tion to avoid decomposition of the hydrochloride. After freeing the base and drying over solid potassium hydroxide it was distilled at 124.2° (cor.) under 3.5 mm.

Anal. Calcd. for C$_{13}$H$_{19}$N: N, 7.40. Found: N, 7.43.

A picrate melted at 194.6°.

Measurement of Ionization Constants.—The method and apparatus used were the same as those previously employed by Goodhue[1] and by Oldham[6] in this Laboratory. The hydrogen-ion concentrations of half neutralized solutions of the bases were determined by means of the hydrogen electrode with a vacuum tube potentiometer. For the determinations in absolute methanol two 0.1 *f* sodium chloride–calomel reference electrodes were used having an e. m. f. of 0.1174 and 0.1175 v. For the determinations in water, the usual saturated potassium chloride–calomel reference electrode was used.

TABLE I

Compound	Solvent	E. m. f.	−log a_H	−log K_B
α-Thienyl-α-pyrrolidine	Methanol	0.7224	10.25	6.47
α-Thienyl-α-pyrrolidine	Water	.7980	9.35	4.65
α-Mesitylpyrrolidine	Methanol	.7062	9.99	6.73
α-Phenylpyrrolidine[a]	Methanol	.7576	10.87	5.83
α-Phenylpyrrolidine[b]	Water	.8143	9.65	4.35

[a,b] These values were taken from the data by Goodhue[1] and Craig,[1] respectively.

(6) Oldham and Johns, THIS JOURNAL, **61**, 3289 (1939).

The values of these constants indicate that thienylpyrrolidine and mesitylpyrrolidine are distinctly weaker bases than phenylpyrrolidine.

Attempted Resolution of Optical Isomers.—The resolution of α-thienyl-α-pyrrolidine was attempted with *d*-tartaric acid, α-bromocamphorsulfonic acid, and *l*-malic acid without success. Glutamic acid yielded a crystalline salt but the free base isolated from it was inactive. Camphoric acid gave a crystalline salt: m. p. 128–129°; [α]^{21}D (ethanol *c*, 4.5) + 15.54°. The base isolated from this salt, [α]^{23}D (ethanol *c*, 12.5) − 3.12° was doubtless only partially resolved. Further purification failed.

The resolution of α-mesitylpyrrolidine was attempted with *d*-tartaric acid and with camphoric acid without success.

Summary

α-Thienyl-α-pyrroline, α-thienyl-α-pyrrolidine, α-mesitylpyrroline, and α-mesitylpyrrolidine have been prepared for the first time.

Ionization constants of the reduced compounds have been determined.
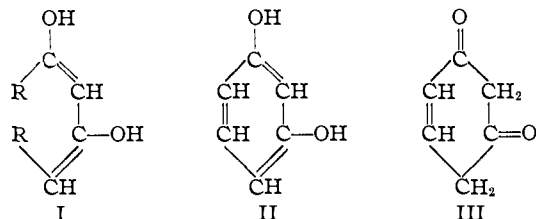
Attempts have been made to resolve these pyrrolidines.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

β-Diketones: Synthesis, Structure and Bactericidal Properties

BY CHARLES D. HURD AND CHARLES D. KELSO[1]

If one considers a β-diketone, R—C—CH$_2$—C—CH$_2$R, in its completely enolized modification (I), it may be compared to resorcinol (II)


I   II   III

for which, incidentally, there is evidence of the diketo structure (III) on the basis of work with Raman spectra[2] and absorption spectra.[3] In view of the known effectiveness of hexylresorcinol as a germicide, it was of interest to see whether β-diketones containing eight to twelve carbon

(1) Parke, Davis and Company Fellow, 1937–39.

(2) Hayashi, *Sci. Papers Inst. Phys. Chem. Research* (Tokyo), **23**, 16 (1933); Kohlrausch and Pongrantz, *Monatsh.*, **65**, 6 (1934).

(3) Valyashko and Scherbaky, *J. Gen. Chem.* (U. S. S. R.), **8**, 1629 (1938).

atoms per molecule would possess similar effectiveness.

Two reactions were considered for the synthesis of the diketones. One was the well-known Claisen condensation of an ester with a ketone. The other was the new reaction[4] between acetoacetyl chloride and a Grignard reagent

CH$_3$COCH$_2$COCl + RMgX ⟶

CH$_3$COCH$_2$COR + MgXCl
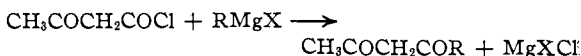
These four diketones were prepared by the Claisen condensation, the last two of them being new compounds: 2,4-octanedione from ethyl acetate and 2-hexanone; 2,4-decanedione from ethyl acetate and 2-octanone; 2-dodecene-4,6-dione from ethyl crotonate and 2-octanone

CH$_3$CH=CHCOOC$_2$H$_5$ + CH$_3$COC$_6$H$_{13}$ ⟶

CH$_3$CH=CH—CO—CH$_2$COC$_6$H$_{13}$ + C$_2$H$_5$OH
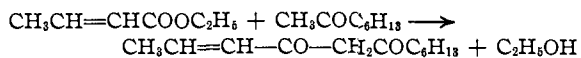
1-hendecene-3,5-dione, CH$_2$=CH—CO—CH$_2$CO-C$_6$H$_{13}$, from ethyl acrylate and 2-octanone.

2,4-Octanedione was prepared also from acetoacetyl chloride and butylmagnesium bromide.

(4) Hurd and Kelso, THIS JOURNAL, **62**, 1548 (1940).

2,4-Hendecanedione and 2,4-dodecanedione were prepared from *n*-heptyl- and *n*-octylmagnesium bromides, respectively. These compounds have been reported previously but their identity was confirmed by analysis since the semicarbazones were liquids and since the boiling points were not considered conclusive for purposes of identification. A new diketone, 5-methyl-2,4-hendecanedione, $CH_3COCH_2COCH(CH_3)C_6H_{13}$, was prepared by the interaction of acetoacetyl chloride and 2-octylmagnesium bromide.

An attempt to prepare 6-ethyl-2,4-decanedione from acetoacetyl chloride and the Grignard reagent of 2-ethyl-1-bromohexane was unsuccessful. 3-Methylhexane was obtained in 36% yield, together with an unidentified liquid (b. p. 96–98° (2 mm.), $n^{20}D$ 1.4445). The material gave no copper salt, and analysis for C and H was closer to a hydrocarbon than to the diketone.

An extensive formation of butyl acetoacetate, $CH_3COCH_2COOC_4H_9$, occurred when the reaction between butylmagnesium bromide and acetoacetyl chloride was run in the presence of air. Evidently there was oxidation of the Grignard reagent to C_4H_9OMgBr which then reacted metathetically with the acid chloride.

The structure of the β-diketones formed in the Claisen condensation is a matter of considerable interest since two possibilities are involved. Ethyl acetate and an alkylacetone may condense to yield either $CH_3COCH_2COCH_2R$ or $CH_3COCHRCOCH_3$. The first of these has been favored on the basis of previous work. In the first place, the same diketone appears to be formed[5] from ethyl acetate and alkylacetone as from ethyl alkylacetate and acetone. This work, however, depends chiefly on the melting point of the copper salts. It is conceivable also that the copper salt of the isomeric diketone would be more soluble and become lost during the recrystallizations.

Kramers[6] investigated 2,4-decanedione and proved the presence of two active hydrogens between the carbonyl groups because methylation (with $CH_3I + C_2H_5ONa$) brought about the introduction of two methyl groups to yield a C_{12} diketone. This work is open to some question also, since Kramers would certainly have separated any 3-methyl-3-pentyl-2,4-pentanedione from his 3,3-dimethyl-2,4-decanedione by fractional distillation.

(5) Claisen and Ehrhardt, *Ber.*, **22**, 1009 (1889); Powell and Seymour, This Journal, **53**, 1049 (1931).

(6) Kramers, *Rec. trav. chim.*, **16**, 116 (1897).

It seems certain, therefore, that the reaction

$$CH_3COOC_2H_5 + CH_3COCH_2R \longrightarrow$$
$$CH_3COCH_2COCH_2R + C_2H_5OH$$

represents the bulk of the Claisen condensation; but the above evidence does not demonstrate the absence of the branched chain isomer, $CH_3COCHRCOCH_3$.

On this point, the fact that the 2,4-octanedione prepared from acetoacetyl chloride and butylmagnesium bromide was the same as that prepared from ethyl acetate and 2-hexanone is strong supporting evidence. Confirmatory evidence that but one of the two possible β-diketones was formed during condensation of 2-hexanone and ethyl acetate was secured as follows. The diketone was treated with hydrazine and the resulting pyrazole was oxidized with permanganate to 3,5-pyrazoledicarboxylic acid. These steps are involved.

$$CH_3COOC_2H_5 \xrightarrow{CH_3COC_4H_9} CH_3COCH_2COC_4H_9 \xrightarrow{N_2H_4}$$
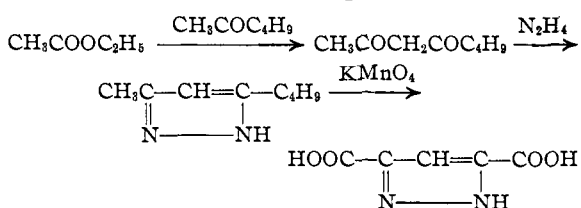
The diketone, therefore, was 2,4-octanedione uncontaminated with any appreciable quantity of 3-propyl-2,4-pentanedione, for the latter would have given rise to pyrazoletricarboxylic acid.

The phenol coefficients of the diketones were determined in the laboratories of Parke, Davis and Company. Through the courtesy of Dr. Oliver Kamm, one of us (C. D. K.) was extended the privilege of assisting in these determinations. The Shippen method was used. The findings are summarized in Table I.

TABLE I

PHENOL COEFFICIENTS OF β-DIKETONES AT 20°

| Compound | Maximum dilution effective against | | Phenol coefficients | |
	B. ty- phosus	Staph. aureus	B. ty- phosus	Staph. aureus
2,4-Octanedione	600	Ineffective	6.6	0
2,4-Hendecanedione	600	Ineffective	6.6	0
2,4-Dodecanedione	600	Ineffective	6.6	0
5-Methyl-2,4-hen- decanedione	600	Ineffective	6.6	0
2-Dodecene-4,6-dione	600	500	6.6	5.5
1-Hendecene-3,5-dione	1000	500	11.1	5.5

The first four diketones have identical bacteriological properties. They exhibit low phenol coefficients against *B. typhosus* but are inactive against *Staphylococcus aureus*. The introduction of a carbon-to-carbon double bond conjugated to

the carbonyl groups in the last two diketones tends to increase the phenol coefficient and renders the compounds effective against *Staphylococcus aureus*. These values do not approach the high phenol coefficients of alkylresorcinols but it may be said that the compounds are mild bactericides.

Experimental Part

Reaction of Grignard Reagents with Acetoacetyl Chloride

2,4-Octanedione.—Acetoacetyl chloride was prepared from acetylketene and an excess of hydrogen chloride, then vacuum treatment at $-70°$ till the weight of the product checked the calculated weight by 0.1 g., as described previously.[4]

The solid from 10 g. of acetylketene was dissolved in 100 cc. of dry ether at $-50°$. One-tenth mole of butylmagnesium bromide in 200 cc. of ether was dropped into this over a period of ninety minutes with stirring. An atmosphere of nitrogen was used during the preparation of the Grignard reagent and during its addition to the acid chloride. The acid chloride was present in a 12% excess. Two hundred cc. of water was added at $-25°$ with stirring after the reaction mixture had been stirred for a half an hour. The white solid which separated during the course of the reaction dissolved. The ether layer was separated and the aqueous layer extracted with ether. The ether solutions were dried over sodium sulfate. The ether was removed and the residue distilled at 20 mm. The fore-run weighed 0.4 g. and boiled from $55-79°$ (20 mm.). The main fraction weighed 1.4 g. (10% yield) and boiled at $79-83°$ at 20 mm.: d^{20}_4 0.9233, $n^{20}D$ 1.4559. Kutz and Adkins[7] list $64-66°$ (5 mm.) as the b. p. of this diketone, their synthesis being by Claisen condensation.

Derivative with Semicarbazide.—One gram of the diketone, 1.5 g. of semicarbazide hydrochloride and 2 g. of sodium acetate were placed in a test-tube together with 15 cc. of water and 5 cc. of alcohol. This was shaken and left at $0°$ for eight hours. The crystals were separated and recrystallized thrice from dilute alcohol; m. p. $89-90°$. The product was 3-methyl-5-butyl-1-pyrazolecarbonamide, CH₃C—CH=C—C₄H₉. Analysis was by Hobson's method.[8]

$$CH_3C—CH{=}C—C_4H_9$$
$$N{\rule{1cm}{0.4pt}}N—CONH_2$$

Anal. Calcd. for $C_9H_5ON_3$: N, available as NH_3, 7.76. Found: N, 7.73.

2,4-Hendecanedione.—These quantities were taken: 35 g. of acetoacetyl chloride in 200 cc. of ether, heptylmagnesium bromide from 46 g. of *n*-heptyl bromide and 6 g. of magnesium in 200 cc. of dry ether. The procedure was the same as before. The main distillate weighed 9.5 g. It was collected at $101-103°$ (4-5 mm.). A slight amount of dehydroacetic acid was removed by treatment with dilute ammonium hydroxide. The oil was extracted with ether, dried, and redistilled: b. p. $93-95°$ (2-3 mm.). The yield was 16%. The derivative with semicarbazide was a liquid. Since the reported boiling point of this dike-

tone is $118°$ (5 mm.) the compound was analyzed. Its constants at $20°$ were: d_4 0.8741, n_D 1.4492.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.90; H, 11.51.

2,4-Dodecanedione.—Octylmagnesium bromide was prepared from 49 g. of *n*-octyl bromide, b. p. $201°$. The general conditions were followed as before, including the purification with ammonium hydroxide. The yield of dodecanedione, b. p. $104-105°$ (2-3 mm.) was 16%: d^{20}_4 0.8887, $n^{20}D$ 1.4490. The b. p. listed in the literature is $150°$ (15 mm.). Again, the derivative with semicarbazide was a liquid.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.70; H, 11.18. Found: C, 72.85; H, 11.47.

5-Methyl-2,4-hendecanedione.—2-Bromooctane, b. p. $79-80°$ (18 mm.), $n^{19}D$ 1.4511, was prepared from 2-octanol and phosphorus tribromide by Gredy's method.[9] The Grignard reagent from 49 g. of it was treated with acetoacetyl chloride as before. This time the ether solution of the product was shaken with three 100-cc. portions of dilute ammonium hydroxide before drying.

On distillation, 17.2 g. of *n*-octane (b. p. $43°$ (25 mm.), $n^{20}D$ 1.3991) was collected in the first fraction, and 5.6 g. at $119°$ (4-5 mm.) in the second. Three-fifths of the Grignard reagent was converted to octane. Analysis showed that the second fraction contained hydrocarbon so it was converted to the copper salt with saturated cupric acetate solution. The yield of copper salt was 3.8 g. or 6%. The latter was crystallized twice from alcohol, once from ligroin, then hydrolyzed with dilute sulfuric acid. The 5-methyl-2,4-hendecanedione thus obtained boiled at $101-102°$ (2 mm.); constants, d^{20}_4 0.8381, $n^{20}D$ 1.4614.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.70; H, 11.18. Found: C, 72.56; H, 11.65.

Butyl Acetoacetate Semicarbazone, $H_2NCONH—N{=}C(CH_3)—CH_2COOC_4H_9$.—Butyl acetoacetate was made by adding two drops of concentrated hydrochloric acid to equivalent quantities of acetylketene and butyl alcohol, then warming to start the exothermic reaction. The ester was washed with water and treated with an excess of semicarbazide hydrochloride and sodium acetate. After two hours at $0°$, the semicarbazone was collected on a filter and recrystallized from dilute alcohol and from petroleum ether; m. p. $102°$.

The same compound was obtained (m. p. and mixed m. p.) by adding semicarbazide hydrochloride and sodium acetate to the reaction product at $-50°$ of acetoacetyl chloride and butylmagnesium bromide in an apparatus containing air instead of nitrogen. Two-fifths of the acetoacetyl chloride was converted to butyl acetoacetate (b. p. $95°$ (15 mm.)) in this experiment. The semicarbazone was analyzed.

Anal. Calcd. for $C_9H_{17}O_3N_3$: N, available as NH_3, 6.52. Found: N, 6.57, 6.56.

Condensation of Ethyl Acetate and 2-Hexanone.—This reaction was performed following the directions of Morgan and Drew.[10] The diketone boiled at $83-85°$ (21 mm.). That it was 2,4-octanedione was confirmed as follows.

(7) Kutz and Adkins, THIS JOURNAL, **52**, 4042 (1930).

(8) Hobson, *J. Chem. Soc.*, 1384 (1929).

(9) Gredy, *Bull. soc. chim.*, [5] **2**, 1038 (1935).

(10) Morgan and Drew, *J. Chem. Soc.*, **125**, 731 (1924).

One gram of it was dissolved in 15 cc. of ether and 0.4 g. of hydrazine hydrate was added. At first a white solid appeared but in half an hour it disappeared and a small amount of water separated. The ether was evaporated and to the residual substituted pyrazole was added 50 cc. of water and 1 g. of sodium carbonate. During a two-hour refluxing period 10 g. of potassium permanganate was added. Refluxing was continued for eighteen hours, then the solution was filtered, the filtrate acidified and evaporated to dryness. The residue, taken up in a minimum amount of cold water, was extracted nine times, with 10-cc. portions of ether. Evaporation of the ether left 0.14 g. of white solid, m. p. 285° with decomposition. The m. p. for 3,5-pyrazoledicarboxylic acid[11] is 287–290° (decompn.); that for 3,4,5-pyrazoletricarboxylic acid[12] is 233°. To purify it further about 0.1 g. was neutralized, evaporated to small volume, acidified and cooled in ice for two hours. The crystals were collected on a filter and rinsed with a little cold water. The solid was free from ash by ignition test. It was dried at 120°. The neutral equivalent was 78.8, whereas that calculated for $C_3H_2N_2(COOH)_2$ is 78.

Condensations with 2-Octanone

Ethyl Crotonate.—The 2-octanone, purified via the sodium bisulfite addition compound, was distilled at 80–81° (32 mm.). Ethyl crotonate, dried over potassium carbonate, boiled at 58–59° (48 mm.). A fine suspension of 3.7 g. of sodium in 100 cc. of dry xylene was made by stirring and vigorously refluxing the xylene. To the hot suspension of sodium was added 9.3 cc. of absolute alcohol (99.95%) dropwise with stirring. When the sodium had changed completely to gelatinous sodium ethoxide, it was cooled and 28.5 g. of ethyl crotonate was added. The mixture was stirred for twenty minutes, then cooled in an ice-bath, and 10 g. of 2-octanone was added dropwise during fifteen minutes. It was stirred for three hours at 0° and fifteen hours at room temperature. Then 100 cc. of water was added. This was stirred for fifteen minutes. The aqueous layer was washed with ether and the xylene layer with water. The aqueous layer was acidified with glacial acetic acid. A solid separated. The liquid was decanted from the solid and was ether extracted. The ether was evaporated. The residual oil solidified when seeded at 0° with crystals of the solid. After recrystallization from dilute alcohol (1:1) it melted at 98–99°. It gave no color with ferric chloride. The yield was 8.4 g. (53%). Analysis was satisfactory for 2-dodecene-4,6-dione.

Anal. (by E. M. Washburn). Calcd. for $C_{12}H_{20}O_2$: C, 73.41; H. 10.27. Found: C, 73.35, 73.19; H, 10.14, 10.08.

The xylene layer was distilled at 5 mm. The main fraction (4.4 g.) was collected at 110–114°. It was β-methyl-α-ethylideneglutaric ester,[13] a dimer of ethyl crotonate. Analysis confirmed this.

Anal. (by Mr. Washburn). Calcd. for $C_{12}H_{20}O_4$: C, 63.15; H, 8.83. Found: C, 63.30; H, 9.04.

(11) Knorr, *Ann.*, **279**, 218 (1894).

(12) Buchner, *Ber.*, **22**, 842 (1889).

(13) Von Pechmann, *ibid.*, **33**, 3323 (1900).

Ethyl Acrylate.—The details followed those of the previous experiment, these quantities being taken: 3.45 g. of sodium, 8.7 cc. of absolute alcohol, 20 g. of ethyl acrylate, and 10 g. of 2-octanone. The ethyl acrylate was furnished by Dr. C. S. Hollander of Röhm and Haas Company, to whom we are very grateful. It was used directly without distillation from the trace of hydroquinone present as a preservative.

In this preparation an oil appeared on acidification. It was separated and chilled for six hours, during which time it solidified. The product was crystallized once from petroleum ether and twice from ethyl acetate. The 1-hendecene-3,5-dione melted at 69–70°; yield, 7.9 g. or 54%.

Anal. (by Mr. Washburn). Calcd. for $C_{11}H_{18}O_2$: C, 72.30; H, 9.95. Found: C, 72.42; H, 10.22.

Ethyl Acetate.—Similar directions were followed: 3.7 g. of sodium, 9.3 g. of absolute alcohol, 21.2 g. of pure ethyl acetate, and 10 g. of 2-octanone. The diketone was purified by means of the copper salt, then regenerated with dilute sulfuric acid and distilled at 129–131° (33 mm.). This agrees with Morgan and Drew.[14] The yield of pure 2,4-decanedione was 4.4 g. or 33%.

Summary

1-Hendecene-3,5-dione and 2-dodecene-4,6-dione were prepared from 2-octanone by the Claisen condensation with ethyl acrylate and ethyl crotonate, respectively. These diketones are new.

2,4-Octanedione, 2,4-hendecanedione, and 2,4-dodecanedione were prepared from acetoacetyl chloride by reaction, respectively, with butyl-, heptyl-, and octylmagnesium bromides. A new diketone, 5-methyl-2,4-hendecanedione, was prepared by interaction of acetoacetyl chloride and 2-octylmagnesium bromide.

New evidence supporting the structure of the β-diketones is their synthesis from acetoacetyl chloride, and the oxidation to 3,5-pyrazoledicarboxylic acid of the reaction product (3-methyl-5-butylpyrazole) of 2,4-octanedione and hydrazine.

Butyl acetoacetate semicarbazone was synthesized in the course of this work.

These C_8 to C_{12} diketones exhibit low phenol coefficients (6.6 to 11.1) against *B. typhosus*, but only those diketones which contain an olefinic double bond (1-hendecene-3,5-dione and 2-dodecene-4,6-dione) show any effectiveness (phenol coefficient, 5.5) against *Staphylococcus aureus*. These values are much lower than those of the alkylresorcinols.

(14) Morgan and Drew, *J. Chem. Soc.*, **125**, 731 (1924).