[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Synthetic Analogs of Cortical Hormones. III. Hydroxymethyl 9,10-Diacetoxyphenanthryl Ketones[1]

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Reductive acetylation of phenanthrenequinone-2-carboxylic acid and phenanthrenequinone-3-carboxylic acid yielded the corresponding 9,10-diacetoxyphenanthroic acids (I and VI). These were converted, through their acid chlorides and corresponding diazo ketones (III and VIII), to hydroxymethyl 9,10-diacetoxy-2-phenanthryl ketone (IV), hydroxymethyl 9,10-diacetoxy-3-phenanthryl ketone (IX) and the acetates (V and X) of these two ketols. Compounds IV and X produced an eosinopenia of 84.5 and 50%, respectively, following administration of doses of 125 mcg./25 g. adrenalectomized mouse.

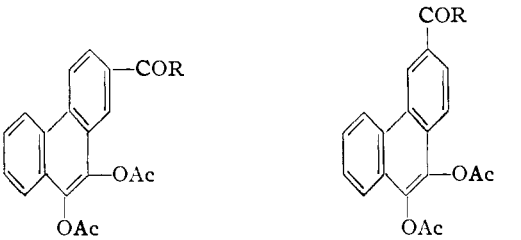
An investigation designed to determine the efficacy of substituting a simple quinonoid or hydroquinonoid system for the oxygenated hydroaromatic nucleus in biologically active corticosteroid ketols has been initiated in this Laboratory.[2] Of some significance to this study is the recent report that introduction of crossed conjugation into ring A of natural corticosteroids results in considerable enhancement of antiarthritic potency.[3,4]

We have already demonstrated that appropriate substituents in the 3-position impart to otherwise inert α,2,5-trihydroxyacetophenone the ability to produce eosinopenia in adrenalectomized mice.[5] In extending our studies to the phenanthrene nucleus, whose bulk more closely approximates that of the steroid ring system, we have synthesized two substances (IV and X) which proved to be more effective in lowering the eosinophil count of adrenalectomized mice than any compound we have reported heretofore.

Methyl 2- and 3-phenanthryl ketone[6] were oxidized in two steps, first to the phenanthroic acids[6,7] and then to the corresponding phenanthrenequinonecarboxylic acids.[8,9] Reductive acetylation of the latter, employing zinc dust with a mixture of acetic acid and acetic anhydride, yielded the respective 9,10-diacetoxyphenanthroic acids I and VI. Although reductive acetylation was found to be incomplete even after prolonged periods of reaction, the unreduced quinonecarboxylic acids were recovered readily through their bisulfite addition products.

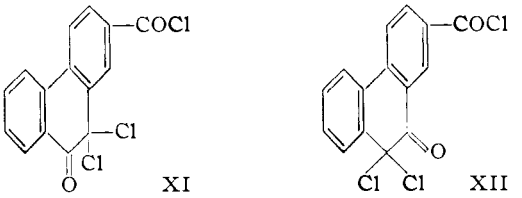
Acids I and VI were converted to diazo ketones III and VIII in high yields by treatment of the corresponding acid chlorides with diazomethane. Conventional treatment of the diazo ketones with dilute sulfuric acid or glacial acetic acid finally provided hydroxymethyl ketones IV and IX, or acetoxymethyl ketones V and X, respectively.

Synthesis of the 9,10-quinonoid analogs of IV, V, IX and X through a similar sequence was prevented by our failure to obtain quinonoid analogs of II and VII. When phenanthrenequinone-2-carboxylic acid was treated with thionyl chloride and pyridine, there was obtained a small quantity of orange solid, m.p. 161–163°. Structure XI or XII is suggested for this product, on the basis of analytical data and the fact that phenanthrenequinone yielded 9,9-dichloro-10-keto-9,10-dihydrophenanthrene under similar reaction conditions.



I, R = OH
II, R = Cl
III, R = CHN_2
IV, R = CH_2OH
V, R = CH_2OAc

VI, R = OH
VII, R = Cl
VIII, R = CHN_2
IX, R = CH_2OH
X, R = CH_2OAc



Hydroxymethyl 9,10-diacetoxy-2-phenanthryl ketone (IV) caused an eosinopenia of 84.5% following administration of doses of 125 mcg./25 g. adrenalectomized mouse (compared to 66% caused by cortisone in doses of 60 mcg./25 g.). The corresponding acetate V appeared to be inactive in doses up to 250 mcg./25 g. mouse.

Hydroxymethyl 9,10-diacetoxy-3-phenanthryl ketone (IX) caused an eosinopenia of 33% following administration of doses of 250 mcg./25 g. mouse (compared to 66% caused by cortisone in doses of 60 mcg./25 g.). The corresponding acetate X caused an eosinopenia of 50% following administration of doses of 125 mcg./25 g. mouse (compared to 66% caused by cortisone acetate in doses of 60 mcg./25 g.).

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Experimental[10]

Methyl 2-and 3-phenanthryl ketone were separated conveniently by adding 300 ml. of ether to the vacuum-distilled

(1) Abstracted from a portion of the Ph.D. dissertation of Upendra K. Pandit.

(2) M. C. Kloetzel, R. P. Dayton and B. Y. Abadir, *J. Org. Chem.*, **20**, 38 (1955).

(3) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955).

(4) A. Nobile, W. Charney, P. L. Perlman, H. L. Herzog, C. C. Payne, M. E. Tully, M. A. Jevnik and E. B. Hershberg, THIS JOURNAL, **77**, 4184 (1955).

(5) M. C. Kloetzel and B. Y. Abadir, *ibid.*, **77**, 3823 (1955).

(6) E. Mosettig and J. van de Kamp, *ibid.*, **52**, 3704 (1930).

(7) E. Mosettig and J. van de Kamp, *ibid.*, **55**, 2995 (1933).

(8) A. Werner and M. Kunz, *Ann.*, **321**, 355 (1902).

(9) A. Werner and A. Ney, *ibid.*, **321**, 356 (1902).

(10) Microanalyses are by Mr. W. J. Schenck; melting points are uncorrected.

mixture of isomers (b.p. 175–178° at 1.5 mm.) prepared[6] from 100 g. of phenanthrene and 55 ml. of acetyl chloride. The crystalline solid which separated when the solution was stirred was recrystallized from benzene to yield 19.5 g. (16%) of pure methyl 2-phenanthryl ketone. When the residue from evaporation of ether and benzene mother liquors was recrystallized from methanol, 72 g. (58%) of pure methyl 3-phenanthryl ketone was obtained.

Reductive Acetylation of Phenanthrenequinonecarboxylic Acids.—A mixture of 4.5 g. of phenanthrenequinone-2-carboxylic acid,[9] 2.5 g. of zinc dust, 25 ml. of glacial acetic acid and 20 ml. of acetic anhydride was heated to reflux for 3 hours and was then poured into cold water. The precipitated solid was washed with water and then thoroughly extracted with hot concentrated sodium bisulfite solution. Recrystallization of the residual solid from 95% ethanol yielded 3.0 g. (50%) of **9,10-diacetoxy-2-phenanthroic acid (I)**, m. p. 243°.

Anal. Calcd. for $C_{19}H_{14}O_6$: C, 67.45; H, 4.17. Found: C, 67.76; H, 4.10.

Phenanthrenequinone-3-carboxylic acid[8] similarly gave **9,10-diacetoxy-3-phenanthroic acid (VI)** in 17% yield, m.p. 274–274.5°.

Anal. Calcd. for $C_{19}H_{14}O_6$: C, 67.45; H, 4.17. Found: C, 67.50; H, 4.17.

9,10-Diacetoxyphenanthroyl Chlorides.—Addition of a drop of pyridine to a mixture of 9,10-diacetoxy-2-phenanthroic acid (2 g.) and thionyl chloride (5 ml.) produced a vigorous reaction. The solid which separated when the mixture was subsequently heated to reflux for 3 hours and finally cooled to 0° was recrystallized from dry chloroform or benzene to yield 1.2 g. (57%) of **9,10-diacetoxy-2-phenanthroyl chloride (II)**, m.p. 232–233°.

Anal. Calcd. for $C_{19}H_{13}O_5Cl$: C, 63.96; H, 3.67; Cl, 9.94. Found: C, 64.18; H, 3.95; Cl, 9.67.

9,10-Diacetoxy-3-phenanthroyl chloride (VII), obtained in 92.5% yield, melted at 218°.

Anal. Calcd. for $C_{19}H_{13}O_5Cl$: C, 63.96; H, 3.67; Cl, 9.94. Found: C, 63.74; H, 3.90; Cl, 9.69.

Preparation of diazomethyl 9,10-diacetoxy-2-phenanthryl ketone (III) was accomplished by adding a cooled chloroform solution of 9,10-diacetoxy-2-phenanthroyl chloride (550 mg.) to an ethereal solution of excess diazomethane at 5°. The solution was allowed to warm spontaneously to room temperature and all solvent was then removed in a current of dry nitrogen. The residual yellow crystalline product melted at 175–176° dec., yield 520 mg. (93%).

Anal. Calcd. for $C_{20}H_{14}N_2O_5$: C, 66.29; H, 3.89; N, 7.73. Found: C, 66.50; H, 4.19; N, 7.73.

Diazomethyl 9,10-diacetoxy-3-phenanthryl ketone (VIII) melted at 164–166° dec., yield 89%.

Anal. Calcd. for $C_{20}H_{14}N_2O_5$: C, 66.29; H, 3.89; N, 7.73. Found: C, 66.39; H, 3.61; N, 7.45.

Hydroxymethyl 9,10-diacetoxy-2-phenanthryl ketone (IV) was produced when diazo ketone III (240 mg.), in dioxane solution, was treated with 15% sulfuric acid. When nitrogen evolution ceased the solution was warmed on a steam-bath for 1.5 hours and then concentrated to 10 ml. Addition of water precipitated the product, which melted at 165–166° after two crystallizations from absolute ethanol; yield 200 mg. (86%).

Anal. Calcd. for $C_{20}H_{16}O_6$: C, 68.17; H, 4.58. Found: C, 67.98; H, 4.59.

Hydroxymethyl 9,10-diacetoxy-3-phenanthryl ketone (IX) was prepared from diazo ketone VIII as described for the 2-isomer, except that the reaction mixture was not heated. After dilution with water the mixture was extracted with ether and the dried ethereal solution was allowed to evaporate. Recrystallization of the residue from ethanol produced the colorless product, m.p. 157–158.5°, in 82.5% yield.

Anal. Calcd. for $C_{20}H_{16}O_6$: C, 68.17; H, 4.58. Found: C, 67.99; H, 4.78.

Acetoxymethyl 9,10-diacetoxy-2-phenanthryl ketone (V) was formed when diazo ketone III (280 mg.) was warmed to 50–60° with glacial acetic acid (5 ml.) until evolution of nitrogen ceased. A few crystals of sodium acetate were added and the mixture was then heated to reflux for 1 hour. Dilution with water precipitated the product which melted at 174° after 2 crystallizations from absolute ethanol; yield 250 mg. (82%).

Anal. Calcd. for $C_{22}H_{18}O_7$: C, 67.00; H, 4.60. Found: C, 67.03; H, 4.42.

Acetoxymethyl 9,10-diacetoxy-3-phenanthryl ketone (X), obtained from VIII in 37% yield, melted at 196–197.5°.

Anal. Calcd. for $C_{22}H_{18}O_7$: C, 67.00; H, 4.60. Found: C, 67.27; H, 4.52.

9,9-Dichloro-10-keto-9,10-dihydrophenanthrene was prepared by heating a mixture of phenanthrenequinone (1 g.), thionyl chloride (5 ml.) and pyridine (3 drops) to reflux for 5 hours and then removing excess thionyl chloride. The residue crystallized upon trituration with petroleum ether (b.p. 63–69°) and yielded 800 mg. (63%) of yellow product, m.p. 168–169°, after recrystallization from chloroform or benzene. Schmidt and Lummp,[11] who prepared this compound from phenanthrenequinone and phosphorus pentachloride, reported the same m.p.

Reaction of Phenanthrenequinone-2-carboxylic Acid with Thionyl Chloride.—Treatment of the acid (5 g.) as described for phenanthrenequinone yielded a solid mixture of products, from which 20 mg. of orange solid (XI or XII), m.p. 161–163°, was isolated after repeated crystallizations from a mixture of chloroform and petroleum ether (b.p. 63–69°). This material decomposed upon standing.

Anal. Calcd. for $C_{15}H_7Cl_3O_2$: Cl, 32.67. Found: Cl, 32.95.

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(11) J. Schmidt and H. Lumpp, *Ber.*, **41**, 4215 (1908).