radioactivity showed 47.2 mc. (51.5%) total radioactivity in 670 mg. of L-xylose-5-*t*. The supernatant contained an additional 28.2% of radioactivity.

Acknowledgment.—The authors wish to express their appreciation to Dr. A. F. Abt for his encouragement during this work.

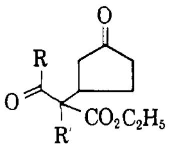
Steroidal Hormone Relatives. IX. Derivatives of Cyclopentanone[1]

J. H. Burckhalter and Bruce A. Brown

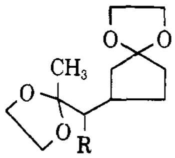
Laboratories of Pharmaceutical Chemistry, The University of Michigan College of Pharmacy, Ann Arbor, Michigan, and University of Rhode Island College of Pharmacy, Kingston, Rhode Island

Received August 1, 1963
Revised January 5, 1965

Ethyl α-(3-oxocyclopentyl)acetoacetate (I) has been made and used in a synthetic approach to steroids.[2] The related ethyl 3-oxocyclopentylmalonate (III) has been made for another purpose.[3] Preparative studies involving several compounds based upon I and III and designed as steroid intermediates constitute the subject matter of the present report.



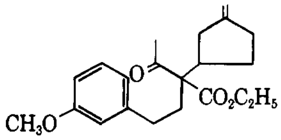
I, R = CH_3; R' = H
II, R = C_6H_5; R' = H
III, R = OC_2H_5; R' = H
IV, R = OC_2H_5; R' = C_2H_5
V, R = OC_2H_5; R' = C_4H_9
VI, R = OC_2H_5; R' = $C_6H_5CH_2$



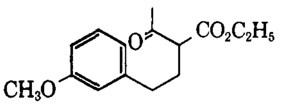
VII, R = $CO_2C_2H_5$
VIII, R = CH_2OH
IX, R = $CONHC_6H_5$

In seeking avenues to 6-aza steroids, the anilide IX was prepared by a Bodroux-type reaction but the yield was too small to encourage further synthesis. In model experiments, the ethylene ketal X of ethyl acetoacetanilide was prepared (see Experimental part), and the ketal of benzyl acetoacetate was converted to acetoacetanilide (XI). However, these procedures failed when applied to the synthesis of anilide IX from intermediates such as VII.

In an attempt to obtain XII as a possible estrone precursor, I was treated with potassium *t*-butoxide and *m*-methoxyphenethyl bromide.[4] However, isolation from the reaction mixture of starting bromide, ethyl acetoacetate, and ethyl 4-(*m*-methoxyphenyl)-2-acetobutyrate (XIII) indicated that a Michael retrogression[5] had occurred and that the anion of ethyl acetoacetate formed in the retrogression was alkylated by the *m*-methoxyphenylethyl bromide present to give XIII. XIII and its semicarbazone proved to be identical with the previously described compounds.[6]



XII



XIII

Experimental

General Procedure for the Michael Addition of Esters and 2-Cyclopentenone.—A pea of sodium was allowed to dissolve in 5 ml. of ethanol. To the solution was added 0.2 mole of the ester. The solution was stirred occasionally for 30 min. and then 0.1 mole of 2-cyclopentenone[7] was added. It was necessary to cool the reaction flask in cold water for 15 min. After 12 hr. the reaction mixture was dissolved in ether and extracted with 10 ml. of 10% acetic acid. The ethereal layer was distilled. When ethyl butylmalonate was employed, it was necessary to eliminate ethanol from the reaction and to replace the sodium with sodamide to accomplish the addition.

Ethyl α-(3-oxocyclopentyl)benzoylacetate (II) had b.p. 179–182° (0.3 mm.), n^{23}D 1.5306, yield 61%.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.62; H, 6.55.

Ethyl α-ethyl-α-(3-oxocyclopentyl)malonate (IV) had b.p. 120–123° (0.15 mm.), n^{23}D 1.4607, yield 74%.

Anal. Calcd. for $C_{14}H_{22}O_5$: C, 62.22; H, 8.14. Found: C, 62.08; H, 8.08.

Ethyl α-butyl-α-(3-oxocyclopentyl)malonate (V) had b.p. 138–140° (0.2 mm.), n^{23}D 1.4630, yield 67%.

Anal. Calcd. for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78. Found: C, 64.24; H, 8.75.

Ethyl α-benzyl-α-(3-oxocyclopentyl)malonate (VI) had b.p. 180–182° (0.25 mm.), n^{23}D 1.5106, yield 67%.

Anal. Calcd. for $C_{19}H_{24}O_5$: C, 68.67; H, 7.23. Found: C, 68.46; H, 7.12.

Benzyl α-(3-oxocyclopentyl)acetoacetate[8] had b.p. 170–172° (0.2 mm.); n^{27}D 1.5204; yield 56%; ν_{max} 1625, 1360, 1150 cm.$^{-1}$ (liquid film).

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.68; H, 6.57.

General Procedure for the Formation of Ethylene Ketals from the Corresponding Ketones.—In a 200-ml. flask, equipped with a dropping funnel, a Dean–Stark trap which contained magnesium sulfate, and a reflux condenser with a calcium chloride tube attached were placed 0.25 g. of *p*-toluenesulfonic acid monohydrate, 100 ml. of benzene, and 12.1 g. (0.05 mole) of ethyl α-(3-oxocyclopentyl)acetoacetate (I).[2] This solution was brought to reflux and 11.2 g. (0.18 mole) of ethylene glycol was added dropwise. The mixture was refluxed for 48 hr., cooled, extracted with a 10% solution of sodium hydroxide, and then extracted with water. After the solvent was removed from the organic layer, the residue was distilled.

Ethyl α-(3-oxocyclopentyl)acetoacetate bisethylene ketal (VII) had b.p. 133–134° (0.2 mm.); n^{24}D 1.4733; yield 56%; $\nu_{max}^{CHCl_3}$ 3000, 1725, 1210, 1120, 1040 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.87; H, 8.12.

Ethyl α-(3-oxocyclopentyl)acetoacetate monoethylene ketal was prepared from equimolar quantities of ester I[2] and ethylene glycol in 70% yield: b.p. 118–120° (0.14 mm.); n^{22}D 1.4702; ν_{max} 2950, 1725, 1120, 1030 cm.$^{-1}$ (liquid film). Ultraviolet spectrum of the product in dioxane and 0.1 *N* sodium hydroxide showed a peak at 272 mμ (ε 7320) with shoulders at 267 (7060) and 259.3 (3810). The peak is absent in the absence of base. Ethyl acetoacetate in base showed 272.5 mμ (ε 21,900).[9] Evidence suggests the ketal formed at the cyclic ketone.

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.94; H, 7.81. Found: C, 60.70; H, 7.94.

Ethyl 3-oxocyclopentylmalonate ethylene ketal was prepared from ethylene glycol and ethyl 3-oxocyclopentylmalonate (III)[3]

---

[1] This investigation was supported by Research Grant HE-05915 from the National Heart Institute, U. S. Public Health Service.

[2] J. H. Burckhalter and J. A. Durden, *J. Org. Chem.*, **25**, 298 (1960).

[3] J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc.*, **82**, 5235 (1960).

[4] W. E. Bachmann and D. G. Thomas, *ibid.*, **64**, 94 (1942).

[5] E. D. Bergmann, D. Ginsburg, and R. Rappo, *Org. Reactions*, **10**, 187 (1959).

[6] W. S. Rapson and R. Robinson, *J. Chem. Soc.*, 1533 (1935).

[7] The Aldrich Chemical Co., Inc., Milwaukee 10, Wis.

[8] Intermediate benzyl acetoacetate prepared by B. R. Baker, R. E. Schaub, M. V. Querry, and J. H. Williams, *J. Org. Chem.*, **17**, 77 (1952).

[9] F. N. McMillan, *Anal. Chem.*, **28**, 1532 (1956).

in equal molar quantities and isolated in a 81% yield: b.p. 125–126° (0.2 mm.); $n^{23}\text{D}$ 1.4586; $\nu_{\max}^{\text{CHCl}_3}$ 3000, 1640, 1380, 1310, 1210, 1150, 1040 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.69; H, 7.72.

Benzyl acetoacetate ethylene ketal was obtained in 64% yield from equal molar quantities of ethylene glycol and benzyl acetoacetate[8]: b.p. 115–120° (0.2 mm.); $n^{19}\text{D}$ 1.5064; $\nu_{\max}$ 1630, 1180, 1045 cm.$^{-1}$ (liquid film).

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.93; H, 6.69.

4-Hydroxy-3-(3-oxocyclopentyl)-2-butanone Bisethylene Ketal (VIII).—A solution of 15 g. (0.05 mole) of the diketal ester VII in 75 ml. of ether was added dropwise to a stirred suspension of 4 g. (0.1 mole) of lithium aluminum hydride in 200 ml. of ether. The mixture was refluxed for 15 hr., stirred at room temperature for 12 hr., and then cooled in an ice bath. To the cooled mixture was added dropwise 12.5 ml. of water, and the mixture was stirred at room temperature for 12 hr. After filtration of the ether extract through Celite, the filtrate was distilled. The product weighed 12.6 g. (97% yield): b.p. 142–145° (0.1 mm.); $n^{28}\text{D}$ 1.4902; $\nu_{\max}^{\text{CHCl}_3}$ 3040, 2950, 1210, 1125, 1045, 750 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59. Found: C, 60.13; H, 8.51.

α-(3-Oxocyclopentyl)acetoacetanilide Bisethylene Ketal (IX).—To an ice-cold, ethereal solution of ethylmagnesium bromide prepared from 2.4 g. (0.1 g.-atom) of magnesium, 10.9 g. (0.1 mole) of ethyl bromide, and 75 ml. of ether was added dropwise a solution of 9.2 g. (0.1 mole) of aniline in 10 ml. of ether. The mixture was stirred at room temperature for 1 hr.; then a solution of 15 g. (0.5 mole) of diketal ester VII in 25 ml. of ether was added dropwise. The mixture was stirred at room temperature for 1 hr. before being hydrolyzed with 10% ammonium chloride solution. Removal of the solvent from the organic layer left a gummy residue which was repeatedly extracted with petroleum ether (30–40°). The residue yielded 9.5 g. of gummy crystals. After repeated recrystallization from carbon tetrachloride, the material weighed 2.0 g. (11% yield): m.p. 135–136°; $\nu_{\max}^{\text{CHCl}_3}$ 1675, 1600, 1520, 1430, 1040 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.77; H, 7.32; N, 4.14.

Acetoacetanilide Ethylene Ketal (X).—A solution of 10 g. (0.06 mole) of ethyl acetoacetate ethylene ketal[10] and 3.4 g. (0.06 mole) of potassium hydroxide in 140 ml. of ethanol was stirred for 12 hr. The solvent was removed under reduced pressure leaving a white solid. This residue was suspended in 300 ml. of chloroform, and the suspension was cooled in an ice bath. A solution of 6.5 g. (0.06 mole) of ethyl chloroformate in 20 ml. of chloroform was added. After being stirred for 30 min. in an ice bath, the suspension was filtered. The filtrate was again cooled and a solution of 5.6 g. (0.06 mole) of aniline was added. The suspension was stirred for 4 hr. in an ice bath before being allowed to warm to room temperature over a period of 18 hr. The solution was extracted with water, 10% sodium bicarbonate solution, and water. Distillation of the ethereal layer yielded 8.5 g. of starting material and 2.3 g. (16% yield) of the ketal anilide, b.p. 150–155° (0.15 mm.), which solidified on standing, m.p. 72–73° (after recrystallization from cyclohexane).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.39; H, 6.74; N, 6.36.

Conversion of Benzyl Acetoacetate Ethylene Ketal to Acetoacetanilide (XI).—A solution of 9.4 g. (0.04 mole) of benzyl acetoacetate ethylene ketal in 30 ml. of ethanol was hydrogenated under an initial pressure of 50 lb. in the presence of 0.3 g. of 10% palladium on carbon for 48 hr. After filtration the solvent was removed from the filtrate at reduced pressure. The crude product, 5.5 g., was dissolved in 50 ml. of chloroform and cooled in an ice–salt bath. To the solution was added 3.8 g. (0.04 mole) of triethylamine followed 15 min. later by a chloroform solution of 4.1 g. (0.04 mole) of ethyl chloroformate. After the mixture had cooled for 30 min., 4.6 g. (0.05 mole) of aniline was added. The solution was allowed to warm to room temperature over a 12-hr. period and was then extracted with hydrochloric acid solution, potassium bicarbonate solution, and water. The solvent was removed at reduced pressure and the residue on cooling solidified; yield 2.3 g. (32%), m.p. 84–85° (after recrystallization from alcohol). A mixture melting point with an authentic sample of acetoacetanilide was not depressed.

Attempted Alkylation of Ethyl α-(3-Oxocyclopentyl)acetoacetate.—In a nitrogen atmosphere 21.4 g. (0.19 mole) of potassium *t*-butoxide[11] was dissolved in 150 ml. of tetrahydrofuran which had been distilled from lithium aluminum hydride. To this solution was added dropwise 40.5 g. (0.19 mole) of ethyl α-(3-oxocyclopentyl)acetoacetate (I). The dark brown solution was stirred for 2 hr.; then 41.2 g. (0.19 mole) of *m*-methoxyphenylethyl bromide[4] was added dropwise. The mixture was stirred at room temperature for 36 hr. before being filtered. Tetrahydrofuran was removed with an aspirator leaving a residue from which a gummy precipitate was obtained by the addition of ether. This precipitate which contained some inorganic material could not be purified. The ether solution was extracted first with water and then with a 10% solution of hydrochloric acid. Removal of the solvent and distillation of the residue from the organic layer yielded 23.9 g. (0.1 mole) of *m*-methoxyphenylethyl bromide and 3.8 g. (0.014 mole) of ethyl 4-(*m*-methoxyphenyl)-2-acetobutyrate (XIII), b.p. 135–145° (0.4 mm.), lit.[6] b.p. 180° (2 mm.). Compound XIII was converted to the semicarbazone of 5-(*m*-methoxyphenyl)-2-pentanone, m.p. 107–109°, lit.[6] m.p. 109°. The first aqueous extract was acidified and extracted with ether. From distillation of this solution, 2.2 g. (0.02 mole) of ethyl acetoacetate was obtained. When potassium was employed to form the anion of I, a yield of 47% of XIII was obtained.

---

[10] E. J. Salmi, *Ber.*, **71**, 1803 (1938).

[11] A special alcohol free potassium *t*-butoxide from M. S. A. Research Corp., Callery, Pa.

1(9)-Octal-2,7-dione

James A. Marshall and Niels H. Andersen[1]

Department of Chemistry, Northwestern University, Evanston, Illinois

Received November 4, 1964

In connection with synthetic studies currently underway in our laboratory, we required 1(9)-octal-2,7-dione (**8**). A direct route to this dione through Birch reduction[2] of 2,7-dimethoxynaphthalene (**1**) followed by hydrolysis of the anticipated bisenol ether **4** seemed feasible. However, shortly after conception of this plan, a report appeared which described the reduction of **1** with lithium in ammonia giving only hydrogenolysis products identified as 6-methoxy-1,2,3,4-tetrahydronaphthalene (**2**) and 2-methoxy-1,4,5,6,7,8-hexahydronaphthalene (**3**).[3] None of the expected product, 2,7-dimethoxy-1,4,5,8-tetrahydronaphthalene, was found.[3] Therefore, investigation of the Birch reduction of 2,7-dimethoxynaphthalene appeared prerequisite to our future studies. The present paper describes the successful reduction of **1** to the bisenol ether **4** and reveals some properties of the vinylogous β-diketone **8** obtained *via* hydrolysis of **4**.

Addition of a 17-fold excess of lithium to a solution of 2,7-dimethoxynaphthalene (**1**) in ammonia–ether–ethanol gave 2,7-dimethoxy-1,4,5,8-tetrahydronaphthalene (**4**), m.p. 64–66.5°, in 38% yield. Reduction of **1** in the identical manner using potassium afforded **4**, m.p. 68.5–69.5°, in 72% yield. When the excess of lithium was decreased to 8-fold, the yield of enol ether **4**, m.p. 66.5–69°, increased to 76%, whereas this material was obtained in 82% yield when the same excess of potassium was employed as the reducing agent under identical reaction conditions. The struc-

---

[1] National Science Foundation Predoctoral Fellow, 1964–1965.

[2] A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950); A. J. Birch and H. Smith, *ibid.*, **12**, 17 (1958).

[3] B. Weinstein and A. H. Fenselau, *J. Org. Chem.*, **29**, 2102 (1964).