tion, and washed with cold water and then acetone; m.p. 192–195° (dec.). An additional 0.4 g. was obtained from the mother liquor: yield, 78%. A mixed m.p. determination with 3,4-dihydro-3-cyclohexyl-6,8-dimethyl-1,3,2H-benzoxazine hydrochloride showed no depression.

**Treatment of 2,6-Dimethylol-4-methylphenol with Benzylamine.**—A solution containing 3.36 g. of 2,6-dimethylol-4-methylphenol[10] (0.02 mole), 2.14 g. of benzylamine (0.02 mole) and 5 ml. of benzene was heated under reflux for three hours. Upon cooling and filtering 2.4 g. of solid was obtained, which after crystallization from ethanol melted at 131–132°. Admixture of 2,6-dimethylol-4-methylphenol with either the crude or recrystallized product did not result in a depression of the m. p. of the latter products. An additional 0.4 g. of the same material was obtained from the filtrate; recovery, 86%.

(10) This compound (m. p. 132-133°) was prepared by the procedure of Ullman and Brittner, *Ber.*, **42**, 2539 (1909). These authors recorded a m. p. of 135°.

## Summary

1. Reaction of *p*-substituted phenols with formaldehyde and primary aliphatic amines in a molar ratio 1:2:1, respectively, resulted in the formation of a new series of compounds, the 3,4-dihydro-3,6-disubstituted-1,3,2H-benzoxazines.

2. An alternate synthesis for the above compounds involving condensation of formaldehyde with *o*-alkylaminomethylphenols was reported.

SALT LAKE CITY, UTAH RECEIVED OCTOBER 1, 1948

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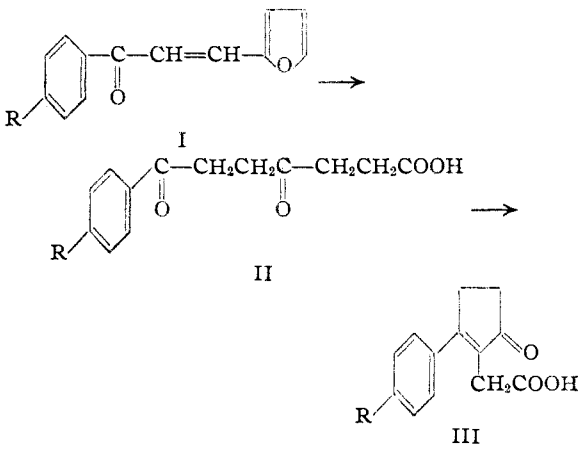
[CONTRIBUTION FROM THE CHARLOTTE DRAKE CARDEZA FOUNDATION, JEFFERSON MEDICAL COLLEGE]

# Some Aryl Substituted Cyclopentenones: A New Synthesis of the Cyclopentenophenanthrene Structure

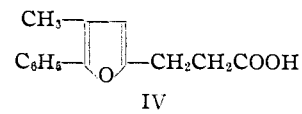
BY D. L. TURNER

The 3-(β-naphthyl)-2-cyclopenten-1-one-2-acetic acid of Robinson[1] has been found to produce myeloid hyperplasia when injected into guinea-pigs in large doses (100 mg.).[2] This observation led us to prepare a series of similar compounds for biological testing.

The desired compounds were made by the general methods of Robinson, and Kehrer and Igler,[3] from the furfurylidene ketones I (Table I) by way of the phenacyl levulinic acids II (Table II). The cyclopentenones III are formed by the alkaline catalyzed ring closure of the diketo-acids (Table III).




Anomalous behavior was shown by furfurylidene propiophenone; on acid hydrolysis, this substance took up the elements of one molecule of water only, and the product contained no carbonyl group. This substance is evidently 3-methyl-2-phenylfuran-5-propionic acid IV; its

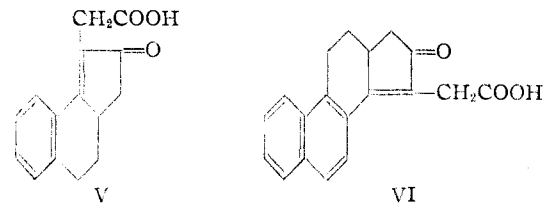



IV

absorption spectrum coincides almost exactly with that of 2-phenylfuran-5-propionic acid[4a] (Fig. 1). Robinson[1] has suggested that an intermediate naphthylfuranpropionic acid was formed in the hydrolysis of furfurylidene-2-acetylnaphthalene.

A similar furan had been isolated previously by Blicke[4b] from the hydrolysis of furfurylideneacetophenone.

The present work provides an easy preparation for the ring systems V and VI, available from α-tetralone and 1-keto-1,2,3,4-tetrahydrophenanthrene, respectively. Similar compounds, lacking




V VI

the acetic acid side-chains, have been made by Wilds,[5,6] who has studed their absorption spectra.[7] The absorption spectrum of the methyl ester of VI was found to be almost identical with that of Wilds' analogous substance (Fig. 2); slight discrepancies were found at low wave lengths where carboxyl group absorption might be expected to make a difference.

(1) Robinson, *J. Chem. Soc.*, 1390 (1938).
(2) Turner and Miller, unpublished.
(3) Kehrer and Igler, *Ber.*, **32**, 1178 (1899); **34**, 1263 (1901).
(4) (a) Robinson and Todd, *J. Chem. Soc.*, 1743 (1939); (b) Blicke, Warzynski, Faust and Gearien, THIS JOURNAL, **66**, 1675 (1944).
(5) Wilds, *ibid.*, **64**, 1421 (1942).
(6) Wilds and Johnson, *ibid.*, **68**, 86 (1946).
(7) Wilds, *et al.*, *ibid.*, **69**, 1985 (1947).

TABLE I

FURFURYLIDENE KETONES

| Substituted acetophenones | Recryst. solvent | Yield, % | M. p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|
| -*p*-ethyl- | *n*-Pentane | 61 | 51–52 | $C_{15}H_{14}O_2$ | 79.6 | 79.7 | 6.2 | 6.2 |
| -*p*-isopropyl- | *n*-Pentane | 75 | 63–64 | $C_{16}H_{16}O_2$ | 80.0 | 80.0 | 6.7 | 6.8 |
| -*p*-*s*-amyl- | | 79 | Liquid[a] | $C_{18}H_{20}O_2$ | 80.6 | 80.7 | 7.5 | 7.5 |
| -*p*-phenyl- | EtOH + MeOH | 81 | 137–139 | $C_{19}H_{14}O_2$ | 83.2 | 82.9 | 5.1 | 5.1 |
| -*m*-nitro- | Ethanol | 68 | 100–101 | $C_{13}H_9NO_4$ | 64.2 | 64.2 | 3.7 | 3.9 |
| *p*-Cyclohexyl- | Ethanol | 95 | 119–120 | $C_{19}H_{20}O_2$ | 81.4 | 81.6 | 7.2 | 7.3 |
| Other ketones | | | | | | | | |
| Propiophenone | *n*-Pentane | 83 | 58–59 | $C_{14}H_{12}O_2$ | 79.2 | 79.2 | 5.7 | 5.8 |
| 4-Methoxy-1-acetylnaphthalene | Methanol | 84 | 80–82 | $C_{18}H_{14}O_3$ | 77.7 | 77.7 | 5.1 | 5.3 |
| 1-Keto-1,2,3,4-tetrahydrophenanthrene | Ethanol | 99 | 119–120 | $C_{19}H_{14}O_2$ | 83.2 | 83.0 | 5.1 | 5.2 |

[a] B. p. 185° (3 mm.); 201° (5 mm.); $n^{25}D$ 1.6731.

TABLE II

ARYL DIKETO ACIDS

| Phenacyl levulinic acids | Method[b] | Recryst. solvent | Yield, % | M. p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|
| *p*-Methyl[a] | K. I. | Benzene | 61 | 112–113 | $C_{14}H_{16}O_4$ | 67.7 | 67.7 | 6.5 | 6.6 |
| *p*-Ethyl- | R. | $CCl_4$ | 60 | 104–105 | $C_{15}H_{18}O_4$ | 68.7 | 68.8 | 6.9 | 7.0 |
| *p*-Isopropyl- | R. | $CCl_4$ | 50 | 85–87 | $C_{16}H_{20}O_4$ | 69.5 | 69.4 | 7.3 | 7.3 |
| *p*-Phenyl- | R. | Acetone | 20 | 184–186 | $C_{19}H_{18}O_4$ | 73.5 | 73.2 | 5.8 | 5.9 |
| *p*-Cyclohexyl- | R. | $CCl_4$ | 32 | 125–127 | $C_{19}H_{24}O_4$ | 72.1 | 71.9 | 7.6 | 7.6 |
| Other acids | | | | | | | | | |
| γ-Keto-δ-(1-keto-1,2,3,4-tetrahydro-2-naphthyl)-valeric acid[c] | K. I. | $CCl_4$ | 16 | 103–104 | $C_{15}H_{16}O_4$ | 69.2 | 69.1 | 6.2 | 6.3 |
| γ-Keto-δ-(1-keto-1,2,3,4-tetrahydro-2-phenanthryl)-valeric acid | R. | Bz-$CHCl_3$ | 53 | 181–182 | $C_{19}H_{18}O_4$ | 73.5 | 73.7 | 5.8 | 5.8 |

[a] From furfurylidene methyl *p*-tolyl ketone. The furfurylidene ketone has been described by Kostanecki and Podrajansky, *Ber.*, **29**, 2248 (1896), and by Maxim and Angelesco, *Bull. soc. chim.*, [4] **51**, 1365 (1932). [b] R. = Robinson method; K. I. = Kehrer and Igler method. [c] From furfurylidene α-tetralone (Peak, Robinson and Walker, *J. Chem. Soc.*, 752 (1936)).

TABLE III

CYCLOPENTENONES

| Substituted 2-cyclopenten-1-one-2-acetic acids | Recryst. solvent | Yield, % | M. p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|
| 3-*p*-Tolyl- | Benzene | 98 | 162–163[d] | $C_{14}H_{14}O_3$ | 73.0 | 73.3 | 6.1 | 6.2 |
| 3-*p*-Ethylphenyl- | Benzene | 100 | 175–176 | $C_{15}H_{16}O_3$ | 73.7 | 73.7 | 6.6 | 6.6 |
| 3-*p*-Isopropylphenyl- | Benzene | 98 | 164–166 | $C_{16}H_{18}O_3$ | 74.4 | 74.5 | 7.0 | 7.0 |
| 3-*p*-*s*-Amylphenyl-[e] | Bz-cyclohex. | | 113–114 | $C_{18}H_{22}O_3$ | 75.5 | 75.6 | 7.7 | 7.9 |
| 3-*p*-Biphenylyl- | Benzene | 50 | 206–207 | $C_{19}H_{16}O_3$ | 78.1 | 77.8 | 5.5 | 5.5 |
| 3-*p*-Cyclohexylphenyl- | Benzene | 75 | 188–189 | $C_{19}H_{22}O_3$ | 76.8 | 76.8 | 7.4 | 7.5 |
| 3-*p*-Methoxyphenyl-[a,b] | Ether | 99 | 132–133 | $C_{14}H_{14}O_4$ | 68.3 | 68.4 | 5.7 | 5.8 |
| 3-*p*-Methoxyphenylmethyl ester[c] | Ether | | 87– 89 | $C_{15}H_{16}O_4$ | 69.2 | 69.3 | 6.2 | 6.2 |
| 3-(4-Methoxy-1-naphthyl)-[f] | Acetone | | 183 | $C_{18}H_{16}O_4$ | 73.0 | 72.9 | 5.4 | 5.5 |
| Fused ring compounds | | | | | | | | |
| 3,3a,4,5-Tetrahydro-2H-benz(*e*)-inden-2-one-1-acetic acid | Benzene | 35 | 177–178 | $C_{15}H_{14}O_3$ | 74.4 | 74.7 | 5.8 | 5.9 |
| 11,12,13,17-Tetrahydro-16H-cyclopenta(a)phenanthren-16-one-15-acetic acid | Benzene | 40 | 221–223 | $C_{19}H_{16}O_3$ | 78.1 | 77.9 | 5.5 | 5.7 |
| Methyl ester of preceding[c] | Ethanol | | 127–128 | $C_{20}H_{18}O_3$ | 78.4 | 78.3 | 5.9 | 6.0 |

[a] By hydrolysis of ester. [b] 7-*p*-Methoxyphenyl-4,7-diketoheptanoic acid has been made by Robinson. Furfurylidene *p*-methoxyacetophenone is described by Maxim and Angelesco, *Bull. soc. chim.*, [5] **1**, 1128 (1934), as well as by Robinson.[4] [c] By esterification with diazomethane. [d] M. p. rose from 153–155° after drying *in vacuo* at 100°. [e] Semicarbazone from ethanol, m. p. 204° (dec). *Anal.* Calcd. for $C_{19}H_{25}N_3O_3$: C, 66.4; H, 7.3. Found: C, 66.7; H, 7.5. [f] Semicarbazone from ethanol, m. p. 217° (dec). *Anal.* Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.6; H, 5.4. Found: C, 64.4; H, 5.7.

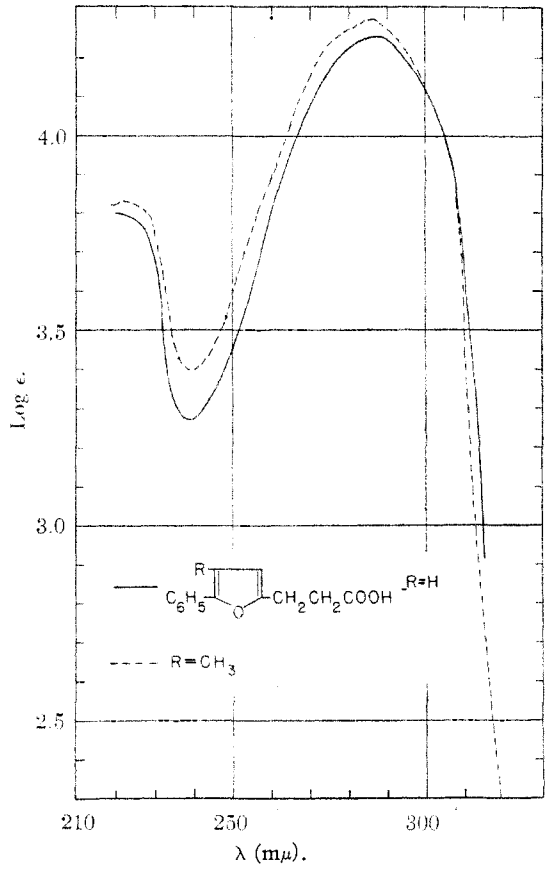



Fig. 1.—Spectra of phenylfurans.

Finally, we describe the preparation of 1-keto-1,-2,3,4,9,10-hexahydrophenanthrene by the method devised by Bachmann, Kushner and Stevenson[8] for the 7-methoxy derivative of this ketone. Since the yield was poor, we did not attempt to convert this ketone to the cyclopentenone. The 7-methoxy group facilitates the two ring closures of this synthetic method. Bachmann and Wendler,[9] and Johnson, Johnson and Petersen[10] have described alternative routes to 1-keto-1,2,3,4,9,10-hexahydrophenanthrene.

This investigation was aided by a grant from the American Cancer Society.

## Experimental[11]

The substituted acetophenones, not commercially available, were made by the general method of "Organic Syntheses."[12] Their properties agreed with those described in the literature.[13] The 1-keto-1,2,3,4-tetrahydrophenanthrene was prepared by the usual methods[14] from β-(1-naphthoyl)-propionic acid. However, the initial acid was made by the method of Lontz,[15] which does not seem to be widely known.

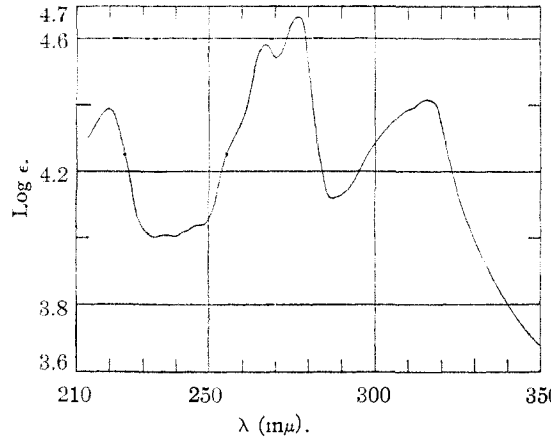



Fig. 2.—Spectrum of methyl 11,12,13,17-tetrahydro-16H-cyclopentaphenanthren-16-one-15-acetate.

**4-Methoxy-1-acetylnaphthalene.**—The methyl ether of α-naphthol (0.5 mole), acetic anhydride (0.5 mole), and iodine (10 g.) were heated together in an oil-bath at 160° for two hours, under a reflux condenser. The mixture was diluted with water and extracted with benzene. The benzene solution was washed with 5% sodium hydroxide, and then with 10% sodium bisulfite solution, then dried and distilled.[16] The product had b.p. 165° (2 mm.). Recrystallization from ether gave 47 g. (53% yield), m.p. 69–71°.[17]

**Furfurylidene Ketones.**—An equimolecular quantity of freshly distilled furfural was added to a solution of 100 g. of ketone in 100 ml. of ethanol. To the mixture was added 10 ml. 45% (by weight) of potassium hydroxide. The quantity of solvent was increased when the ketone was insoluble. The furfurylidene derivatives from *p*-ethyl- and *p*-isopropylacetophenone, and that from propiophenone, were obtained crystalline by diluting the reaction product with water and extracting with chloroform. The chloroform solution was washed with water, dried, and distilled. The residue could then be crystallized from *n*-pentane. Like chalcones, the furfurylidene ketones undergo photochemical alteration on standing.

**Diketo Acids.**—The Robinson[1] method indicated in Table II differs from that of Kehrer and Igler[3] by the addition of acetic acid to the hydrolysis mixture.[18]

**3-Methyl-2-phenylfuran-5-propionic Acid.**—The usual acid hydrolysis method of Robinson applied to furfurylidene propiophenone gave a 10% yield of this material in three extractions. The only other product was the usual residue of black tar. Recrystallized from benzene, the crystalline product from the acid hydrolysis mixture had m.p. 139–140°. Treated with boiling potassium hydroxide solution, under the conditions[1] for the preparation of the cyclopentenones (Table III), it was unaltered. It did not react with reagents for the carbonyl group.

*Anal.* Calcd. for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1. Found: C, 72.7; H, 6.3.

**Cyclopentenones.**—These were obtained by the method of Robinson,[1] except as noted below.

(8) Bachmann, Kushner and Stevenson, THIS JOURNAL, **64**, 974 (1942).

(9) Bachmann and Wendler, *ibid.*, **68**, 2580 (1946).

(10) Johnson, Johnson and Petersen, *ibid.*, **68**, 1926 (1946).

(11) The m. p. determinations of this paper were taken with Anschütz thermometers, but are otherwise uncorrected.

(12) Blatt (ed.), "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 3.

(13) *p-s*-Amylacetophenone is described by Hennion, THIS JOURNAL, **64**, 2421 (1942); *p*-cyclohexylacetophenone by Mayes and Turner, *J. Chem. Soc.*, 500 (1929). The others can be found in "Beilstein."

(14) Drake and McVey, *J. Org. Chem.*, **4**, 464 (1939).

(15) Lontz, U. S. Patent 2,339,789 (1944).

(16) This preparation is based on a method described by Kosak and Hartough, THIS JOURNAL, **68**, 2639 (1946), and by Chodroff and Klein, *ibid.*, **70**, 1647 (1948).

(17) Gattermann, Erhardt and Maisch, *Ber.*, **23**, 1199 (1890), give m. p. 71-72°.

(18) The yields reported in Table II might be increased by more complete extraction of the diketo-acids.

**3-*p*-*s*-Amylphenyl-2-cyclopenten-1-one-2-acetic Acid.**—To 50 g. of furfurylidene *p*-*s*-amylacetophenone was added 500 ml. of ethanol and 125 ml. of concentrated hydrochloric acid. After refluxing for ten hours, the solvent was distilled and the residual tar was refluxed with a mixture of 250 ml. of acetic acid, 250 ml. of concentrated hydrochloric acid and 500 ml. of water for two hours. The mixture was cooled, diluted with water, and extracted with ether. The ethereal solution was washed with water until the acetic acid was removed, and then the acidic hydrolysis products were removed with 9% sodium bicarbonate solution. The alkaline solution was acidified and extracted with carbon tetrachloride. Evaporation of the solvent gave 31 g. of oil. This was heated to 95° for one hour in 3 liters of 2% potassium hydroxide solution. The solution was treated with "Nuchar," filtered, and acidified. The resulting oil was taken up in ether; evaporation of the ether and rubbing the residue in carbon tetrachloride–*n*-pentane induced crystallization. The crystalline product weighed 12 g.

**3-(4-Methoxy-1-naphthyl)-2-cyclopenten-1-one-2-acetic Acid.**—The diketo-acid intermediate was again an oil, obtained as described for the preceding preparation. This oil (from 140 g. of furfurylidene ketone) was remethylated by dissolving in a slight excess of 10% sodium hydroxide and stirring with dimethyl sulfate for three hours without heating. The product was diluted with 1500 ml. water and 100 ml. 45% potassium hydroxide was added; it was boiled for one hour, treated with "Nuchar" and acidified. The acid precipitated as an oil, which crystallized on standing overnight; yield 21 g. The yield in this preparation, and in the preceding, could be increased by repeating the original acid extraction from the hydrolysis of the furfurylidene ketones several times.

**γ-(2,2-Dicarboxy-1,2,3,4-tetrahydronaphthylidene-1)-butyric Acid.**—Ethyl β-phenethylmalonate[19,20] (b. p. 148–150° (3 mm.)) was converted to the sodium derivative and caused to react with the acid chloride of ethyl hydrogen glutarate as described by Bachmann, Kushner and Stevenson[8] in their preparation of ethyl 5-keto-6,6-dicarbethoxy-8-*m*-anisyloctanoate, quantities being altered in accordance with the difference in molecular weights. Volatile material was removed from the product up to 180° (2–3 mm.). The residue was not distilled but was used in crude form for cyclization.[21] To 7 g. residue was added 50 ml. commercial 66° Be. sulfuric acid, previously cooled to 0°. The temperature rose to 7°. The mixture was then allowed to stand in a refrigerator at −22° for twenty hours. It was poured into ice-water and extracted with ether. The ether was dried and distilled. The residue was refluxed for three hours with 30 ml. of 45% aqueous potassium hydroxide and 20 ml. methanol. The methanol was distilled and the residue was diluted with water, and extracted with ether. Evaporation of the ether gave an oil that crystallized on adding chloroform. The crystalline product, 710 mg., was recrystallized from chloroform; the substance decomposed at 182–183°.

*Anal.* Calcd. for $C_{16}H_{16}O_6$: C, 63.2; H, 5.3. Found: C, 63.4; H, 5.2.

This ring closure could not be effected with 100% phosphoric acid.[8]

Bachmann's procedure for converting γ-(6-methoxy-2,2-dicarboxy-1,2,3,4-tetrahydronaphthylidene-1)-butyric acid to 7-methoxy-1-keto-1,2,3,4,9,10-hexahydrophenanthrene,[8] involving refluxing for one hour with hydrochloric acid in acetic acid, was applied to 2.6 g. of the above tricarboxylic acid. Instead of the expected hexahydrophenanthrene ketone, there was obtained only a trace of neutral material and 1.0 g. of an acid, m.p. 87–88°, which is evidently the γ-(3,4-dihydro-1-naphthyl)-butyric acid of Bachmann and Wendler.[9] The acid was crystallized from dilute acetic acid and then from carbon tetrachloride.

*Anal.* Calcd. for $C_{14}H_{16}O_2$: C, 77.7; H, 7.5. Found: C, 77.5; H, 7.3.

This monocarboxylic acid (0.8 g.) was converted to 1-keto-1,2,3,4,9,10-hexahydrophenanthrene by the method used by Stork[22] for the corresponding methoxy acid. The semicarbazone, previously described by Johnson, Johnson and Petersen,[10] was obtained in a yield of 0.5 g. It decomposed at 253–254°.[23]

*Anal.* Calcd. for $C_{15}H_{17}N_3O$: C, 70.6; H, 6.7. Found: C, 70.5; H, 6.7.

**Absorption Spectra.**—Measurements were made with a Beckmann quartz spectrophotometer. Absolute ethanol was used as solvent for the cyclopentaphenanthrene compound and 95% ethanol for the furans. The three substances were crystallized three times from ether–pentane to remove possible benzene of crystallization; they were dried *in vacuo*. Measurements were taken at intervals of 1 mμ about the maxima and minima, and at intervals of 2 mμ at other places. The results are shown in Table IV and in Figs. 1 and 2.

TABLE IV

ULTRAVIOLET ABSORPTION SPECTRA

| Compound | Maxima λ (mμ) | Maxima log ε | Minima λ (mμ) | Minima log ε |
|---|---|---|---|---|
| Methyl-11,12,13,17-tetrahydro- | 220 | 4.39 | 228 | 4.08 |
| 16H-cyclopentaphenanthren- | 236 | 4.00 | | |
| 16-one-15-acetate | 267 | 4.58 | | |
| | 277 | 4.66 | 287 | 4.12 |
| | 316 | 4.41 | | |
| 11,12,13,17-Tetrahydro-16H- | 218.5 | 4.32 | 228 | 4.03 |
| cyclopentaphenanthren-16- | 266 | 4.56 | | |
| one (data of Wilds[7] for major | 276 | 4.63 | | |
| maxima and minima) | 316 | 4.47 | 267 | 4.12 |
| 5-Propionic acids- | | | | |
| 2-phenyl-3-methylfuran- | 287 | 4.30 | 239 | 3.40 |
| 2-Phenylfuran- | 287 | 4.26 | 238 | 3.27 |

**Biological Activity.**—Most of the substances described here were tested by Dr. F. R. Miller of this Laboratory and found to be inactive. The 3-*p*-tolyl-cyclopentenone-acetic acid is the only one that produces myeloid hyperplasia comparable to that produced by myelokentric acid.[24] This work will be reported elsewhere.

## Summary

1. A series of 3-substituted 2-cyclopenten-1-2-acetic acids has been prepared by the method of Robinson.

2. The method has been extended to cyclic ketones. This provides an easy synthesis of 11,12,13,17-tetrahydro-16H-cyclopentaphenanthren-16-one-15-acetic acid.

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(19) Fischer and Schmitz, *Ber.*, **39**, 2208 (1906).

(20) Rupe and Wolfsleben, *Ann.*, **395**, 111 (1913).

(21) *Cf.* Wilds and Johnson, THIS JOURNAL, **70**, 1166 (1948).

(22) Stork, *ibid.*, **69**, 2936 (1947).

(23) Johnson, Johnson and Petersen give m. p. 257–258° (dec.).

(24) "Approaches to Tumor Chemotherapy," A. A. A. S., Washington, D. C., 1947, pp. 64–76.