Acetylation of VI.—Three hundred mg. of VI was dissolved in a mixture of 1 ml. of pyridine and 1 ml. of acetic anhydride. After standing overnight, it was poured into water, and crystallized on standing. The acetate (XIXb) recrystallized from isoöctane in large cubes, similar in appearance to potassium chloride.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.7; H, 8.33. Found: C, 67.8; H, 8.35.

Attempted Reaction of VI with Aniline.—Two hundred mg. of VI was heated at 100° with 0.5 ml. of aniline for one hour. Compound VI was recovered unchanged.

Reaction of VI with Halogen.—Treatment of VI with one or more moles of bromine or chlorine in glacial acetic acid gave orange colored oils which were not further identified.

Acetylation of VII.—Compound VII was acetylated in the same manner as VI. The only product could not be induced to crystallize, so could not be obtained analytically pure. However, the oil no longer gave an enol test, so was presumably an enol-acetate.

Halogenation of VII.—Bromination of compound VII (1.2 g.) in acetic acid was accomplished in good yield by adding an excess 30% bromine in acetic acid to a solution of VII. The product (XXIII) was obtained by addition of water. It was recrystallized from dilute acetic acid in two modifications. The stable form consisted of long, bright orange spears, while the metastable form occurred as garnet colored prisms. The stable form melted at 110–111.5°.

Anal. Calcd. for $C_{13}H_{20}O_2Br_2$: C, 42.5; H, 5.48. Found: C, 42.4; H, 5.65.

The two forms were not polymorphic crystal modification; rather they were two different chemical species, probably *cis–trans* isomers, since the two forms when melted under a cover glass showed a distinct line of demarcation on cooling. On standing the pink form changes slowly to the orange form. The ultraviolet absorption spectrum showed a shoulder at 2400 Å. but no maxima or minima. No hydroxyl band could be detected in the infrared.

The orange compound XXIII was quantitatively reconverted to VII by warming with zinc dust in acetic acid and by hydrogenation on platinum. A solution of XXIII in propanol reacted with hydrazine hydrate to give nitrogen and XXI.

Chlorination of compound VII likewise gave an orange crystalline compound, m.p. 82–83°, very similar in appearance to the bromo compound.

Anal. Calcd. for $C_{13}H_{20}O_2Cl_2$: C, 56.0; H, 7.23. Found: C, 55.8; H, 7.30.

Reaction of VII with One Mole of Bromine.—Treatment of 0.4618 millimole of compound VII in 20 ml. of glacial acetic acid with 1 ml. of bromate–bromide solution equivalent to 0.4618 millimole of bromine gave a pink solution which deposited pink needles (XXa) on dilution with water. The pink compound was taken up in ether, dried and evaporated on the steam-bath. The pink color gradually faded and a white solid remained after the ether had evaporated. This was recrystallized from dilute acetic acid to give (XXI) feathery leaflets, m.p. 131–131.2°.

Anal. Calcd. for $C_{13}H_{21}O_2Br$: C, 54.0; H, 7.32. Found: C, 54.0; H, 7.30.

The pink compound, in another experiment, was filtered out after precipitation, dried and examined under the microscope. It consisted of pink needles (XXa) admixed with some (XXI). It was analyzed without further purification.

Anal. Calcd. for $C_{13}H_{21}O_2Br$: C, 54.0; H, 7.32. Found: C, 53.4; H, 7.35.

This compound XXI had an absorption spectrum with a strong maximum at 2850 Å. in neutral and acid solutions. In alkali, the spectrum showed maxima at 3255, 2780 and 2440 Å. The spectrum in alkali changed with time. Acidification of the alkaline solution gave a compound (XXII) with a maximum at 2740 Å. Compound XXI gives a strong OH band in the infrared.

Compound (XXII) was isolated and purified, m.p. 154.5–155°.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 69.1; H, 9.81. Found: C, 69.1; H, 9.97.

Compound XXI was obtained by treating the dibromo compound (XVIII) with *o*-phenylenediamine.

Treatment of XXI or XX with bromine in acetic acid gave the identical bromo compound obtained previously, while reduction of XX or XXI with zinc and acetic acid gave (VII).

Acknowledgments.—We wish to thank Mr. G. M. Coppinger and Mr. G. F. Bailey for the spectrophotometric data, Dr. F. T. Jones for crystallographic examinations, Miss Elizabeth McComb for potentiometric titrations, Miss Geraldine Secor and Mrs. Mary Kilpatrick for ultimate analyses, and Mr. L. M. White for molecular weights. Special thanks are also due to an unknown referee, who pointed out certain discrepancies in our interpretation of spectra, in a very painstaking review.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE PAINT DIVISION OF THE PITTSBURGH PLATE GLASS COMPANY]

Transesterification. I. β-Keto Esters

BY ALFRED R. BADER, LOWELL O. CUMMINGS AND HENRY A. VOGEL

A series of β-keto esters of higher alcohols has been prepared in essentially quantitative yields by transesterification with methyl and ethyl β-keto esters under mild conditions in the absence of catalysts. The generality of this reaction and its usefulness is discussed.

As part of a more extensive study of ester interchanges we have investigated the transesterification of methyl and ethyl acetoacetate with a series of alcohols. Such transesterifications of acetoacetic esters have been previously studied, mostly at high temperatures and with basic catalysts with the lower alcohols,[1] *l*-menthol,[2] allylic alcohols,[3] and glycerol,[4] but it has not been realized that these reactions differ from conventional transesterifications and can proceed without catalyst and at steam-bath temperatures. We have prepared the acetoacetates of a series of alcohols in essentially quantitative yields and believe that most primary and secondary alcohols can be esterified in this manner provided that they dissolve in methyl and ethyl acetoacetate and do not, as may some benzylic alcohols,[5] C-alkylate the β-keto ester. Tertiary alcohols react more sluggishly, and we have ob-

(1) T. Peters, *Ber.*, **20**, 3318 (1887); *Ann.*, **257**, 353 (1890).

(2) P. Cohn, *Monatsh.*, **21**, 200 (1900); A. Lapworth and A. C. O. Hann, *J. Chem. Soc.*, **81**, 1499 (1902); A. McKenzie, *ibid.*, **89**, 365 (1906); H. Rupe and E. Lenzinger, *Ann.*, **395**, 87 (1913); H. Rupe and H. Kägi, *ibid.*, **420**, 33 (1920); G. Bruni, *Atti del Reale Istituto Veneto di Scienze*, **70**, II, 921 (1911); *Chem. Zentr.*, **83**, I, 1763 (1912).

(3) M. F. Carroll, *J. Chem. Soc.*, 704, 1266 (1940); 507 (1941); W. Kimel and A. C. Cope, THIS JOURNAL, **65**, 1992 (1943).

(4) R. Alpern and C. Weizmann, *J. Chem. Soc.*, **99**, 84 (1911).

(5) R. Fosse, *Compt. rend.*, **145**, 1290 (1907); *Bull. soc. chim.*, [4] **3**, 1075 (1908).

TABLE I

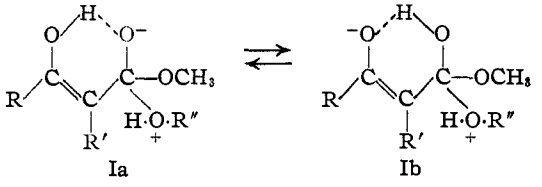
ACETOACETATES

Parent alcohol	Formula	M.p. or b.p., °C.	Solvent of recryst.	$n^{25}D$	$[\alpha]^{25}D$,[a] $CHCl_3$	Analyses,[b] % Found Carbon	Found Hydrogen	Calcd. Carbon	Calcd. Hydrogen
Cholesterol	$C_{31}H_{50}O_3$	96	Ethanol–water		−33	78.61, 78.50	10.46, 10.51	79.09	10.71
Cholestanol	$C_{31}H_{52}O_3$	97	Methanol		+12	78.68, 78.72	11.13, 11.07	78.75	11.09
β-Sitosterol	$C_{33}H_{54}O_3$	99–100	IPE[c]–methanol		−24	79.20, 79.44	10.88, 10.94	79.46	10.91
Stigmasterol	$C_{33}H_{52}O_3$	113–114	IPE–methanol		−44	79.42, 79.60	10.60, 10.70	79.79	10.55
Dehydroepiandrosterone	$C_{23}H_{32}O_4$	163	Methanol		+ 1	74.13, 74.15	8.76, 8.66	74.16	8.66
1-Octanol	$C_{12}H_{22}O_3$	140–141 (16 mm.)		1.4372		66.85, 66.83	10.37, 10.32	67.25	10.35
1-Dodecanol	$C_{16}H_{30}O_3$	8–10	Methanol	1.4436		70.78, 70.80	11.32, 11.33	71.06	11.18
1-Octadecanol	$C_{22}H_{42}O_3$	40–41	Methanol			74.55, 74.45	11.96, 12.13	74.52	11.94
Cyclohexanol	$C_{10}H_{16}O_3$	130–131 (16 mm.)		1.4576		64.94, 64.96	8.92, 8.78	65.19	8.76
Menthol[3]	$C_{14}H_{24}O_3$	30–32	Ether						
Butyl carbitol	$C_{12}H_{22}O_5$	168–170 (10 mm.)		1.4415		58.04	8.90	58.51	9.01
Decamethylene glycol	$C_{18}H_{30}O_6$	33–34	Methanol			62.55	8.85	63.13	8.83

[a] Determined by Dr. C. J. W. Brooks. No mutarotation could be observed. [b] Determined by Micro-Tech Laboratories, Skokie, Illinois. [c] Isopropyl ether.

tained only a low yield of the acetoacetate of diacetone alcohol, the one tertiary alcohol studied. Other β-keto esters react similarly and the benzoylacetates and acetonedicarboxylates of cholesterol and 1-octadecanol have been prepared.

The shift in equilibrium is of course due to the removal of methyl or ethyl alcohol from the reaction mixture, yet esters such as ethyl *n*-butyrate, methyl caprylate, methyl crotonate, methyl benzoate and methyl levulinate do not react with alcohols under conditions more drastic than those required to complete the reactions with methyl or ethyl acetoacetate. We are now studying the transesterification of acids of strength similar or greater than that of acetoacetic acid to ascertain whether it is the inductive effect of the acetyl group which, by enhancing the electrophilic character of the ester carbonyl, facilitates the transesterification of acetoacetic esters or whether the ease of reaction is due to active hydrogen catalysis or to inherent structural features which stabilize such intermediates as Ia and Ib.



Ia Ib

No transesterification takes place when disubstituted β keto esters such as ethyl diethylacetoacetate[6] are employed, and we are not yet certain whether this is due solely to steric hindrance of esters of tertiary acids or whether an active hydrogen atom is a prerequisite for reaction.

This facile transesterification provides one of the few means to esterify an alcohol in neutral medium. Most acetoacetates of higher alcohols crystallize easily and all are more soluble in most organic solvents than the alcohols from which they are derived. Thus acetoacetates make good derivatives of alcohols, and may find use in the purification of natural products. The transesterification proceeds so easily that acetoacetates of higher alcohols may conceivably be formed under physiological conditions and be metabolic intermediates. In this connection it is of interest to note that cholesteryl acetoacetate differs from all other β-keto esters prepared by us in that it is difficult to crystallize from organic solvents as it forms quite stable gels.

(6) A. McKenzie, *J. Chem. Soc.*, **89**, 381 (1906).

Experimental

The β-keto esters used were Eastman Kodak Co. white label chemicals purified by vacuum distillation. The alcohols were crystallized to constant melting point or vacuum distilled just prior to use.

All solid acetoacetates were prepared by heating solutions of the parent alcohols in excess methyl or ethyl acetoacetate on the steam-bath for 3 to 15 hours and allowing the lower alcohols to distil off as formed. The excess methyl or ethyl acetoacetate was then removed by distillation *in vacuo* and the almost pure products were recrystallized as shown in Table I. The yields of analytically pure acetoacetates were always higher than 90%. Liquid acetoacetates were prepared similarly and were purified by fractional distillation.

The structures of two acetoacetates were proved by infrared spectroscopy, and the formation of a semicarbazone and a β-aminocrotonate.

Cholesteryl acetoacetate semicarbazone, prepared from cholesteryl acetoacetate, m.p. 96°, $\lambda_{max.}^{Chf.}$ 5.75, 5.83 μ,[7] $\lambda_{max.}^{isooctane}$ 242.5 mμ (log ε 3.4)[8] melts at 189–190°, $[\alpha]^{25}D$ −25° (chloroform).

Anal. Calcd. for $C_{32}H_{53}O_3N_3$: C, 72.82; H, 10.12; N, 7.96. Found: C, 73.10; H, 10.32; N, 7.90.

Octadecyl β-aminocrotonate was prepared by passing gaseous ammonia through a methanolic solution of octadecyl acetoacetate, m.p. 40–41°, to which a crystal of ammonium acetate had been added. Recrystallized from methanol, it melts at 70–71°, $\lambda_{max.}^{ethanol}$ 274 mμ (log ε 4.3).

Anal. Calcd. for $C_{22}H_{43}O_2N$: C, 74.73; H, 12.26; N, 3.96. Found: C, 74.80, 74.95; H, 12.33, 12.31; N, 3.70.

Cholesteryl benzoylacetate obtained quantitatively from cholesterol (5 g.) and ethyl benzoylacetate (25 g.) and crystallized from a mixture of ethanol and butyl acetate melts at 151°.

Anal. Calcd. for $C_{36}H_{52}O_3$: C, 81.15; H, 9.84. Found: C, 81.11, 80.97; H, 9.88, 9.69.

Octadecyl benzoylacetate prepared similarly and crystallized from acetone melts at 55–57°.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.92; H, 10.30.

Cholesteryl acetonedicarboxylate obtained from cholesterol and ethyl acetonedicarboxylate and crystallized from a mixture of methanol and isopropyl ether melts at 173°. It was accompanied by a more soluble oil, presumably the mixed ester, which could not be obtained crystalline.

Anal. Calcd. for $C_{59}H_{94}O_5$: C, 80.22; H, 10.73. Found: C, 80.57, 80.51; H, 10.71, 10.79.

(7) We are indebted to Dr. Leon Mandell for the determination of this spectrum.

(8) We wish to thank Mrs. Ruth Ferguson for the determinations of ultraviolet spectra.

Octadecyl acetonedicarboxylate prepared similarly and crystallized from ethanol melts at 65.0–65.5°.

Anal. Calcd. for $C_{41}H_{80}O_5$: C, 75.40; H, 12.34. Found: C, 75.43, 75.37; H, 12.00, 11.94.

2-Acetoacetoxy-2-methyl-pentanone-4.—A solution of diacetone alcohol (300 g.) in methyl acetoacetate (1000 g.) was heated on the steam-bath for 24 hours. Fractionation through a short column yielded 1210 g. of unreacted starting materials and 54 g. of a fraction, b.p. 120–130° at 10 mm., from which 41 g. of pure acetoacetate was obtained on redistillation; b.p. 125–127° at 10 mm., $n^{25}D$ 1.4424, $\lambda_{max.}^{ethanol}$ 241.5 mμ (log ε 3.07), 306.5 mμ (log ε 2.34).

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.22, 60.14; H, 8.19, 8.31.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

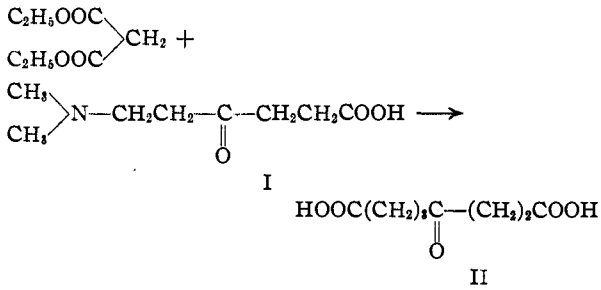
Polycyclic Compounds. II. Reactions of the Mannich Base of Levulinic Acid

BY R. M. DODSON[1] AND PAUL SOLLMAN[2]

6-Dimethylamino-4-ketocaproic acid, the Mannich base of levulinic acid, was successfully condensed with diethyl malonate to give, after hydrolysis and decarboxylation, γ-ketosuberic acid. In a similar manner, the condensation of phenylacetone with 6-dimethylamino-4-ketocaproic acid, yielded β-(4-phenyl-3-keto-1-cyclohexenyl)-propionic acid. The structure of this keto-acid was proved by its conversion to the known 4-phenylbenzoic acid and to the known *trans*-β-(4-phenylcyclohexyl)-propionic acid. A one–three shift of a double bond during the Wolff–Kishner reduction of an α,β-unsaturated ketone is reported.

The synthesis of cyclic ketones by the use of the methiodide of the Mannich base of simple ketones was developed by du Feu, McQuillin and Robinson[3] and has been extensively studied in recent years. In certain cases, the usefulness of this synthetic method would be increased if the reagent possessed an additional functional group or potential functional group. For this reason 4-keto-1,1-dimethylpiperidinium iodide and thiacyclohexan-4-one methiodide[4] have recently been used in the preparation of certain cyclic ketones instead of the more readily available Mannich base methiodides. For a similar reason, in connection with a possible synthesis of estrone, we have investigated the use of 6-dimethylamino-4-ketocaproic acid (the Mannich base of levulinic acid) for the synthesis of cyclic ketones.

In order to study the simplest possible example, one in which cyclization of the primary condensation product was improbable, 6-dimethylamino-4-ketocaproic acid (I) was condensed with diethyl malonate. The resulting product was hydrolysed and decarboxylated to γ-ketosuberic acid (II) in an over-all yield of 56%. Attempts at forming



a quaternary salt of the Mannich base (I) and simultaneously condensing it with diethyl malonate[5] resulted in a lower yield (18%) of the γ-ketosuberic acid (II).

The condensation of phenylacetone with the Mannich base of levulinic acid (I) produced a monoketo-acid (40%) which can be formulated as either IV or V depending on the direction of cyclization of the intermediate 1,5-diketone (III). Since a hydrogen attached to a methyl group is ordinarily more acidic than that attached to a methylene group, one would expect the base-catalyzed cyclization of III to yield β-(4-phenyl-3-keto-1-cyclohexenyl)-propionic acid (IV) rather than the substituted acetic acid V. That IV represented the structure of the compound obtained was established in the following ways.

First, the ultraviolet absorption spectrum of the unsaturated ketoacid, when determined in 95% ethanol, possessed a maximum at 234 mμ (log ε 4.17). This is in accord with structure IV in which the double bond possesses two β-substituents.[6] A compound corresponding to V should possess an absorption maximum at approximately 247 mμ.

Conclusive proof of structure of IV was obtained by its conversion to the known 4-phenylbenzoic acid. The Wolff–Kishner reduction of β-(4-phenyl-3-keto-1-cyclohexenyl)-propionic acid (IV) produced a mixture of olefins which contained approximately 68% of β-(4-phenyl-3-cyclohexenyl)-propionic acid (VI) and presumably 32% of β-(4-phenyl-1-cyclohexenyl)-propionic acid. Compound VI, $\lambda_{max.}$ 247 mμ (log ε 4.11) could be readily obtained from this mixture by crystallization. The ultraviolet absorption spectrum of VI is very similar to that of 1-phenylcyclohexene, $\lambda_{max.}$ 247 mμ (log ε 4.08).[7] In the conversion of IV to VI, the shift of the double bond from Δ^1 to Δ^3 was not unexpected. It has been shown that the Wolff–Kishner reduction of α,β-unsaturated ketones often

(1) G. D. Searle and Company, Chicago, Illinois.

(2) Abstracted from the Ph.D. thesis of Paul Sollman.

(3) E. C. du Feu, F. J. McQuillin and R. Robinson, *J. Chem. Soc.*, 53 (1937).

(4) H. M. E. Cardwell and F. J. McQuillin, *ibid.*, 708 (1949); H. M. E. Cardwell, *ibid.*, 715 (1949).

(5) For a similar but more successful reaction see N. F. Albertson, S. Archer and C. M. Suter, THIS JOURNAL, **67**, 36 (1945).

(6) R. B. Woodward, *ibid.*, **64**, 76 (1942).

(7) A. C. Cope, F. S. Fawcett and G. Munn, *ibid.*, **72**, 3399 (1950).