Studies in Chalcones and Related Compounds Derived from 2-Hydroxy-5-acetaminoacetophenone. III. Synthesis of 6-Amino-2-methylchromone and 6-Aminoflavone by the Claisen Reaction

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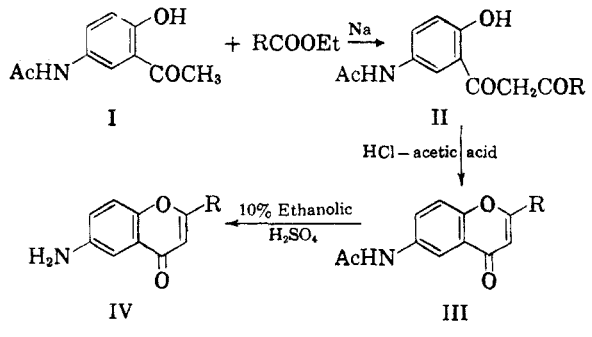
In earlier parts of this series,[1] the authors described several 6-acetaminoflavones obtained by selenium dioxide oxidation of different chalcones obtained from 2-hydroxy-5-acetaminoacetophenone.

This method could not be applied for obtaining the chromones. The Claisen condensation was therefore studied and the syntheses of 6-acetamino- and 6-amino-2-methylchromone and of 6-acetamino- and 6-aminoflavone are described in this paper.

2-Hydroxy-5-acetaminoacetophenone (I) was condensed with ethyl acetate under the conditions of the Claisen reaction to yield the β-diketone, 2-hydroxy-5-acetamino-ω-acetylacetophenone (II: R = CH_3), which on cyclization gave 6-acetamino-2-methylchromone (III: R = CH_3). The latter was then deacetylated to 6-amino-2-methylchromone (IV: R = CH_3). If 2-hydroxy-5-amino-acetophenone hydrochloride was used, 6-amino-2-methylchromone was formed directly; no β-diketone could be isolated.

The Claisen reaction of I with ethyl benzoate gave 2-hydroxy-5-acetamino-ω-benzoylacetophenone (II: R = Ph), which on cyclization with HI gave 6-aminoflavone (IV: R = Ph). When, however, a hydrochloric–acetic acid mixture was used for ring closure, 6-acetaminoflavone (III: R = Ph), identical with that obtained by selenium dioxide oxidation of chalcone, was obtained.



A study of the Kostanecki-Robinson acylation of 2-hydroxy-5-acetaminoacetophenone is in progress.

(1) (a) A. A. Raval and N. M. Shah, *J. Org. Chem.*, **21**, 1408 (1956); (b) *J. Org. Chem.*, **22**, 304 (1957).

EXPERIMENTAL

2-Hydroxy-5-acetamino-ω-acetylacetophenone (II: R = CH_3). A mixture of 2-hydroxy-5-acetaminoacetophenone[2] (1 g.), finely divided metallic sodium (1 g.) and ethyl acetate (25 ml.) was refluxed on a water bath for 6 hr.; the reaction mixture changed from pale green to deep yellow color. It was then cooled and methanol (5 ml.) was added to it to dissolve unreacted sodium.

The mixture was then diluted with ice cold water and acidified with glacial acetic acid. A pale yellow solid separated which was crystallized from dilute acetic acid as pale brown long needles, 0.75 g., m.p. 171–172°.

Anal. Calcd. for $C_{12}H_{13}NO_4$: N, 5.95. Found: N, 6.10.

The compound is soluble in dilute alkali with the formation of a red color. It dissolves readily in ethanol, acetic acid, ethyl acetate, and methanol. It gives a red color with ethanolic ferric chloride.

6-Acetamino-2-methylchromone (III: R = CH_3). To 2-hydroxy-5-acetamino-ω-acetylacetophenone (0.5 g.) dissolved in glacial acetic acid (25 ml.), concentrated hydrochloric acid (2 ml.) was added and the solution was heated on a wire gauze at 110–112° for 15 min., when colorless shining plates started to separate. The mixture was then diluted with water to precipitate a pale yellow solid. It was filtered, washed with dilute alkali (5%), and crystallized from acetic acid as colorless shining plates, 0.4 g., m.p. 270–271°.

Anal. Calcd. for $C_{12}H_{11}NO_3$: N, 6.45. Found: N, 6.36.

The compound is soluble in acetic acid and benzene, but less soluble in ethanol and ethyl acetate. It is insoluble in dilute alkali as well as dilute mineral acids. It does not give an ethanolic ferric chloride color test.

The *diacetyl derivative*, prepared by the acetic anhydride–sodium acetate method, crystallized from ethanol in the form of colorless shining needles, m.p. 278–279°.

Anal. Calcd. for $C_{14}H_{13}NO_4$: N, 5.40. Found: N, 5.26.

6-Amino-2-methylchromone (IV: R = CH_3). (*a*) 6-Acetamino-2-methylchromone (0.2 g.) in ethanol (25 ml.) was treated with dilute sulfuric acid (10%; 30 ml.) to slight turbidity, which was removed by adding more ethanol (20 ml.). The clear solution was refluxed on a water bath for 5 hr. On removal of ethanol, a clear solution was obtained, which on treatment with ammonia gave a brown solid. It was collected and crystallized from ethanol from which the compound separated in the form of golden yellow shining needles, turning brown after 260° and melting at 275°.

Anal. Calcd. for $C_{10}H_9NO_2$: N, 8.00. Found: N, 7.80.

(*b*) A mixture of 2-hydroxy-5-aminoacetophenone hydrochloride (0.5 g.), finely divided sodium metal (0.5 g.), and ethyl acetate (15 ml.) was refluxed on a water bath for 6 hr. as before. On working it up similarly, a yellowish brown solid separated, which was collected. It crystallized from ethanol, separating as golden yellow shining needles, turning brown after 260° and melting at 275°. The yield was 0.2 g.

The product is insoluble in dilute alkali, but dissolves readily in dilute mineral acids. It is also soluble in common organic solvents. It does not give an ethanolic ferric chloride color test.

The *diacetyl derivative*, prepared by the acetic anhydride–sodium acetate method, was identical with the diacetyl derivative described earlier.

2-Hydroxy-5-acetamino-ω-benzoylacetophenone (II: R = Ph). 2-Hydroxy-5-acetaminoacetophenone (1 g.), finely divided sodium metal (1 g.), and ethyl benzoate (20 ml.) were refluxed on an oil bath at 180–200° for 6 hr. The cold reaction mixture, washed as before and acidified with acetic acid, was then subjected to steam distillation; a yellow solution was obtained. It was extracted with ether, and the ethereal extract dried with anhydrous calcium chloride. After removal of ether, the solid obtained was twice crys-

(2) F. Kunckell, Ber., **34**, 125 (1901); Julia and Baillarge, *Bull. soc. chim. France*, 639 (1952); *Chem. Abstr.*, **47**, 3815 (1953) [*cf.* ref. 1a.]

tallized from ethanol to give 0.8 g. of pale yellow needles, m.p. 117–118°.

Anal. Calcd. for $C_{17}H_{15}NO_4$: N, 4.71. Found: N, 4.58.

It is soluble in ethanol, acetic acid, ethyl acetate, and acetone. It gives a reddish brown color with an ethanolic ferric chloride. It is soluble in dilute alkali, but insoluble in dilute mineral acids.

6-Acetamino-flavone (III: R = Ph). 2-Hydroxy-5-acetamino-ω-benzoylacetophenone (0.5 g.) in a mixture of acetic acid (15 ml.) and concentrated hydrochloric acid (3 ml.) was heated at 118–120° for 0.5 hr. On diluting with ice cold water, a brown solid separated; it was collected, washed with dilute alkali (5%) and crystallized from ethanol to give yellowish brown needles, m.p. 174°; the mixed melting point with an authentic sample was undepressed.

The *diacetyl derivative* prepared by the acetic anhydride–pyridine method, crystallized from ethanol in form of brown granules, m.p. 256–258°, mixed melting point with an authentic sample remaining undepressed.

6-Aminoflavone (IV: R = Ph). 2-Hydroxy-5-acetamino-ω-benzoylacetophenone (0.5 g.) and concentrated hydriodic acid (10 ml.) were refluxed on an oil bath at 140° for 3 hr. The reaction mixture was poured into ice cold water containing sodium bisulfite. The clear solution on treatment with ammonia gave a pale brown solid; it was collected and washed with dilute alkali and crystallized from ethanol to give brown needles, m.p. 192°, mixed melting point with an authentic sample remaining undepressed.

The *diacetyl derivative*, prepared as before, crystallized from ethanol in form of brown granules, m.p. 256–258°; the mixed melting point with the sample obtained earlier was undepressed.

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9,10-Dimethyl-3,4-benzpyrene[1,2]

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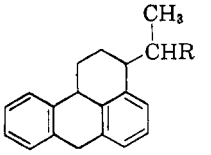
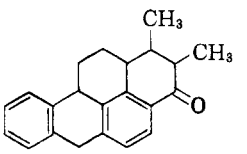
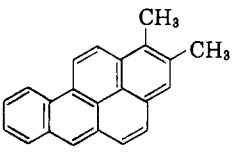
The synthesis of 9,10-dimethyl-3,4-benzpyrene (IV) has been accomplished *via* α-(1,2,3,11b-tetrahydro-7*H*-*meso*-benzanthrenyl-3)propionic acid (I), an intermediate available from previously reported research.[4] The Wilds modification of the Arndt-Eistert synthesis with diazoethane[5] converted α-(1,2,3,11b-tetrahydro-7*H*-*meso*-benzanthrenyl-3)propionyl chloride to α-methyl-β-(1,2,3,-11b-tetrahydro-7*H*-*meso*-benzanthrenyl-3)butyric acid (II) in 80% yield. Cyclization of II with anhydrous hydrogen fluoride produced 8-keto-9,10-dimethyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (III). Reduction of the ketone III with aluminum isopropoxide in toluene gave a carbinol which was directly dehydrated and dehydrogenated over palladium-charcoal to provide 9,10-dimethyl-3,4-benzpyrene (IV) in 20% yield from III.



I, R = COOH
II, R = CH(CH₃)COOH



III



IV

The acid II, the ketone III, and its *p*-nitrophenylhydrazone were isolated as oily mixtures of diastereoisomers which could not be crystallized. Precedence for this reaction sequence was established by the synthesis of 9-methyl-3,4-benzpyrene described previously.[6]

The hydrocarbon IV formed an unstable purple picrate derivative and gave an ultraviolet absorption spectrum characteristic of 3,4-benzpyrene. The hydrocarbon has been submitted to Northwestern University Medical School for carcinogenic testing.

EXPERIMENTAL[7]

8-Keto-9,10-dimethyl-1,2,2a,5,8,9,10,10a-octahydro-3,4-benzpyrene (III). This ketone (3.5 g.) was obtained as a viscous yellow oily mixture of isomers from 5.8 g. (0.020 mole) of α-(1,2,3,11b-tetrahydro-7*H*-*meso*-benzanthrenyl-3)propionic acid (I) via the acid II using previously published procedures.[6]

9,10-Dimethyl-3,4-benzpyrene (IV). Reduction of 3.15 g. (0.0104 mole) of the oily ketone III was carried out with 5.0 g. (0.0245 mole) of aluminum isopropoxide and 50 ml. of C.P. toluene. After 50 hr. of intermittent distillation using a Hahn condenser, the distillate gave a negative test with 2,4-dinitrophenylhydrazine reagent. The reaction mixture was worked up in the usual manner[6] and the crude alcohol thus obtained was directly dehydrated and dehydrogenated at 240–345° over 0.5 g. of 10% palladium-charcoal for 1.5 hr. After cooling, the hard cake was dissolved in benzene and the solution was filtered. This solution was chromatographed over alumina to give an initial fraction containing an oil which did not give a darkly colored solution with picric acid. Further elution of the column with benzene yielded fractions containing an orange solid which was decolorized with Norit and crystallized twice from ethyl acetate producing 0.57 g. (11% over-all yield from I) of 9,10-dimethyl-3,4-benzpyrene (IV) as small yellow needles, m.p. 174–175.5°.

(1) From the dissertation presented by Jules L. Adelfang to the graduate faculty of the University of New Mexico in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) This investigation was supported in part by a research grant (C-1595) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(3) Graduate Research Assistant, February 1956 to August 1957.

(4) J. L. Adelfang and G. H. Daub, *J. Am. Chem. Soc.*, **77**, 3297 (1955).

(5) A. L. Wilds and A. L. Meader, *J. Org. Chem.*, **13**, 763 (1948).

(6) J. L. Adelfang and G. H. Daub, *J. Am. Chem. Soc.*, **79**, 1751 (1957).

(7) All melting points are uncorrected.