of calcium iodide occurred with evolution of heat. The reaction temperature was held at 140° most of the time, and finally raised to 150°. Vigorous gas evolution occurred, with formation of finely divided, white precipitates in the reaction mixture. Ethylene was detected from the effluent gas. The condensate (78.2 g) which was found to contain small amounts of diethyl ether and ethylene oxide, was distilled to give a fraction boiling below 105° for analysis and for isolation of methyl isopropyl ketone. The yield of the latter substance attained 28.0 g (0.65 mole/mole of ester), highest among the reactions of this series. To isolate the methyl isopropyl ketone, the distillate was shaken with several portions of saturated sodium chloride solution to remove ethyl alcohol, dried over sodium sulphate, and fractionated. The fraction consisting of a mixture of ethyl iodide and methyl isopropyl ketone, boiling between 65 and 75°, first distilled over. The

fraction boiling between 90 and 95° consisted of almost pure methyl isopropyl ketone. About one-half of the ketone produced in the reaction was recovered.

(18) **Action of Calcium Iodide on Ethyl Dimethylacetoacetate in the Presence of Phenol.**—The reaction was conducted in the same manner as expt 6, except that 79 g (0.5 mole) dimethyl-acetoacetic ester was used in place of acetoacetic ester. The condensate (90.5 g) was redistilled to give the fraction boiling below 105°, which was analyzed by the usual procedure.

(19) **Gas Chromatography of the Distillates.**—The condensates resulting from a part of the reactions described above were gas chromatographed. A Pye argon gas chromatograph was used. The column was packed with kieselguhr containing 30% of polyethylene glycol (mol wt 1000). Operating conditions were fixed as follows: temperature, 50°; flow rate, 30 ml/min; voltage, 1000 v; sensitivity, $\times$ 10; chart speed, 10 in/hr.

The condensate, redistilled as indicated in each of the foregoing experiments, was dried over silica gel, and its density was determined. The dried sample was injected into the gas chromatograph in amounts varying from 0.04 to 0.1 ml. The distillates from expt 1 to 6 gave gas chromatograms of identical components. They exhibited five peaks, corresponding to the presence of diethyl ether, acetone, ethyl iodide, ethyl acetate, and ethyl alcohol in the sample. Identity of components was verified by comparing the gas chromatograms of distillates with those of authentic samples. Also from gas chromatograms were estimated amounts in number of moles of those substances in each distillate. Similar operations were performed with distillates resulting from reactions with methylacetoacetic ester and dimethylacetoacetic ester. Each gas chromatogram of distillates from expt 10 and 12 exhibited four peaks corresponding to the presence of diethyl ether, ethyl iodide, methyl ethyl ketone, and ethyl alcohol. Neither ethyl acetate nor ethyl propionate appeared in the gas chromatograms, undoubtedly this was due to proximity of their peaks to those of ethyl iodide and methyl ethyl ketone. The gas chromatograms of distillates from expt 17 and 18 also exhibited four peaks corresponding to the presence of diethyl ester, ethyl iodide, methyl isopropyl ketone, and ethyl alcohol. The peaks of ethyl acetate and ethyl isobutyrate did not appear. Highly volatile distillates obtained by careful fractionation of distillates from expt 5 and 17 were also gas chromatographed. Gas chromatograms showed the presence of ethylene oxide and acetaldehyde. Gas chromatography of the high-boiling fraction (85–120°) of distillate from expt 1 revealed the presence of methyl ethyl ketone.

Nuclear Magnetic Resonance Spectra of Substituted Naphthoquinones.   Influence of Substituents on Tautomerism, Anisotropy, and Stereochemistry in the Naphthazarin System[1]

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Echinoderms elaborate many closely related structural pigments (spinochromes) based on a naphthoquinone skeleton in trace amount. As an aid to structural elucidation of these trace compounds the nmr spectra of a large number of substituted naphthoquinones were examined. The chemical shifts of the substituents and of the nuclear protons were correlated with the quinoid or benzenoid nature of the rings. The chemical shifts of acetyl, ethyl, methoxyl, and acetoxyl substituents and their influence upon each other at various ring positions were examined systematically. The shifts were correlated satisfactorily and could be applied to structural assignments of unknown compounds in the series.

In our continuing investigation of the structural pigments of echinoderms we have been conducting a general survey of this phylum of animals. The echinoids (sea urchins) have received closest attention since they are plentiful, readily accessible, and have a high-pigment content. Recent work has unequivocally established the structures of six echinoid pigments of

the naphthoquinone type.[2] Some progress in the examination of the pigments of crinoids (sea lilies) has been made, but the pigments, largely anthraquinones, were isolated from the tissue and the detection of structural pigments was not implied.[3] A naphthoquinone pigment has been identified from a holothuroid (sea

(1) Supported by Public Health Service Grant GM 10413.

(2) I. Singh, R. E. Moore, C. W. J. Chang, and P. J. Scheuer, *J. Am. Chem. Soc.*, **87**, 4023 (1965), and references therein.

(3) M. D. Sutherland and J. W. Wells, *Chem. Ind. (London)*, 291 (1959).