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Syntheses of Reductones. A New Method of Synthesizing 2-Acetoxy-1, 3-dicarbonyl Compounds

Noboru SUGIYAMA, Makoto YAMAMOTO, Tadao TAKANO and Choji KASHIMA

Department of Chemistry, Tokyo Kyoiku University, Otsuka, Tokyo

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2-Acetoxy-1, 3-dicarbonyl compounds were synthesized by two methods, one consisting of the condensation of 1, 3-dicarbonyl compounds with an electrophilic reagent, followed by acetoxylation. By this method three new compounds, ethyl 5-phenyl-2-acetoxy-3-oxopentanoate (XVII), ethyl 5, 5-diphenyl-5-hydroxy-2-acetoxy-3-oxopentanoate (XVIII), and ethyl 2-acetoxy-3-oxoheptanoate (XIX), were obtained. The other method consisted of the acetoxylation of 1, 3-dicarbonyl compounds, followed by condensation. By this method three other new compounds, 6-phenyl-6-hydroxy-3-acetoxy-2, 4-dioxohexane (IV), 6-phenyl-6-hydroxy-3-acetoxy-2, 4-dioxohexane (VIII), and 6-phenyl-3-acetoxy-2, 4, 6-trioxohexane (X), were obtained.

Reductones which have a –CO–CH(OH)–CO– [or its tautomeric form, –C(OH)=C(OH)–CO–] grouping in the molecule exert some kinds of physiological influence on a plant or an animal organism.[1] Altenin,[2,3] which produces the black spot disease on the leaves and fruits of the pear, ascorbic acid[4] and some hormones[5] are examples.

One of the simplest reductones, 3-hydroxy-2, 4-dioxopentane, is obtained by the hydrolysis of 3-acetoxy-2, 4-dioxopentane (I),[6] which is itself easily obtained by the acetoxylation of acetylacetone.[7,8]

Hauser has reported[9-11] that acetylacetone and ethyl acetoacetate condensed in liquid ammonia, with various electrophilic reagents at the methyl group, when catalyzed by alkali amide.

In a previous paper[12] we reported how modifications of these condensation and acetoxylation reactions were used to synthesize ω-phenyl 3-acetoxy-2, 4-dioxoalkanes (II). This paper will

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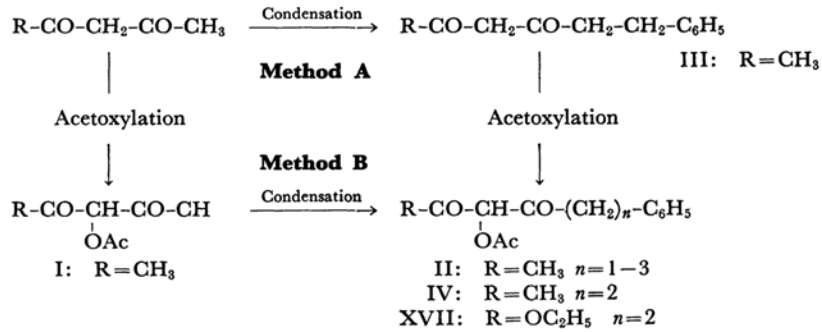

Schema 1. The syntheses of 2-acetoxy-1, 3-dicarbonyl compounds.

TABLE 1. THE SELECTION OF SYNTHETIC METHOD

Product	Method	Amide	Halide (X)	Acetoxylation	Yield, %
IV	A	$NaNH_2$	Cl	a	22.4
	A	$NaNH_2$	Cl	b	27.2
	A	$NaNH_2$	Br	a	39.2
	A	$NaNH_2$	Br	b	47.6
	B	$NaNH_2$	Br	a	0
	B	$NaNH_2$	Br	b	0
	B	$LiNH_2$	Br	a	4.3
	B	$LiNH_2$	Br	b	5.1
XVII	A	KNH_2	Br	a	40.0
	A	KNH_2	Cl	a	—
	B	KNH_2	Cl	a	trace
	B	$NaNH_2$	Cl	a	trace

Halide: C_6H_5-CH_2-X

Acetoxylation: a, $Pb(OAc)_4$; b, SO_2Cl_2-AcOK

describe the syntheses and the hydrolysis of 2-acetoxy-1, 3-dicarbonyl compounds.

Results and Discussion

For the synthesis of 2-acetoxy-1, 3-dicarbonyl compounds, the following two methods, A and B (illustrated in Schema 1), were employed. The synthesis of 6-phenyl-3-acetoxy-2, 4-dioxohexane (IV) will be described in detail as an example.

Method A. Acetylacetone was condensed with benzyl chloride in the presence of two moles of alkali amide in liquid ammonia; it thus produced 6-phenyl-2, 4-dioxohexane (III) in a 40% yield. When benzyl bromide was used instead of benzyl chloride, the yield of III increased to 70%. III was acetoxylated with lead tetraacetate to produce IV in a 56% yield. IV was also obtained from III by chlorination with sulfuryl chloride, followed by treatment with potassium acetate; its yield was 68%, as Table 1 shows.

Method B. Acetylacetone was acetoxylated to 3-acetoxy-2, 4-dioxopentane (I), which was then condensed with benzyl bromide in liquid ammonia to produce IV in a poor yield.

For the synthesis of IV, method A seemed to be

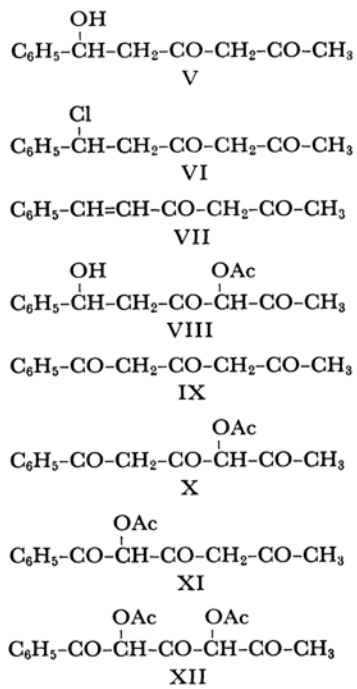

Fig. 1

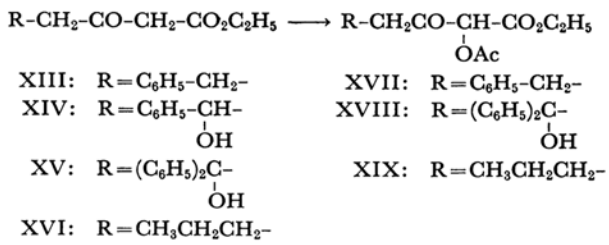

Fig. 2.

better than method B. However, method A is not applicable to a compound containing a hydroxyl group, such as V, because of the formation of such chlorinated or dehydrated compounds as VI or VII. Furthermore, method A is not suitable for the synthesis of X from the tricarbonyl compound IX, since it will be acetoxylated to produce not only X but also XI and XII. In order to obtain 6-phenyl-6-hydroxy-3-acetoxy-2, 4-dioxohexane (VIII) of 6-phenyl-3-acetoxy-2, 4, 6-trioxohexane (X), method B is then, preferable because of the simplicity of its product.

VIII was synthesized by the condensation of I with benzaldehyde in liquid ammonia. The structure of VIII is proved by its spectral data. The ultraviolet absorption spectrum showed an absorption maximum at 278 mμ in an ethanol solution, a maximum which shifted to 301 mμ in an alkaline solution, the characteristic bathochromic shift of β-dicarbonyl compound.[13]

X was synthesized by the condensation of I was methyl benzoate. The spectral data and the elemental analysis support the structure of X.

Compounds XVII, XVIII and XIX were obtained only by method A (see Table 1).

Synthesis of XVII. Ethyl acetoacetate was condensed with benzyl bromide to form ethyl 5-phenyl-3-oxopentanoate (XIII). The structure of XIII was supported by the spectral data and by the results of elemental analysis. The signals of the nuclear magnetic resonance spectrum of this compound supported the structure XIII: it showed a singlet at 2.79 τ (aromatic 5H), a triplet at 8.79 τ (methyl 3H of CH_3CH_2O–), a quartet at 5.92 τ (methylene 2H of CH_3CH_2O–), a singlet at 6.74 τ (α-methylene 2H of –CO–CH_2–CO_2–), and a multiplet at 7.25—7.50 τ (4H of C_6H_5–CH_2CH_2–CO–). There is no signal for the terminal methyl group which had been observed at 7.80 τ in ethyl acetoacetate.[11] These facts indicate that the condensation of benzyl bromide with ethyl acetoacetate occurred at the terminal methyl group and not at the α-methylene group. In the same way, ethyl 5-phenyl-5-hydroxy-3-oxopentanoate (XIV), ethyl 5, 5-diphenyl-5-hydroxy-3-oxopentanoate (XV), and ethyl 3-oxoheptanoate (XVI) were synthesized from ethyl acetoacetate with benzaldehyde, benzophenone, and *n*-propyliodide respectively in liquid ammonia.

XIII, XV and XVI were acetoxylated with lead tetraacetate in an acetic acid solution to give XVII, XVIII, and XIX. The structures of these compounds were supported by the spectral data and by the results of elemental analysis.

The corresponding acetoxylated compound was not isolated from XIV by the same procedure. It seemed difficult to acetoxylate a compound of the XIV (or V) type by this procedure.

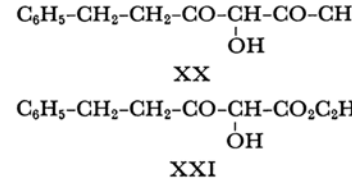

Fig. 3.

By the treatment of IV or XVII with ethanolic 1 N hydrochloric acid, the corresponding reductones, XX and XXI, were obtained. The structure of XX and XXI were confirmed by the infrared spectra.

Various 2-acetoxy-1, 3-dicarbonyl compounds and reductones can be synthesized by the present method.

Experimental

6-Phenyl-3-acetoxy-2, 4-dioxohexane (IV). *Method A:* 6-Phenyl-2, 4-dioxohexane (III) was prepared according to Hauser,[9] and then it was acetoxylated as in a) or b).

a) In a 100 m*l* three-necked flask 1.9 g of III in 30 m*l* of acetic acid were placed. To the stirred solution there were then added 4.4 g of lead tetraacetate in small portions, with the temperature kept at 20—30°C. With each addition of the lead tetraacetate, the colorless solution turned yellow or orange, but again became colorless after about 10 min. Then the next portion of the reagent was added. After the addition of the last portion of the lead tetraacetate, the end point of the reaction, the nonexistence of the lead tetraacetate was checked by a negative brown-color reaction. This color reaction is effected by the addition of a drop of a reaction mixture containing some residual lead tetraacetate to a few m*l* of water. The reaction mixture is then added to 150 m*l* of water, and the aqueous solution is extracted with ether. The organic layer was

13) R. P. Dryden and A. Winston, *J. Phys. Chem.*, **62**, 635 (1958).

washed with a dilute sodium bicarbonate solution and with water, dried over anhydrous sodium sulfate, and evaporated to give IV in a 58% yield (by gas chromatography).

Found: C, 68.05; H, 6.58%. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%.

IR: 1760—1710 (νC=O, acetoxyl, ketones), 750, 705 cm^{-1} (phenyl)

UV: λ_{max}^{EtOH} 270 (ε 1920), 284 mμ (ε 2340), $\lambda_{max}^{NaOH/EtOH}$ 305 mμ (ε 18100)

b) Similarly to the procedure used for the preparation of II in our previous report,[12] compound III was chlorinated with sulfuryl chloride and then treated with potassium acetate to give IV, which showed an infrared absorption spectrum identical with that of the sample obtained above.

Method B: In a 500 m*l*, three-necked flask 300 m*l* of anhydrous liquid ammonia were placed. A minimum amount of lithium (a tiny part of the total of 0.76 g of lithium) was added to produce a permanent blue color. To the stirred solution there was then added a catalytic amount of ferric nitrate, followed by 0.76 g of lithium in small portions. The resulting dark blue solution turned colorless or gray in 60—90 min. To this solution there were then added 7.9 g of I in 20 m*l* of anhydrous ether in small portions. After it has been stirred for an hour, the resulting solution turned to a greenish yellow suspension of the dilithio salt of I, to which there was added an equimolar benzyl bromide at −33°C. After three hours stirring, the lithium amide in the reaction mixture was converted to lithium chloride with 5.0 g of solid ammonium chloride. The liquid ammonia was evaporated rapidly on a water bath, as 100 m*l* of ether were added from a dropping funnel. The resulting ethereal suspension was acidified with 30 m*l* of cold concentrated hydrochloric acid and 100 g of crushed ice. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to yield 2.3 g (18.6%) of IV, which was identified with the sample obtained above by gas chromatography and by a study of its infrared spectrum.

6-Phenyl-6-hydroxy-3-acetoxy-2, 4-dioxohexane (VIII). According to method B, VIII was prepared by the condensation of 9.48 g of I with 6.36 g of benzaldehyde. The reaction mixture was then extracted with ether, and the organic layer was treated as usual to give an oily substance, which was chromatographed on a silica gel (Merck 7729) column with a benzene-ethyl acetate (10 : 1 v/v) mixture. When treated with ferric chloride, I showes a faint purple color. The fraction which showed a deep purple color with ferric chloride was collected and evaporated to yield 2.6 g of a faint orange oil. This substance was analyzed directly, because it could not be purified by distillation on account of its unstability to heat.

Found: C, 63.84; H, 6.16%. Calcd for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10%.

IR: 3450 (νOH), 1745—1720 (νC=O, acetoxyl, ketones), 750 cm^{-1} (monosubstituted phenyl group)

6-Phenyl-3-acetoxy-2, 4, 6-trioxohexane (X). According to method B, X was prepared from 0.06 mol of I and equimolar methyl benzoate. After the solution had been stirred for an hour, the liquid ammonia was replaced by 150 m*l* of anhydrous ether. The resulting suspension was stirred for an hour and then carefully acidified with a slight excess of dilute aqueous acetic acid. The organic layer was separated, and the aqueous layer was extracted with 100 m*l* of ether. The combined ethereal solution was then washed with water to remove the excess acetic acid, dried over anhydrous sodium sulfate, and evaporated. The residue was mixed with 100 m*l* of a saturated methanolic solution of copper acetate to produce the copper chelate complex. The mixture was then poured into 150 m*l* of water, and the precipitate of copper chelate was collected, washed with water, and recrystallized from methanol to give 2.9 g (16%) of dark green needles (mp 219—220°C (decomp)).

Found: C, 57.60; H, 4.43%. Calcd for $C_{28}H_{26}O_{10}$-Cu: C, 57.39; H, 4.44%.

IR: 1745—1720 (νC=O, acetoxyl, ketones), 715 cm^{-1} (phenyl)

UV: λ_{max}^{EtOH} 277 (ε 4400), 281 mμ (ε 4370), $\lambda_{max}^{NaOH/EtOH}$ 302 mμ (ε 23800)

IR of copper chelate: 1735 (νC=O, acetoxyl), 1590 (enolated double bond), 715 cm^{-1} (phenyl)

Ethyl 5-Phenyl-2-acetoxy-3-oxopentanoate (XVII). According to method A, 6.5 g of ethyl acetoacetate were condensed with 8.6 g of benzyl bromide in liquid ammonia. The reaction mixture was then chromatographed on silica gel (Merck 7729) with a benzene-ethyl acetate (10 : 1 v/v) mixture, and the reaction which showed an orange yellow color when treated with ferric chloride was collected. After the evaporation of the solvent, the residue was distilled to produce 12.1 g (61%) of XIII (bp 173—174°C/17 mmHg).

Found: C, 70.70; H, 7.39%. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%.

IR: 1745 (νC=O, ester), 1715 (νC=O, ketone), 750, 710 cm^{-1} (phenyl)

UV: λ_{max}^{EtOH} 249 (ε 1630), 253 (ε 1550), 258 mμ (ε 1320), $\lambda_{max}^{NaOH/EtOH}$ 277 mμ (ε 16000)

With lead tetraacetate 3.3 g of XIII was acetoxylated. After the solvent had been removed, the residue was distilled to give 2.7 g (65%) of XVII as a yellow oil (bp 209—210°C/16 mmHg).

Found: C, 64.51; H, 6.43%. Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52%.

IR: 1770—1720 (νC=O, acetoxyl, ester and ketone), 750, 720 cm^{-1} (phenyl)

UV: λ_{max}^{EtOH} 249 (ε 500), 254 (ε 550), 259 mμ (ε 545), $\lambda_{max}^{NaOH/EtOH}$ 280 mμ (ε 15800)

Ethyl 5, 5-Diphenyl-5-hydroxy-2-acetoxy-3-oxopentanoate (XVIII). According to method A, XVIII was prepared from 6.0 g of XV[11] by acetoxylation with lead tetraacetate. The crude product was then chromatographed on silica gel (Merck 7729) column with a benzene-ethyl acetate (10 : 1 v/v) mixture. The fraction which showed an orange color when treated with ferric chloride was collected and then evaporated to afford 0.39 g (5.5%) of XVIII as a light yellow oil.

Found: C, 67.59, 67.65; H, 6.09, 6.00%. Calcd for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99%.

IR: 3480(νOH), 1770—1720 (νC=O, acetoxyl, ester and ketone), 755, 700 cm^{-1} (phenyl)

UV: λ_{man}^{EtOH} 254 (ε 730), 259 mμ (ε 730), $\lambda_{max}^{NaOH/EtOH}$ 280 mμ (ε 9700)

Ethyl 2-Acetoxy-3-oxoheptanoate (XIX). According to method A, 6.5 g of ethyl acetoacetate were condensed with 8.5 g of *n*-propyl iodide. After the evaporation of the solvent, the residue was distilled to

give 6.5 g (63%) of XVI as a colorless oil (bp 109—113°C/31 mmHg).

Found: C, 62.59; H, 9.37%. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36%.

IR: 1745 (νC=O, ester), 1715 cm^{-1} (νC=O, ketone)

UV: λ_{max}^{EtOH} 247 mμ (ε 1530), $\lambda_{max}^{NaOH/EtOH}$ 275 mμ (ε 20100)

NMR: (in CCl_4) 8.85 τ (triplet, 3H) for CH_3CH_2O–, 5.86 τ (quartet, 2H) for CH_3CH_2O–, 6.70 τ (singlet, 2H) for –CO–CH_2–CO_2–, 8.29—9.10 τ (multiplet, 7H) for $CH_3CH_2CH_2CH_2$–.

The product which was obtained by the acetoxylation of XVI with lead tetraacetate was distilled to afford to 3.8 g (65%) of XIX, as a light yellow oil (bp 138—140°C/17 mmHg).

Found: C, 57.12; H, 7.86%. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88%.

IR: 1770—1730 cm^{-1} (νC=O, acetoxyl, ketone and ester)

UV: λ_{max}^{EtOH} 252 mμ(ε 260), $\lambda_{max}^{NaOH/EtOH}$ 280 mμ (ε 17500)

Ethyl 5-Phenyl-5-hydroxy-3-oxopentanoate (XIV). Similarly, 6.5 g of ethyl acetoacetate were condensed with 5.3 g of benzaldehyde to give 3.5 g (30%) of XIV as a yellow liquid.

Found: C, 65.74 65.98; H, 6.87 6.89%. Calcd for $C_{13}H_{16}O_4$: C, 66.10; H, 7.88%.

IR: 3450 (ν OH), 1745 (ν C=O, ester), 1720 (ν C=O, ketone), 750, 705 cm^{-1} (phenyl)

UV: λ_{max}^{EtOH} 244 (ε 2010), 249 (ε 2080), 254 mμ (ε 1900) $\lambda_{max}^{NaOH/EtOH}$ 276 mμ (ε 16600)

NMR: (in CCl_4) 8.84 τ (triplet, 3H) for CH_3CH_2O–, 5.95 τ (quartet, 2H) for CH_3CH_2O–, 6.68τ (singlet, 2H) for –CO–CH_2–CO_2–, 7.24 τ (doublet, 2H) for –CO–CH_2–CH(OH)–, 6.23 τ (multiplet, 1H) for the methine proton of –CH(OH)–, 5.08 τ (broad, 1H) for the hydroxyl proton, and 2.80 τ (singlet, 5H) for the aromatic protons.

The attempted acetoxylation of XIV with lead tetraacetate failed.

Condensation of Ethyl 2-Acetoxy-3-oxobutanoate with Benzyl Bromide or Benzophenone. By method B, 9.4 g of ethyl 2-acetoxy-3-oxobutanoate were allowed to react with an equimolar benzyl chloride in liquid ammonia. The reaction mixture was then separated by chromatography on silica gel (Merck 7729) with a benzene - ethyl acetate (2 : 1 v/v) mixture. The colorless liquid thus obtained in 2.4 g yield was proved to be 3-phenyl-2-hydroxypropionate by elemental analysis and by a study of its spectral data. No carbonyl compound was detected in the reaction mixture.

Found: C, 67.33; H, 7.22%. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27%.

IR: 3480 (ν OH), 1735 (νC=O, ester), 755, 700 cm^{-1} (phenyl)

UV: λ_{max}^{EtOH} 249, 254, 260, 265 and 269 mμ.

The same condensation with benzophenone (7.25 g) afforded none of the dicarbonyl compound, but it did afford 0.8 g of a white powder which was proved to be ethyl 3, 3-diphenyl-2, 3-dihydroxypropionate (mp 128—129°C); moreover, 5.0 g (69%) of benzophenone were recovered.

Found: C, 70.97; H, 6.23%. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34%.

IR: 3400 (ν OH), 1710 (ν C=O, ester), 755 cm^{-1} (phenyl)

UV: λ_{max}^{EtOH} 253 mμ

NMR: (in $CDCl_3$) 9.12 τ (triplet, 3H) for CH_3-CH_2O–, 6.04 τ (quartet, 2H) for CH_3CH_2O–, 6.12 τ (singlet, 1H) for the methine proton of –CH(OH)–CO_2–, and 2.40—2.70 τ (multiplet, 10H).

Ethyl 5-Phenyl-2-hydroxy-3-oxopentanoate (XXI). Into 10 m*l* of 1 N, HCl-EtOH, 2.78 g of XVII were dissolved, after which the solution was left to stand at room temperature for 24 hr. After the evaporation of the solvent, the residue was chromatographed on silica gel (Merck 7729) column with a benzene - ethyl acetate (2 : 1 v/v) mixture. 1.2 g (51%) of XXI were thus obtained as white needles (mp 126—127°C).

Found: C, 66.48; H, 6.26%. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83%.

IR: 3400 (ν OH), 1745 (ν C=O, ester), 1715 (ν C=O, ketone), 750, 700 cm^{-1} (phenyl).