

3. β -Spinastenol yields a saturated alcohol, spinastanol, on absorption of one mole of hydrogen.

4. New esters of α -spinastenol, β -spinastenol and spinastanol are described.

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Preparation of 1,3-Diketones by the Claisen Reaction

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Rather large quantities of a number of 1,3-diketones were needed in this Laboratory for studies involving the relation of their structures to the mode of cleavage by water, alcohol and hydrogen.¹ Our experience in the preparation of these diketones (see Table I) by the condensation of an ester with a simple ketone according to the Claisen reaction has, we believe, illuminated somewhat the preparational process.

Sodium ethoxide, especially by the procedure marked "A" in the experimental part, appears to be preferable to sodium as a condensing agent.² Only in the case of diacetylmethane was sodium definitely superior with respect to the yield of products calculated upon the basis of the amount of monoketone used. If the yields were calculated upon the basis of the sodium ethoxide or sodium the comparison would be in all cases very unfavorable to sodium since as shown by Kutz 2 g. atoms of sodium are required as contrasted with 1 g. molecule of sodium ethoxide.

Even though sodium gave a higher percentage conversion of monoketone to diketone, the reagent suffers under certain disadvantages that greatly militate against its use. The condensation of an ester with a ketone using sodium as the condensing agent is a hazardous operation. One serious accident and several minor ones have occurred in this Laboratory in connection with the preparation. The serious accident was due to contributory negligence upon the part of the operator but even the most skilled and experienced occasionally allow a reaction to become too violent. The difficulty lies in the fact that usually reaction occurs slowly if at all when the reactants are mixed at 0-5°, but it does begin in most cases as the mixture warms up to room tem-

perature. Once under way the reaction goes rapidly and unless the reaction mixture is watched very carefully, and rapidly cooled, goes with violence. It is, of course, not difficult to use sodium if only a fraction of a mole is involved.

The formation of a β -keto ester through the interaction of two molecules of ester may be avoided to a greater extent with sodium ethoxide than with sodium. In certain attempted preparations of $\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{C}(\text{CH}_3)_3$ through the condensation of ethyl acetate and pinacolone with sodium, a product having a good boiling range for the diketone contained as much as 50% acetoacetic ester while that from sodium ethoxide contained no ester. Sodium also tends to produce acyloins. For example no diketone was obtained as a result of the use of sodium with ethyl hexahydrobenzoate and acetone, instead the acyloin, $\text{C}_6\text{H}_{11}\text{C}(\text{O})\text{CH}(\text{OH})\text{C}_6\text{H}_{11}$, was isolated in 70% yield accompanied by a 5-6% yield of dicyclohexylglycolic acid.

Three methods are available for the isolation and purification of the diketone. The purification is readily made if the diketone is a solid such as are acetylbenzoylmethane, furoylbenzoylmethane, etc., which precipitate upon acidification of the reaction mixture. Morgan and others have recommended the separation of the liquid diketones as the copper salts. However, we have found that in most cases it suffices to extract the diketone from an acid solution and then to purify it by fractionation through a Widmer column. Presumably the preparation of the copper salt of the diketone is intended to eliminate any β -keto ester present in the reaction product. It is unnecessary to form the copper salt, (a) if no β -keto ester is present, or (b), if the β -keto ester differs sufficiently in boiling point from the diketone so that it may be separated by fractionation. Analysis of the products has shown, for example, that isovaleryl-, trimethylacetyl- and

(1) For references see Sprague, Beckham and Adkins, *THIS JOURNAL*, **56**, 2669, 2676 (1934).

(2) Nothing in this paper should be construed as in conflict with the conclusion of McElvain and others that the acetoacetic ester or Claisen condensation is dependent upon sodium ethoxide even when sodium is the reagent added.

isobutyrylacetylmethanes prepared through the use of sodium ethoxide in the cold contained no β -keto ester. The purity of the compounds was not increased and the yield of diketone was lowered when the copper salt method of purification was used.

Quite a different situation was encountered if sodium was used in the preparation of the diketone. When the copper salt was not used for the purification of trimethylacetylacetylmethane the analysis of the product was about 7% low for carbon and 1% low for hydrogen, indicating the presence of about 50% of acetoacetic ester. If the copper salt of the diketone was properly prepared the regenerated diketone gave a good analysis for carbon and hydrogen. However, the formation of a copper salt of a diketone does not ensure that the regenerated and fractionated di-

analyze about 2% low in carbon. The reason for this is as follows. The keto forms of β -keto esters do not form copper salts but their enol forms do, so that if the reaction mixture from the Claisen condensation is acidified and copper acetate added immediately a good deal of the copper salt of the enol ester as well as of the diketone is precipitated. If, however, the mixture is allowed to stand until the enol has gone to the keto form then the copper salt of the diketone may be relatively free of the copper salt of the keto ester. The impure copper salt may of course be purified by recrystallization (from methanol) but obviously it is better to prepare the diketone by a method which does not bring about its contamination by the keto ester.

The variations in yields of diketones given in Table I are, with a few exceptions, not very large.

TABLE I
PREPARATION OF SIMPLE 1,3-DIKETONES, RC(O)CH₂C(O)R'

R	R'	Methyl ketones (moles)	Ethyl ester (moles) ^a	Reagent moles	Yield, %	B. p., °C.	Mm.
Me ^{3,6}	Me	Me (2)	Acetate (6)	NaOEt (2)	35 ¹⁴	134-136	
Me	Me	Me (2)	Acetate (12)	Na (4)	58	133-136	
<i>i</i> -Pr ⁴	Me	<i>i</i> -Pr (1)	Acetate (3)	NaOEt (1)	40	161-164	
<i>i</i> -Pr	Me	<i>i</i> -Pr (0.5)	Acetate (3)	Na (1)	54	160-162.5	
<i>i</i> -Bu ⁵	Me	<i>i</i> -Bu (1)	Acetate (5)	Na (2)	25	164-167	
<i>t</i> -Bu	Me	<i>t</i> -Bu (1)	Acetate (3)	NaOEt (1)	15-25	164-167	
<i>i</i> -Bu ⁴	Me	<i>i</i> -Bu (4)	Acetate (8)	NaOEt (4)	60	71-76	18
<i>i</i> -Bu	Me	<i>i</i> -Bu (2)	Acetate (12)	Na (4)	64	74-77	17
<i>i</i> -Bu	Me	<i>i</i> -Bu (1)	Acetate (3)	NaOEt (1)	56	74-77	17
Et ³	Me	Et (2)	Acetate (12)	Na (4)	35	154-157	
Pr ³	Me	<i>n</i> -Pr (2)	Acetate (12)	Na (4)	45	87-90	38
<i>n</i> -Bu ³	Me	<i>n</i> -Bu (2)	Acetate (12)	Na (4)	56-62	79-81	17
<i>s</i> -Bu ³	Me	<i>s</i> -Bu (2)	Acetate (12)	Na (4)	47	96-100	45
Cyclohexyl ^{3,7}	Me	Cyclohexyl (0.25)	Acetate (2.5)	Na (0.5)	50	101-105	7
Furyl ⁸	Me	Me (2)	Furoate (2)	NaOEt (2)	40-45	107-110	10
Tetrahydrofuryl	Me	Me (0.4)	Tetrahydrofuroate (0.4)	NaOEt (0.4)	60	95-97	8
Ph ³	Me	Ph (2)	Acetate (4)	NaOEt (2)	65-70	134-136	16
Ph	Me	Ph (2)	Acetate (12)	Na (4)	65	M. p. 59-60	
Mesityl ⁸	Me	Mesityl (0.5)	Acetate (1.5)	NaOEt (0.5)	70	143-146	8
						M. p. 46-47	
Furyl ⁹	Ph	Ph (1)	Furoate (1)	NaOEt (1)	55	160-165	3
						M. p. 68	
<i>p</i> -Biphenyl	Me	<i>p</i> -Biphenyl (0.5)	Acetate (7.0)	NaOEt (0.5)	50	M. p. 156-157	

^a Except where 12 moles of ester were added, diisopropyl ether or toluene were used as the reaction mediums.

ketone will be free of β -keto ester. For example a sample of trimethylacetylacetylmethane was purified through the copper salt and found to

The methyl ketones containing an isobutyl, phenyl or mesityl group gave the highest yield (65-70%) of diketones, while most of the others gave yields in the neighborhood of 50%. However, in seven cases attempts to prepare diketones with sodium ethoxide failed. The ethyl esters of trimethylacetic and valeric acids would not condense with pinacolone nor with methyl *n*-butyl ketone. The ethyl esters of neither

(3) Adkins, Kutz and Coffman, *THIS JOURNAL*, **52**, 3218, 4036 (1930).

(4) Morgan and Drew, *J. Chem. Soc.*, **125**, 743 (1924).

(5) Courturier, *Compt. rend.*, **150**, 928 (1910).

(6) Claisen and Ehrhardt, *Ber.*, **22**, 1014 (1889).

(7) Godchot, *Compt. rend.*, **151**, 1132 (1910).

(8) Fuson and Woodward, *THIS JOURNAL*, **55**, 3474 (1933).

(9) Semmler and Ascher, *Ber.*, **42**, 2359 (1909).

TABLE II
PREPARATION OF ALKYLATED 1,3-DIKETONES $RC(O)CHR'C(O)CH_3$ (WEYGAND¹⁰)

Salt of diketone ^a R	Moles	R'	Alkyl halide Halogen	Moles	Times, hours	Yield, %	B. p., °C.	Mm.
Ph ¹¹	1	Et	I	2.0	10	50	128-132	7
Ph	1	<i>n</i> -Bu	I	1.6	36	50	156-160	10
Ph	0.5	<i>n</i> -Heptyl	I	1.0	43	53	178-183	8
Ph ¹²	1	Benzyl	Cl	5.5	41	50	210-217	10
Me ¹³	1	Et	I	1.5	2	30	168-172	
<i>i</i> -Bu	0.5	Et	I	1.5	40	45	77-78	17
<i>i</i> -Bu	.5	Benzyl	Cl	3.0	40	47	155-163	10
<i>i</i> -Bu	.25	(Benzyl) ₂	Cl	11.0	8	22	165-174	1
<i>i</i> -Bu	.5	<i>n</i> -Bu	I	1.0	40	56	113-117	11
Me	.63	Benzyl	Cl	2.0	4	45	143-146	10
Me	.16	(Benzyl) ₂	Cl	1.0	5	39	200-220	10

M. p. 111-112

^a Except for benzyl chloride, 500 cc. of acetone or dioxane was used as a solvent per mole of diketone. The dibenzyl diketones were made by first preparing the monobenzyl compounds and then realkylating. The yields given are for the second alkylation.

TABLE III
ANALYSIS OF 1,3-DIKETONES NOT HITHERTO REPORTED

	Formula	Carbon, %		Hydrogen, %	
		Calcd.	Found	Calcd.	Found
<i>p</i> -Phenylbenzoylacetylmethane	C ₁₆ H ₁₄ O ₂	80.63	80.65	5.92	6.05
Tetrahydrofuroylacetylmethane	C ₈ H ₁₂ O ₂	61.54	61.38	7.69	7.48
<i>n</i> -Butylbenzoylacetylmethane	C ₁₄ H ₁₈ O ₂	77.02	77.16	8.32	8.54
<i>n</i> -Heptylbenzoylacetylmethane	C ₁₇ H ₂₄ O ₂	78.40	78.21	9.30	9.41
<i>n</i> -Butylacetyltrimethylacetylmethane	C ₁₂ H ₂₂ O ₂	72.66	72.3	11.19	11.08
Benzylacetyltrimethylacetylmethane	C ₁₅ H ₂₀ O ₂	77.53	77.5	8.68	8.45
Ethylacetyltrimethylacetylmethane	C ₁₀ H ₁₈ O ₂	70.53	70.7	10.65	10.3
Dibenzylacetyltrimethylacetylmethane	C ₂₂ H ₂₆ O ₂	81.94	81.9	8.13	7.5

hexahydrobenzoic nor α -phenylacetic nor ethyl β -phenylpropionic acids would condense with acetone.

The alkylated 1,3-diketones (Table II) were prepared by the reaction of the sodium salt of the simple diketone with an alkyl halide in acetone or dioxane according to the method of Weygand. The sodium salt of the simple diketone as obtained in its preparation may be used but it is not so readily soluble in acetone so that the reaction time must be extended. The enol content of the diketones prepared as described in this paper are reported elsewhere.¹

Experimental Part

Condensation of a Ketone and an Ester.—A. The sodium ethoxide, ester and solvent (if any) were stirred for fifteen to twenty minutes and then cooled in an ice-bath. (The sodium ethoxide was prepared from equimolecular amounts of powdered sodium and ethanol in ether or xylene.) The ketone was then added slowly over a period of one-half to one hour. The ice-bath was re-

moved frequently at first to make sure that condensation, as evidenced by the evolution of heat or the disappearance of sodium ethoxide, had begun. After all the ketone had been added the reaction mixture was stirred for two to three hours in the ice-bath and then allowed to stand at room temperature for twelve to sixteen hrs. The mixture was then cooled in an ice-bath and an equal volume (or more if the solid did not dissolve) of ice water added. The aqueous and organic layers were separated and washed 2-3 times with ether and water, respectively. The combined aqueous layers were acidified with 65 cc. of glacial acetic acid per mole of sodium ethoxide used in the condensation. The above is the preferred procedure.

B. The condensation was also carried out under a reflux by adding the ketone during fifteen to thirty minutes to the ester-sodium ethoxide-solvent mixture without cooling. The reaction mixture was then refluxed on a steam-bath for two to five hours, and after cooling worked up as above.

C. Four atoms of sodium (finely powdered under xylene) was placed with the ester (12 moles) in a 3-necked, 5-liter round-bottomed flask, provided with a reflux condenser having an inner tube 2.5 cm. in diameter. The flask was surrounded by ice, the stirrer started and one-third of the ketone (total amount 2 moles) added. The ice-bath was removed until the reaction had started as evidenced by the generation of heat. Great care must be exercised in running this reaction as once started it is exceedingly vigorous and may result in dangerous explosions, as the heat is generated so fast that very large quantities of vapors are quickly formed. For this reason great care

(10) Weygand, *Ber.*, **61**, 687 (1928).

(11) Dieckmann, *ibid.*, **45**, 2687 (1912); **55**, 2479 (1922).

(12) Trotman, *J. Chem. Soc.*, **127**, 94 (1925).

(13) Morgan and Rawson, *J. Soc. Chem. Ind.*, **44**, 462 (1925).

(14) No one of several operators has ever been able to duplicate the yield of 60-82% reported by Kutz.

must be exercised that the temperature does not appreciably exceed room temperature. This was accomplished by a continual watching of the reaction flask by placing a hand on the outside whenever the ice-bath was removed. The time necessary for the reaction to start varies greatly, sometimes only a few moments and sometimes six or eight hours. (In the preparation of trimethylacetylacetyl-methane the reaction did not start until the mixture was heated.) At the first sign of reaction the ice-bath was replaced and after the reaction was under way as evidenced either by the separation of a light yellow solid, or a very marked darkening of the solution, the remainder of the ketone was slowly added (one hour). Stirring was continued for two hours after the addition of the ketone, and the reaction mixture allowed to stand in an ice-bath overnight. Water and acid were then added as in the condensation with sodium ethoxide.

Isolation and Purification of Diketone.—If the diketone was a solid it was filtered from the acid solution obtained by the various processes given above and recrystallized. If a liquid it was either extracted with ether or converted to the copper salt.

Extraction.—The diketone layer produced on acidification was taken up in ether, and the water layer extracted 3 or 4 times with ether. The combined ether extracts were washed with water and two or three times with saturated sodium bicarbonate solution. After drying over calcium chloride and removing the ether the products were fractionated through a Widmer column.

Copper Salt.—The acidified reaction mixture, after being allowed to stand for an hour or so, was poured into an ammoniacal solution of copper acetate (using 100 g. of copper acetate in 500–600 cc. of concd. ammonium hydroxide per mole of ketone originally used). After standing for two hours, the copper salt was filtered off and washed with water until the wash water was practically colorless. The copper salt was decomposed by shaking with 20% sulfuric acid and ether. The ether solution of the diketone was washed with saturated bicarbonate, dried over calcium chloride and fractionated.

In the preparation of benzoyl-*p*-phenylbenzoylmethane it was necessary to modify the procedure in the following respects. The *p*-phenylacetophenone was dissolved in 500 cc. of warm ethyl acetate and added to a mixture of sodium ethoxide and 200 cc. of ethyl acetate. The ethyl acetate solution of the *p*-phenylacetophenone must be kept warm during addition, and it was necessary to have the ethyl acetate-sodium ethoxide mixture refluxing before addition of the ketone solution in order that the precipitated sodium salt would not cake in the flask. Since the sodium salt is insoluble in water, it was filtered off and washed thoroughly with hot benzene, dried, ground to a fine powder, suspended in 1 liter of water containing 120 g. of acetic acid and vigorously stirred for four to five hours. The free diketone was filtered and washed with distilled water until neutral to litmus. The crude diketone was air dried (67 g., 56%, m. p. 154–156°) and recrystallized from 500 cc. of ethyl acetate. However, the small amount of unchanged salt which remained in the diketone was more conveniently removed by placing the crude diketone in extractor and extracting with 500 cc. of

ethyl acetate. The diketone may be distilled (b. p. 200–210°, 3 mm.) but must be recrystallized before distillation since traces of undecomposed salt seemed to cause a large amount of decomposition on distillation. The recrystallized material melted 155–156° (60 g., 50%) and was yellow but the distilled diketone was only faintly colored (and melted 156–157°). It gave a red color with ferric chloride in alcohol solution.

The acyloin (b. p. 167–172°, 16 mm., m. p. 46–47°) obtained as the result of the reaction of sodium and ethyl hexahydrobenzoate has been reported but not as a solid.¹⁵ The oxime had a m. p. of 157–158°. The dicyclohexylglycolic acid obtained from the same reaction was no doubt produced by the benzoic acid rearrangement of the diketone $C_6H_{11}C(O)C(O)C_6H_{11}$.¹⁶ The acid was characterized by analysis, neutral equivalent and conversion to dicyclohexyl ketone. The latter was identified by its oxime, m. p. 157–158°.¹⁷

Alkylation of Simple 1,3-Diketones.—The method of Weygand¹⁰ was used but the procedure was modified to the following. To a suspension of 23 g. (one mole) of powdered sodium in 300 cc. of dry ether cooled in ice a solution of 162 g. (one mole) of benzoylacetyl-methane in one liter of ether was added slowly with stirring. A yellow sodium salt precipitated and the mixture was allowed to stand overnight. The ether was distilled and 500 cc. of dry acetone or dioxane added. The solvent was refluxed until the salt all went into solution (ten minutes) and 312 g. (two moles) of ethyl iodide was added over a period of thirty minutes. The solution was refluxed on a steam-bath until it was neutral to moist litmus. This required from eight to ten hours. The acetone and excess ethyl iodide were distilled off and sufficient water added to dissolve the precipitated sodium iodide. The product was taken up in ether and after washing with water, it was dried with calcium chloride and fractionated.

Summary

A number of 1,3-diketones have been prepared by the Claisen or acetoacetic ester condensation from an ester and a monoketone. Sodium ethoxide is concluded to be a better condensing agent than sodium for three reasons: (a) the reaction may be more readily controlled especially if a mole or more of monoketone is being used; (b) less β -keto ester and other products of side reaction are formed; (c) only one-half as much sodium is required. If proper precautions were taken in the preparation of the diketone there was no necessity for the isolation of the diketone through the copper salt. If the copper salt method of isolation is used, then the formation of a salt of the keto ester which may be present as an impurity must be guarded against.

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(15) Danilow and Venus-Danilowa, *Ber.*, **62**, 2861 (1928).

(16) Snell and McElvain, *This Journal*, **53**, 750 (1931).

(17) Marvel and Gauerke, *ibid.*, **50**, 1178 (1928).