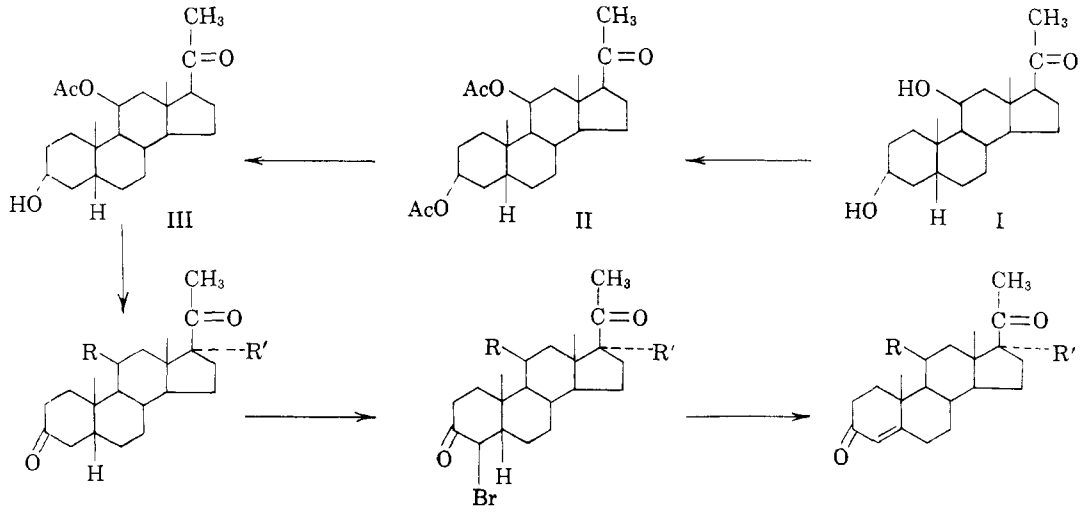

IV, R = OH; R′ = H
V, R = R′ = OH
VI, R = OCHO; R′ = H
VII, R = $OCOCH_3$; R′ = H
VIII, R = R′ = OCHO
IX, R = R′ = $OCOCH_3$

X, R = OCHO; R′ = H
XI, R = $OCOCH_3$; R′ = H
XII, R = R′ = OCHO
XIII, R = R′ = $OCOCH_3$

XIV, R = OCHO; R′ = H
XV, R = $OCOCH_3$; R′ = H
XVI, R = $OCOCH_3$; R′ = OH
XVII, R = $OCOCH_3$; R′ = $OCOC_5H_{11}$
XVIII, R = $OCOCH_3$; R′ = OCHO
XIX, R = R′ = OCHO
XX, R = R′ = $OCOCH_3$

room temperature for 20 hr. Water was added and the mixture extracted with methylene chloride. The organic extracts were washed with dilute sodium hydroxide and water, dried and evaporated to a residue. Crystallization from ether-hexane gave 270 mg., m.p. 215–230°. The analytical sample, crystallized from acetone, melted at 250–255°, $[\alpha]_D$ +92.2° (dioxane), λ_{max}^{MeOH} 240 mμ (ε 16,000).

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.40; H, 7.78.

11β-Acetoxypregnane-3,20-dione (VII). A mixture of 3.68 g. of 3α,11β-dihydroxypregnane-20-one (I)[6] in 18.5 mg. of acetic acid, 11 ml. of acetic anhydride, and 0.74 g. of *p*-toluenesulfonic acid was allowed to stand at room temperature for 5 hr., then poured into water and extracted with methylene chloride. The organic extracts were washed with water, 5% sodium bicarbonate solution, and water, dried and concentrated to a residue. Crystallization from aqueous methanol gave 2.73 g. of the 3,11-diacetate (II), m.p. 129.5–132.0°. The analytical sample, crystallized from aqueous acetone, melted at 134.0–135.2°, $[\alpha]_D$ +134.1° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.76; H, 8.88.

A mixture of 8.36 g. of II, 50 ml. of methanol, 8 ml. of water, and 2.05 g. of potassium bicarbonate was refluxed for 2 hr., then neutralized with acetic acid, concentrated under reduced pressure, and extracted with methylene chloride. The organic extract was washed with water, dried, and evaporated to an oil which resisted crystallization. This was dissolved in 80 ml. of acetone and 20 ml. of water and treated with 8 g. of *N*-bromosuccinimide and 2 ml. of concd. hydrochloric acid for 2 hr. at 10°. Sodium sulfite solution was added to destroy excess oxidizing agent, and the acetone removed on the steam bath. The precipitated solid was removed by filtration, dried, and crystallized from ether to give 3.93 g. of VII, m.p. 130–135°, $[\alpha]_D$ +106.4° (dioxane).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.50; H, 9.31.

11β-Acetoxyprogesterone (XV). A solution of 3.74 g. of VII in 5 ml. of methylene chloride and 30 ml. of *tert*-butyl alcohol was brominated at room temperature by the addition of 1.68 g. of bromine; the color was discharged in 2.5 hr. The solution was concentrated under reduced pressure to *ca.* 10 ml., then poured into water. The precipitated solid was removed by filtration and air dried. Crystallization from aqueous acetone gave 2.94 g. of 4-bromide (XI), m.p. 150–157° dec. A solution of 0.50 g. of XI in 40 ml. of *tert*-butyl alcohol and 15 ml. of methylene chloride was treated with 0.28 g. of semicarbazide under a CO_2 atmosphere, and the resulting mixture stirred overnight. It was then concentrated under reduced pressure, and water was added to precipitate 0.50 g. of semicarbazone. This was dissolved in 10 ml. of acetic acid, 2 ml. of water, and 2 ml. of 85% pyruvic acid and allowed to stand at room temperature for 72 hr. The solution was poured into water and extracted with methylene chloride. The organic extracts were washed with dilute sodium bicarbonate solution and water, then evaporated to an oily residue (0.39 g.). This was chromatographed on Florisil and the fractions eluted with 50% benzene–methylene chloride, 100% methylene chloride, and 1% methanol–methylene chloride were combined to give 140 mg. of a resin which resisted crystallization, λ_{max}^{MeOH} 239 mμ (ε15,200).

CHEMICAL RESEARCH AND BIOCHEMISTRY DEPARTMENTS
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Synthesis of 2-Hydroxy(*p*-methoxyphenyl)-bicyclo[3.3.1]nonane-6,9-dione

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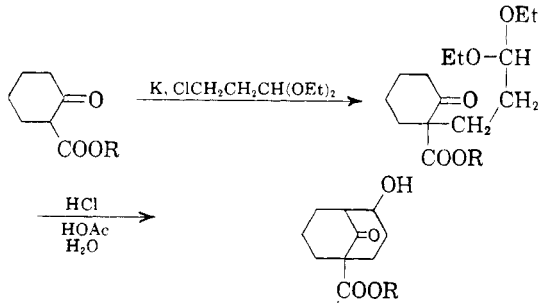
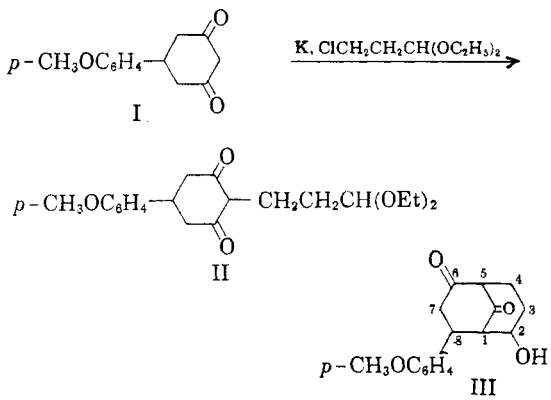
2-Hydroxy-8-(*p*-methoxyphenyl)bicyclo[3.3.1]-nonan-6,9-dione (III) has been synthesized by C-alkylation of 5-(*p*-methoxyphenyl)cyclohexane-dione-1,3 (I) with β-chloropropionaldehyde diethyl acetal in a hydrocarbon solvent and cyclization of the product.

Arthur C. Cope and coworkers[1-3] have prepared derivatives of the bicyclo[3.3.1]nonan-9-one ring system. They have also succeeded in synthesizing substituted cyclooctapolyenes by removing the carbonyl bridge from the bicyclic ketone. In one of their investigations, namely, the preparation of eight-membered ring compounds substituted by carboxyl groups, they prepared in two steps an intermediate 1-carbethoxy-4-hydroxybicyclo[3.3.3]nonan-9-one from the potassium enolate of α-carbethoxycyclohexanone and β-chloropropionaldehyde diethyl acetal.

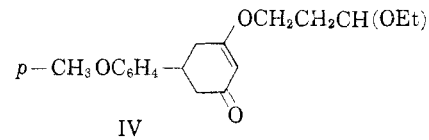


This suggests that 5-(*p*-acetoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 and derivatives[4,5] which have convenient functional groups may be used as intermediates for the synthesis of bicyclic diketones with a *para* hydroxyphenyl radical on position 8, (III). This paper reports the synthesis of a compound assumed to be 2-hydroxy-8-(*p*-methoxyphenyl)bicyclo[3.3.1]nonan-6,9-dione (III) from 5-(*p*-methoxyphenyl)cyclohexanedione-1,3 (I) and β-chloropropionaldehyde diethyl acetal in a hydrocarbon solvent.



The method used was similar to that of Cope and Synerholm[3] with some modifications. The sequence of syntheses involved is given: anisaldehyde → diethyl-*p*-methoxybenzylidenemalonate → 5-(*p*-methoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 → 5-(*p*-methoxyphenyl)-cyclohexanedione-1,3 (I) → 2-(β-propionaldehydediethylacetal)-5-(*p*-methoxyphenyl)-cyclohexanedione-1,3 (II) → 2-hydroxy-8-(*p*-methoxyphenyl)-bicyclo(3.3.1)-nonan-6,9-dione (III). The compound 5-(*p*-methoxyphenyl)cyclohexanedione-1,3 was also prepared by another method[6] as follows: anisylideneacetone → 5-(*p*-methoxyphenyl)-6-carbethoxycyclohexanedione-1,3 → 5-(*p*-methoxyphenyl)-cyclohexanedione-1,3.

In the preparation of (II) from (I) besides the C-alkylation which gives compound (II) the potassium enolate may react with β-chloropropionaldehydeacetal to produce by *O*-alkylation an enolic ether derivative (IV).



IV

Accordingly, the reddish crude material, produced by the alkylation of (I) to form (II), may contain, as a by-product, compound (IV). Owing to structural effects there are differences in the solubilities of (II) and (IV) as well as in the solubility of their respective osazones. Advantage of this was taken in the isolation of the compounds reported in the experimental part.

The material presumed to be (II) which cyclized to form compound (III) is not the *O*-alkylation product (IV), for in the cyclization of (II) to (III), the reagents HCl–HOAc–H_2O used at the boiling temperature of the mixture would favor the hydrolysis of the enolic ether (IV) to give (I) which has a much different % composition than (III). Enolic ethers are known to hydrolyze easily in an acid solution.[7,8]

That the material (II) is not the *O*-alkylation product (IV) is demonstrated by the preparation of a derivative whose nitrogen analysis shows it to be a bisphenylhydrazone and whose alkoxyl analysis shows that the methoxyl group and two alkoxyl groups have been retained. The analysis of the bis-2,4-dinitrophenylhydrazone also supports structure (II).

The only alternate structure for (III) which deserves consideration is one derived from (II) by simple hydrolysis of the acetal to an aldehyde. Such structure is excluded by the fact that (III) gave a negative Schiff's test.

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EXPERIMENTAL

Diethyl p-methoxybenzylidenemalonate. This substance was prepared from anisaldehyde and diethylmalonate using diethylamine as a condensing agent. The method of synthesis is similar to that described by Knoevenagel and Groos.[9] The product had a melting point of 39°, yield 49%.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 65.14; H, 6.38.

5-(p-Methoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3. This compound was prepared from diethyl *p*-methoxybenzylidenemalonate and ethyl acetoacetate using sodium ethoxide as condensing agent. The method used has been described[4,5] previously. The product melted at 157°, yield 60%.

Anal. Calcd. for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12. Found: C, 63.11; H, 6.16.

5-(p-Methoxyphenyl)cyclohexanedione-1,3. This substance was prepared by hydrolysis and decarboxylation of 5-(*p*-methoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 according to the method previously described.[4,5] It dissolves in boiling water and recrystallizes at lower temperatures, m.p. 178°.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 71.54; H, 6.46. Found: C, 71.38; H, 6.34.

This compound was prepared also from 5-(*p*-methoxyphenyl)-4-carbethoxycyclohexanedione-1,3 using similar procedure to that of Lespagnol and Schmitt.[6]

5-(p-Methoxyphenyl)-2-(3,3-diethoxypropyl)cyclohexanedione-1,3. Potassium (2.8 g.) was added to 400 ml. of dry xylene and the mixture heated with stirring in a 1000-ml. three-neck flask equipped with a condenser, dropping funnel, and mercury sealed stirrer. The air in the apparatus was displaced with nitrogen. When the potassium had melted, 18 g. of 5-(*p*-methoxyphenyl)cyclohexanedione-1,3 suspended in 200 ml. of xylene was added over a period of 2 hr. After all the potassium had reacted 11 g. of β-chloropropionaldehyde diethyl acetal[10] was added in 50 ml. of xylene and the mixture refluxed for 16 hr. at an oil bath temperature of 155°. The resulting red product was filtered and washed with ether. From the residue a brownish-orange colored *bisphenylhydrazone* derivative was prepared under alkaline conditions, m.p. 87°.

Anal. Calcd. for $C_{32}H_{40}N_4O_3 \cdot 2H_2O$: N, 9.91. Found: N, 9.92; 10.03.

This experiment was repeated later with some modifications. The crude red material was washed with ether. The residue was dissolved in an alcohol-water mixture and heated with excess phenylhydrazine. The osazone formed was soluble in the alkaline solution. The solution was heated in a water bath to remove some of the alcohol. After cooling, addition of water caused the separation of 4 ml. of viscous red liquid which was kept for the treatment described in the following paragraph. The rest of the cold alkaline water solution was made nearly neutral by the addition of dilute acetic acid. The precipitate formed was washed, filtered, and dried in a desiccator. It had brownish-orange color and melted at 86°. The analytical results indicate that it is the *bisphenylhydrazone derivative of* (II). This compound is identical with the one obtained above.

Anal. Calcd. for $C_{32}H_{40}N_4O_3 \cdot 2H_2O$: N, 9.91. Found: N, 9.82, 10.00. One OCH_3 and $2(OC_2H_5)$, 21.45. Found: 21.24.

The 4 ml. of viscous red liquid was heated on a water bath to evaporate the solvents. A little brownish-orange colored hydrazone of (IV) was obtained; it sintered at 90 and melted at 142°.

Anal. Calcd. for $C_{26}H_{34}O_4N_2 \cdot H_2O$: N, 6.14. Found: N, 6.06.

Two grams of the red material was dissolved in distilled water. The solution was cooled and then neutralized with dilute acetic acid. A white precipitate formed which was filtered and recrystallized from dilute methyl alcohol; m.p. 170° (II).

Anal. Calcd. for $C_{20}H_{28}O_5$: C, 68.40; H, 8.04. Found: C, 68.55; H, 8.40.

Bis-2,4-dinitrophenylhydrazine derivative of (II). The procedure followed is described by Shriner and Fuson.[11] The derivative was purified by recrystallization from ethyl alcohol-ethyl acetate mixture; m.p. 207°–207.5°.

Anal. Calcd. for $C_{32}H_{36}O_{11}N_8 \cdot H_2O$: C, 52.89; H, 4.95; N, 15.42. Found: C, 53.15; H, 4.69; N, 15.17.

8-(p-Methoxyphenyl)-2-hydroxybicyclo[3.3.1]nonan-6,9-dione (III). To a mixture of 16 ml. glacial acetic acid, 4 ml. concentrated HCl and 8 ml. water, 5 g. of 5-(*p*-methoxyphenyl)-2-(3,3-diethoxypropyl)cyclohexanedione-1,3 was added. The mixture was heated until all the material dissolved and then allowed to stand for 30 hr. The crude product was filtered and recrystallized from dilute methyl alcohol. Yield 30%, m.p. 174–175°. It does not give Schiff's test.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 69.79; H, 6.09. Found: C, 69.73, 69.87, 69.72; H, 6.44, 6.32, 6.38.

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2-Chloroadenine and 2-Chloroadenosine[1]

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Biological interest in the potent hypotensive[2] and ulcerigenic[3] activities, and the effects on smooth muscle[4] of 2-chloroadenosine prompted further investigation of its preparation. The nucleoside was originally prepared by partial reduction of 2,8-dichloro-9-β-D-ribofuranosyladenine[5] and, when the chloromercuri method became available,[6] by the direction condensation of the chloromercuri derivative of 2-chloroadenine with 2,3,5-tri-*O*-acetyl-D-ribosyl chloride. At that time 2-chloroadenine was available only through the partial reduction of 2,8-dichloroadenine, followed by separation from admixed adenine and 2,8-dichloroadenine.[6] Considerable difficulty was also

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