[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Claisen Acylation of Methyl Ketones with Branched Chain Aliphatic Esters[1]

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The objective of this work was to develop a method for acylating methyl ketones with esters having branching at the α-carbon to form β-diketones in satisfactory yields. It was concluded that the phenyl esters were suitable and that the acylation could be effected satisfactorily by sodium amide or lithium amide. The ethyl or methyl esters were evidently not sufficiently reactive. The method appears to be the best known for the preparation of branched chain β-diketones, especially those having branching at both ends. The copper chelates of such β-diketones are much more soluble in ligroin than those of straight chain β-diketones.

Acylations of methyl ketones with ethyl propionate and higher aliphatic esters have produced the best yields of β-diketones when effected by sodium amide,[2] sodium hydride,[3] or lithium amide.[4] The most efficient use of reactants has appeared to require either two moles of base to one of ketone and one or more of ester (Method A) or two moles each of base and ketone to one of ester (Method B). The significance of these proportions of reactants can be seen from a consideration of the abbreviated form of the mechanism represented below.

$$CH_3COR \xrightarrow{NaNH_2} Na(CH_2COR) \xrightarrow{R'COOR''}$$

$$R'COCH_2COR \xrightarrow[\text{Method A}]{NaNH_2} \underset{I}{Na(R'COCHCOR)} + NH_3$$

$$R'COCH_2COR \xrightarrow[\text{Method B}]{Na(CH_2COR)} I + CH_3COR$$

In general, acylations with straight chain ethyl or methyl esters and with ethyl isovalerate have produced good yields (50–80%). However, the acylation of acetone with ethyl isobutyrate by sodium amide[2] or sodium hydride[3] has given somewhat lower yields (40–42%), and of pinacolone with ethyl trimethylacetate, by sodium amide, a still lower yield (28%). We have similarly obtained low yields (10–20%) in the acylations of methyl *n*-amyl ketone with ethyl isobutyrate, methyl 2-ethylbutyrate and methyl 2-ethylhexoate using sodium amide by methods A or B under the usual conditions (two hours reflux in ethyl ether). Since both the methyl ketones and the resulting β-diketones are converted by sodium amide essentially completely to their anions, the relatively low yields obtained with these esters having branching at the α-carbon are evidently not due to an unfavorable equilibrium. Since branched chain esters undergo alkaline hydrolysis considerably more slowly than corresponding straight chain esters, the branched chain esters might also be expected to acylate ketone anions relatively more slowly.[5] It therefore seemed possible that the yields of β-diketones from branched chain esters might be improved merely by increasing the usual reaction time. Actually, in the acylation of methyl *n*-amyl ketone with ethyl isobutyrate by Method A, the yield was increased from 22 to 41% by increasing the reaction time from two to six hours. However, in the acylations of methyl *n*-amyl ketone with methyl 2-ethylbutyrate by Method B and of pinacolone with methyl trimethylacetate by Method A, the yields were not improved by a similar increase in reaction time. Method B gave higher boiling material which apparently was formed from an aldol condensation between the ketone anion and the original ketone regenerated in this method.

Since branched chain ethyl or methyl esters are apparently not sufficiently reactive to acylate the ketone anion before much of the ketone undergoes self condensation even in Method A, a study was made of corresponding acylations with more reactive acylating agents having the desired branching at the α-carbon. Although acid chlorides and anhydrides are known to be particularly active acylating agents, the acylation of methyl *n*-amyl ketone with 2-ethylbutyryl chloride by sodium amide (Method B) produced only an 8% yield of the β-diketone. Under similar conditions 2-ethylbutyric anhydride produced a 22% yield of the β-diketone. In both cases side reactions appeared to predominate.[5] However, satisfactory results were obtained with phenyl esters[6] which, judging from the relative rates of alkaline hydrolysis, should be considerably more reactive than ethyl or methyl esters.[5]

It can be seen from Table I that satisfactory yields (43–64%) were obtained in the acylation of methyl *n*-amyl ketone and of certain other methyl ketones with phenyl isobutyrate, phenyl 2-ethylbutyrate, phenyl 2-ethylhexoate and phenyl trimethylacetate using sodium amide by Method B. The yields were usually much lower by Method A. It is fortunate that Method B gives the better yields not only because the ester on which the yield is based is the relatively less available reactant but also because the β-diketones of most of the branched chain ketones failed to form solid copper salts, the formation of which appears to be required for the satisfactory isolation of β-diketones in Method A. In the limited number of cases studied

(1) Paper XLVII on Condensations; Paper XLVI, THIS JOURNAL, **72**, 3805 (1950). This work was carried out under Contract N7onr-455, with the Office of Naval Research.

(2) (a) Adams and Hauser, THIS JOURNAL, **66**, 1220 (1944); (b) Levine, Conroy, Adams and Hauser, *ibid.*, **67**, 1510 (1945).

(3) Swamer and Hauser, *ibid.*, **72**, 1352 (1950).

(4) Zellars and Levine, *J. Org. Chem.*, **13**, 160 (1948); Harris and Levine, THIS JOURNAL, **70**, 3360 (1948).

(5) Hauser, Ringler, Swamer and Thompson, *ibid.*, **69**, 2649 (1947).

(6) Enol esters might also be expected to produce satisfactory yields. However, the acylation of methyl *n*-amyl ketone with the enol 2-ethylbutyrate of methyl *n*-amyl ketone produced only a 7% yield of the β-diketone. The acetylation of methyl *n*-amyl ketone with the enol acetate of methyl *n*-amyl ketone produced a 22% yield of the β-diketone. In both cases sodium amide was employed using equivalent amounts of the three reactants. The enol 2-ethylbutyrate of methyl *n*-amyl ketone, obtained in 65% yield by refluxing equivalent amounts of 2-ethylbutyryl chloride with the ketone for 42 hours, boiled at 134° (35 mm.). *Anal.* Calcd. for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.60; H, 11.28. (Micro-Tech Laboratories, Skokie, Illinois.)

TABLE I

β-DIKETONES FROM BRANCHED CHAIN ALIPHATIC PHENYL ESTERS AND METHYL KETONES BY SODIUM AMIDE

Phenyl ester	Methyl ketone	β-Diketone	Yield, %	B.p. °C.	Mm.	Analyses,[a] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Isobutyrate	*n*-Amyl	2-Methyldecanedione-3,5[b]	50[c]	105–106	10	71.69	71.82	10.94	10.48
2-Ethylbutyrate	*n*-Amyl	3-Ethylundecanedione-4,6[d]	51,[e] 62[f]	127–130	10	73.54	73.73	11.39	11.29
2-Ethylhexoate	*n*-Amyl	5-Ethyltridecanedione-6,8[d]	43[g]	143–145	10	74.95	75.84	11.74	11.83[h]
Trimethylacetate	*n*-Amyl	2,2-Dimethyldecanedione-3,5[i]	46	112–115	10	72.68	72.98	11.19	10.91
2-Ethylbutyrate	Isobutyl	2-Methyl-7-ethylnonanedione-4,6[j]	56	103–106	10	72.68	72.54	11.19	11.19
2-Ethylhexoate	Acetophenone	1-Phenyl-4-ethyloctanedione-1,3[d]	43	169–171	5	78.01	78.29	9.00	8.93
Trimethylacetate	*t*-Butyl	2,2,6,6-Tetramethylheptanedione-3,5[k]	64	93–94	35	...	...	...	...
2-Ethylbutyrate	Unsymm. diethylacetone	3,7-Diethylnonanedione-4,6[l]	62	111–113	10	73.54	73.75	11.39	11.10

[a] Ref. 7. [b] Light blue copper enolate, m.p. 101–102°. [c] Method A gave 9% yield. Sodium hydride gave 21% yield by Method B. [d] Copper enolate obtained as a liquid. [e] Method A gave 10% yield. Sodium hydride gave 41% yield by Method B. [f] Obtained with lithium amide. [g] A 74% yield was obtained with lithium amide, but the product analyzed even less satisfactorily than that obtained with sodium amide. [h] Analysis by Micro-Tech Laboratories, Skokie, Ill. [i] Purple copper enolate, m. p. 43–44°. [j] Blue copper enolate, m.p. 68–69° [k] Purple copper enolate m.p. and mixed m.p. 192–193°. See ref. 2a. [l] Purple copper enolate, m.p. 53–54°.

sodium hydride gave lower yields than sodium amide. However, the acylation of methyl *n*-amyl ketone with phenyl 2-ethylbutyrate was effected in somewhat better yield (62%) with lithium amide than with sodium amide (51%).

It is recognized that most of the β-diketones listed in Table I might be prepared satisfactorily by the acylation of appropriate branched chain methyl ketones with straight chain methyl or ethyl esters. For example, β-diketone II might be synthesized by the acylation of unsymmetrical diethyl acetone with ethyl *n*-hexoate. However, unsymmetrical diethyl acetone is not as readily available as the methyl *n*-amyl ketone, whereas the 2-ethylbutyric acid from which the phenyl ester is prepared appears to be as readily available as methyl or ethyl *n*-hexoate. Moreover, the synthesis of the two symmetrical β-diketones III and IV require branched chain esters as well as branched chain methyl ketones and in such cases the phenyl esters but not the methyl or ethyl esters appear to be satisfactory.

$(C_2H_5)_2CHCOCH_2COC_5H_{11}$
II

$(C_2H_5)_2CHCOCH_2COCH(C_2H_5)_2$
III

$(CH_3)_3CCOCH_2COC(CH_3)_3$
IV

It should be pointed out that, in contrast to most straight chain β-diketones, the branched chain β-diketones such as II, III and IV form copper enolates which are soluble in low boiling ligroin.

Experimental[7,8]

Phenyl Esters.—The following acid chlorides were prepared by heating 2 moles of the appropriate acid with 2.4 moles of thionyl chloride at 60° for 5 hours: isobutyryl chloride, b.p. 90–93° (79%); 2-ethylbutyryl chloride, b.p. 136–140° (74%); 2-ethylhexoyl chloride, b.p. 86–88° (35 mm.) (91%); trimethylacetyl chloride, b.p. 104–107° (90%).

The phenyl esters were prepared from the acid chlorides by a modification of the method of Spassow.[9] Magnesium turnings (1 mole), phenol (1 mole) and 100 ml. of dry benzene were placed in a 1-liter round-bottomed flask fitted with a mercury sealed stirrer, reflux condenser and dropping funnel. The flask was heated to reflux the benzene, and 1 mole of the acid chloride in 100 ml. of dry benzene was added during one hour. Refluxing was continued until hydrogen chloride evolution ceased (2 to 3 hours). After cooling, the liquid was decanted, diluted with ether, washed with two 50-ml. portions of 5% sodium hydroxide solution, then with water and dried over Drierite. The solvents were distilled, and the phenyl esters distilled *in vacuo:* Phenyl isobutyrate,[10] b.p. 118–119° (35 mm.) (73%); phenyl 2-ethylbutyrate b.p. 117–118° (10 mm.) (81%).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.76; H, 8.26.

Phenyl 2-ethylhexoate, b.p. 137° (10 mm.) (91%).

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.62; H, 9.15.

Phenyl trimethylacetate, b.p. 118–119° (35 mm.) (83%).

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.10; H, 7.97.

Unsymmetrical Diethylacetone.—This ketone, b.p. 135–139°,[11] was prepared in 52% yield from diethyl malonate and 2-ethylbutyryl chloride by a procedure previously developed in this Laboratory.[12]

Acylations of Methyl Ketones with Phenyl Esters. (A) Sodium Amide.—In general these acylations were effected by a modification of a previously described procedure,[2a] using Method B.[2b] To a stirred suspension of sodium amide[2a] (0.66 mole) in 300 ml. of ether was added 0.6 mole of the ketone in 50 ml. of ether, followed, after 5 to 10 minutes, by 0.3 mole of the ester in 50 ml. of ether. After refluxing for 2 hours, the mixture was neutralized with ice and acid. The ether phase was washed with saturated sodium bicarbonate solution, dried over Drierite, and the solvent removed. The residue was fractionated *in vacuo*. The results are summarized in Table I.

Certain acylations were also carried out with sodium amide by Method A.[2b] However, the copper salt procedure[2a] usually employed in this method was unsatisfactory

(7) Analyses are by Clark Microanalytical Laboratories, Urbana, Illinois.

(8) We are indebted to Carbide and Carbon Chemicals Corporation for generous samples of 2-ethylbutyric acid, 2-ethylhexoic acid and methyl *n*-amyl ketone used in this work.

(9) Spassow, *Ber.*, **75**, 779 (1942).

(10) Baumgarten, Walker and Hauser, THIS JOURNAL, **66**, 303 (1944).

(11) Bardan, *Bull. soc. chim.*, **49**, 1875 (1931).

(12) Hauser and Walker, THIS JOURNAL, **68**, 1386 (1946).

since the copper salts were either liquids or were very soluble in ligroin. Generally the β-diketones were isolated by fractionation as described above in Method B.

(B) Lithium Amide.—Commercial lithium amide[13] (0.6 mole) was suspended in 300 ml. of dry ether, and 0.6 mole of ketone in 50 ml. of dry ether was added. After refluxing for 15 minutes, a solution of 0.3 mole of the ester in 50 ml. of ether was added. Refluxing was continued for 3 hours and the reaction mixture was worked up as described above for acylations with sodium amide.

(C) Sodium Hydride.—Acylations with this reagent were carried out by the procedure described previously.[3]

(13) We are indebted to the Metalloy Corporation, Minneapolis, Minnesota, for a generous supply of lithium amide.

Copper Enolate Derivatives.—To a sample of the β-diketone obtained by fractionation (about 5 g.) dissolved in an equal volume of methanol was added 100 ml. of a saturated solution of copper acetate (40 g. of copper acetate hydrate in 350 ml. water), and the mixture allowed to cool. If the copper enolate solidified, it was filtered by suction and recrystallized from 95% ethanol. If the enolate did not solidify, it was extracted from the aqueous portion with ligroin (b.p. 30–60°), the ligroin evaporated and the residue recrystallized from 95% ethanol. A second recrystallization from ethanol yielded pure samples, the melting points of which are given in the notes of Table I. In several instances the enolates were liquid and attempts to obtain solid derivatives failed.

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Some Derivatives of 4-Amino-2-hydroxybenzoic Acid (*p*-Aminosalicylic Acid)

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A number of derivatives and analogs of 4-amino-2-hydroxybenzoic acid have been prepared for tuberculostatic test. None of those tested was as active as the parent compound either *in vitro* or *in vivo*.

The versatile intermediates 2-acetoxy-4-nitrobenzoyl chloride and 2-hydroxy-4-nitrobenzimino ether hydrochloride have been prepared and characterized.

Following the announcement by Lehman[1] of the effectiveness of *p*-aminosalicylic acid (PAS) in tuberculosis we prepared several derivatives of this compound to explore the possibility of improving its activity.[2]

The N-alkylated compounds (Table I, nos. 8, 9, 10, 11) were prepared by application of a modified Kolbe procedure on the appropriately substituted *m*-aminophenol. The orientation is assumed by analogy with the formation of PAS by the same process. Structure is confirmed in the case of the N-methyl derivative in that the compound from this procedure is identical with that obtained by methylation of PAS.[3]

The amidines (nos. 18, 19) were made by the catalytic reduction of the corresponding nitro compounds. These latter were in turn prepared from 2-hydroxy-4-nitrobenzonitrile through the imino ether (no. 36).

We were able to prepare in good yield the intermediate 2-acetoxy-4-nitrobenzoyl chloride. Reaction of this with the appropriate amines followed by reduction led to the amides listed in Table I (nos. 12, 13, 14, 15). A number of these are available by reaction of the amines with esters of PAS or 2-hydroxy-4-nitrobenzoic acid.[4,5] The chloride has the advantage of course that it readily reacts with weak amines and also can be used in Schotten–Baumann procedures. In this respect an attempt was made to prepare in this series the analogs of sulfathiazole and sulfadiazine. Condensation of the acid chloride with the aminoheterocycles was successful (nos. 34, 35) but due to the extraordinary insolubility of the amino compounds the reduction and purification were not completed. It was not determined whether the nitrohydroxybenzoyl moiety was attached to the amino group or the ring nitrogen of the heterocycles.

In an attempt to obtain amides directly from PAS which is more available than the nitro acid, we prepared 4-carbethoxyamino-2-hydroxybenzoyl chloride. This intermediate reacted readily with amines and alcohols (nos. 27, 28, 29) but attempts to hydrolyze preferentially the carbethoxy group were unsuccessful.

The bacteriostatic activities[6] of the derivatives listed in Table I in no case equal and in only a few cases approach that of the parent PAS. The appreciable activity of no. 8 may be a reflection of the ready metabolism of N-methyl groups generally,[7,8] whereby PAS is generated. With this exception, substitution of the amino group results in drastic loss of *in vitro* activity. Similarly it appears that a free hydroxyl group is necessary. Variation of the carboxyl group with the exception of esterification results in greatly reduced activity. The high activity of the glycine amide (no. 14) is only apparent since it is abolished in the presence of serum. It would appear possible that the high activity of the methyl ester (no. 16) might arise because of hydrolysis to PAS in the course of the fourteen-day duration of the *in vitro* test.

Compounds nos. 2, 5, 6, 8, 12, 16, 17, 21, 22 and 23 were tested in mouse tuberculosis.[6] These were essentially inactive except with nos. 5 and 17 where some slight activity was evident on the basis of full activity for PAS.

These data taken in conjunction with other re-

(1) Lehman, *Lancet*, **250**, 15 (1946).

(2) While this work was in progress some of these derivatives, especially esters and amides, have been reported by other workers. Representatives of these classes of compounds have been included in the present report, however, in order to present a more complete picture of the effect of structure on activity.

(3) Rosdahl, *Svensk Kem. Tid.*, **60**, 12 (1948).

(4) Jensen, Rosdahl and Ingvorsen, *Acta Chem. Scand.*, **2**, 220 (1948).

(5) Schaefer and Doub, THIS JOURNAL, **71**, 3564 (1949).

(6) The data reported here, both *in vitro* and *in vivo*, were obtained by Dr. Guy P. Youmans, Department of Bacteriology, Northwestern University Medical School. The authors are deeply indebted to him for permission to use his results.

(7) Gordon and Jackson, *J. Biol. Chem.*, **110**, 153 (1935).

(8) Abbott and Lewis, *ibid.*, **131**, 479 (1939).