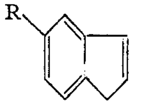
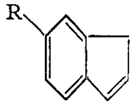
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Tautomerism of Indene[1]

BY C. F. KOELSCH AND ROBERT A. SCHEIDERBAUER

According to modern concepts of tautomerism, the nonbenzenoid double bond of indene should occupy a fixed position, but in the most recent experimental study[2] of the structure of indene it was concluded that the hydrocarbon contained a "mobile system," I $\rightleftarrows$ II.[3]





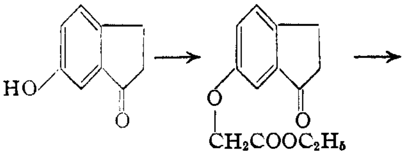
I, R = H
III, R = OCH_3
V, R = OCH_2COOH

II, R = H
IV, R = OCH_3
VI, R = OCH_2COOH

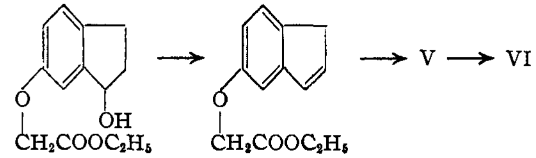
Close examination of the evidence on which this conclusion was based, however, shows that it can be interpreted in a different way, and that it may even be inconsistent with the conclusion drawn. The "identity" of the oily products ("III $\rightleftarrows$ IV") formed in the pyrolysis of 5-methoxy- and of 6-methoxyindanylamine was proved in part by the isolation of one and the same dibromide from the bromination products of either substance. But the yields of this dibromide were not stated. If the yields were less than quantitative, the evidence is of no value, for each pyrolysis product might then consist of a static mixture of III and IV. If the yields were substantially quantitative, the mobile system III $\rightleftarrows$ IV could not be involved, for the addition of bromine, a "fission test," should yield a mixture of dibromides. Similar criticisms apply to the other data used to prove the identity of III with IV.

It has now been possible to prepare two solid indenes (V and VI) easily shown to be not identical. The isomerism of these two substances is explicable only if a definite position is assigned to the non-benzenoid double bond of each indene. Therefore in each of these compounds, and by analogy in indene itself, the non-benzenoid double bond occupies a fixed position. The tautomerism of indene, like that of other compounds showing prototropy, is possible only through the cooperation of a base.

The reactions leading to V and VI are indicated in the following chart.



VII VIII



IX X

Experimental

6-Hydroxyindanone, VII.—Crude 6-nitroindanone[4] (16 g.) washed well with water, was reduced rapidly when its solution in 100 g. of alcohol was shaken with hydrogen in the presence of 50 mg. of Adams platinum black. Crystallization from alcohol gave 6-aminoindanone, m. p. 168–171°, in 47–54% yields (based on un-nitrated hydrindone) in each of ten experiments. The aminoketone sulfate was diazotized, and the resulting deep red solution was decomposed by dropping it into hot 30% sulfuric acid. The yield of pure product (m. p. 151–153°) was best in small scale experiments; for example, 50 g. of amine gave less than 50%, but 25 g. of the amine gave more than 70% of the desired phenol.

Ethyl 1-Ketoindanyl-6-oxyacetate, VIII.—To a solution of 7 g. of sodium in 300 ml. of absolute alcohol were added 48 g. of VII and then 67 g. of ethyl bromoacetate. The mixture was warmed for ninety minutes, then a solution of 2.3 g. of sodium in 50 ml. of alcohol was added, and heating was continued for ten minutes more. Part of the product crystallized on cooling; the rest was obtained by adding water. The keto ester formed colorless flat needles from alcohol, m. p. 111–112°; yield 58 g., 76%.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.7; H, 6.0. Found: C, 66.5; H, 6.3.

When the keto ester was warmed with 10% potassium hydroxide, it dissolved rapidly, giving a dark solution. Acidification precipitated a **polymeric (?) acid,** yellow needles from alcohol (charcoal), m. p. 227–229°.

Anal. Calcd. for $(C_{11}H_{10}O_4)_x$: C, 64.1; H, 4.9. Found: C, 63.8; H, 5.2.

When the keto ester was boiled with 15% sulfuric acid for twenty minutes it dissolved. Cooling the solution gave **1-ketoindanyl-6-oxyacetic acid,** long flat needles from water, m. p. 161.5–162.5°, yield 80%.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.1; H, 4.9. Found: C, 64.0; H, 5.0.

The phenylhydrazone of VIII formed yellow needles from alcohol, m. p. 113–115°, that rapidly became brown in air and could not be dried satisfactorily for analysis. It was reduced in alcohol at 140° in the presence of Raney nickel, and the oily product was subjected to steam distillation. Aniline volatilized (identification, acetanilide, 1.035 g., 44%), and from the residue there was obtained 1.36–1.39 g. (39–40%) of **1-aminoindanyl-6-oxyacetic acid,** an amphoteric substance insoluble in organic solvents, but soluble in hot water. It formed colorless needles that sintered at about 225° and decomposed at 269°.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.7; H, 6.3. Found: C, 62.7, 62.8; H, 6.4, 6.5.

Warmed in ethanol while hydrogen chloride was introduced during ninety minutes, the amino acid gave **ethyl 1-aminoindanyl-6-oxyacetate hydrochloride** in 73% yield. The ester-salt separated from alcohol and ether in the form of waxy needles that melted at 171–172°.

Anal. Calcd. for $C_{13}H_{17}NO_3 + HCl + C_2H_5OH$: C, 56.6; H, 7.5. Found: C, 56.5; H, 7.3.

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(1) From the Ph. D. Thesis of Dr. Scheiderbauer, May, 1941.

(2) Ingold and Piggott, *J. Chem. Soc.*, **123**, 1469 (1923).

(3) Such a structure, or something similar to it, is not now as inherently improbable as it would have been ten years ago. See, for example Wawzonek and Laitinen [THIS JOURNAL, **64**, 2367 (1942)]; also compare the formulation of the formazyl group used by Hunter and Roberts [*J. Chem. Soc.*, 820 (1941)].

(4) Ref. 2, p. 1485; the 4-isomer was not removed.

Pyrolysis of the ester salt yielded ammonium chloride but no identifiable organic substance.

The **oxime** of ethyl 1-ketoindanyl-6-oxyacetate was obtained by boiling VIII with hydroxylamine hydrochloride and sodium acetate in alcohol for one hour (yields 90–95%). It crystallized from alcohol in the form of white needles, m. p. 130.5–132°.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.6; H, 6.0. Found: C, 62.1; H, 6.2.

No pure compound could be obtained from the oxime ester when it was hydrogenated in alcohol (platinum black or Raney nickel) or in alcoholic hydrochloric acid (platinum black). Reduction in acetic anhydride (platinum black) proceeded readily, yielding **ethyl 1-acetylaminoindanyl-6-oxyacetate**, white needles from alcohol, m. p. 116–117°. The same compound was obtained from the amino ester hydrochloride previously described by treatment with acetic anhydride and aqueous sodium acetate.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9. Found: C, 64.3, 65.2; H, 7.2, 7.4.

The acetylamino ester gave no identifiable pyrolysis product; 51% of it was recovered unchanged and no other substance was isolated after it had been boiled for five hours with 10% alcoholic sulfuric acid.

1-Hydroxyindanyl-6-oxyacetic Acid.—A solution of 3.2 g. of VIII in 20 ml. of alcohol containing 0.2 g. of Raney nickel was heated for one hour at 105° under hydrogen at 1175 lb. pressure. The catalyst and the solvent were removed, and the resulting oil (IX?), which could not be induced to crystallize, was boiled with 15 ml. of 10% potassium hydroxide until it had dissolved. The product was precipitated with hydrochloric acid and crystallized from acetone. It formed rosets of colorless needles that melted at 82–84°, effervesced and resolidified at 105°, then melted again at 147–150°; yield, 1.9 g., 67%.

Anal. Calcd. for $C_{11}H_{12}O_4 + H_2O$: C, 58.4; H, 6.2. Found: C, 59.0; H, 6.3.

Ethyl Indenyl-5-oxyacetate, X.—A solution of 8 g. of VIII in alcohol was reduced as described in the preceding paragraph, the solvent was removed, and the resulting crude IX was distilled slowly under reduced pressure from a crystal of potassium acid sulfate. The distillate was fractionated, giving the pure ester in yields of 63–78% (five experiments); the compound boiled at 200–205° at 30 mm. and formed colorless crystals from alcohol, m. p. 48–48.5°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.6; H, 6.4. Found: C, 71.4; H, 6.3.

The unsaturated ester reduced potassium permanganate in acetone immediately.

Indenyl-5-oxyacetic Acid, V.—The hydrolysis of X to V could be carried out by means of dilute potassium hydroxide, but the product was always contaminated with the isomeric acid (VI) and polymeric material. Hydrolysis of X with 10% sulfuric acid even in the presence of hydroquinone gave only resinous products. The hydrolysis was best accomplished by boiling X (8.5 g.) with 200 ml. of 2% sodium carbonate for thirty minutes. The product crystallized from ether–ligroin in the form of colorless plates, m. p. 118–119°; yield, 85–89%.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3. Found: C, 69.3; H, 5.5.

Determinations of the molecular weights of V and of VI were considered essential to guard against the possibility that one of these acids was a polymer of the other. Rast determinations in camphor failed because the acids polymerized below the melting point (176°) of the solvent; similar determinations in camphene (m. p. 49°) failed because the acids were nearly insoluble in this substance. The Barger method, involving isothermal balancing of vapor pressures of solutions,[5] gave satisfactory results. The solvent was alcohol, and the reference compound was azobenzene. Nine determinations were made, and these indicated that the molecular weight of V was between 136 and 240; calculated, 190.

When V (0.4 g.) was dissolved in alcohol containing platinum black and then shaken with hydrogen at atmospheric pressure, it absorbed the calculated amount of the gas in two minutes. The resulting **indanyl-5-oxyacetic acid** separated from dilute alcohol in the form of feathery needles, m. p. 154–155°; yield, 0.34 g.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.7; H, 6.3. Found: C, 68.4; H, 6.4.

The saturated acid did not react with potassium permanganate in cold acetone.

Indenyl-6-oxyacetic Acid, VI.—A solution of 1.5 g. of V in 20 ml. of 5% potassium hydroxide was boiled for fifteen minutes, then cooled and acidified. The resulting bright yellow precipitate was crystallized repeatedly from alcohol using charcoal to remove polymeric material. Pure VI formed colorless plates, m. p. 140.5–143°; yield, 0.16 g., 11%.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3; mol. wt., 190. Found: C, 69.3; H, 5.8; mol. wt. (Barger), between 126 and 251.

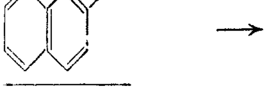
The unsaturated acid decolorized potassium permanganate in cold acetone immediately; a mixture of it with indanyl-5-oxyacetic acid melted at 136–149°.

Before the pair of isomeric indenes described above had been synthesized, several other routes to a similar end were explored. None of these could be followed to a successful conclusion, but because of their general interest, some of them are described briefly in the following paragraphs.

A. Anisaldehyde (109 g.), ethyl acetate (330 ml.), sodium (23 g.) and alcohol (4 ml.) gave[6] ethyl *p*-methoxycinnamate in yields of 58–61%. This ester resisted reduction with hydrogen in the presence of copper chromite. Saponification of 153 g. of the ester yielded 116 g. (88%) of *p*-methoxycinnamic acid, and electrolytic reduction[7] of this furnished *p*-methoxyhydrocinnamic acid in a yield of 90%. Fischer esterification gave 66% of the corresponding ethyl ester, b. p. 158–162° at 22 mm. This ester appeared to condense normally with ethyl oxalate, but only red oils could be obtained when the resulting oxalo compound was treated with sulfuric acid.[8]

p-Methoxyhydrocinnamoyl chloride and aluminum chloride in nitrobenzene gave 6-methoxyindanone in yields of only 3–17% (reported[9] 20%), and when the reaction was carried out in benzene, there was obtained only *β*-(*p*-methoxyphenyl)-propiophenone, m. p. 97°, in yields of 44–59%.

B. The following synthesis yielded an indene of the desired structural type, but the physical properties of the compound were unsuitable for the purpose at hand.



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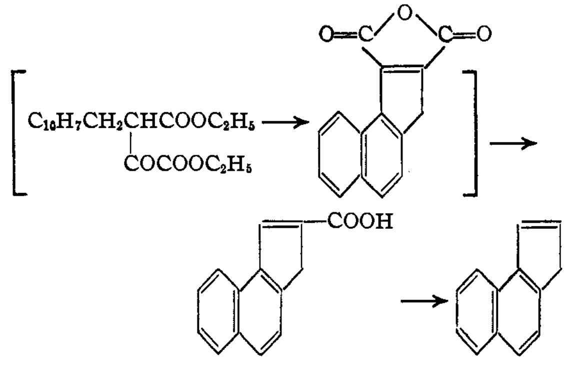
[5] Niederl and Niederl, "Micromethods of Quantitative Organic Elementary Analysis," John Wiley and Sons, Inc., New York, N. Y., 1938, p. 184.

[6] *Cf.* "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 246.

[7] *Ibid.*, page 304.

[8] *Cf.* Bougault, *Compt. rend.*, **159**, 745 (1914); v. Auwers and Möller, *J. prakt. Chem.*, **109**, 124 (1925); Fieser and Hershberg, This Journal, **58**, 2316 (1936); Fieser and Holmes, *ibid.*, p. 2321.

[9] Chakravarti and Swaminathan, *J. Indian Chem. Soc.*, **11**, 101 (1934).



β-(2-Naphthyl)-propionic acid[10] (125 g.) was converted into its ethyl ester (77% yield by Fischer esterification, 95% yield by Thielepape's modification[11]) which gave a crude, oily, base-soluble oxalo derivative[8] in yields of 44–63%. This derivative (35 g.) with 80% sulfuric acid (300 ml.) at 85° for one hour gave an oily product. The crude substance was brought into solution by boiling it with 10% sodium hydroxide for forty-five minutes; acidification precipitated **3-benz[e]indene-2-carboxylic acid.** This substance formed a white powder from acetic acid, m. p. 263–265° with decomposition; yield, 31–40%.

Anal. Calcd. for $C_{14}H_{10}O_2$: C, 80.0; H, 4.8; neut. equiv., 210. Found: C, 80.0; H, 5.2; neut. equiv., 196.

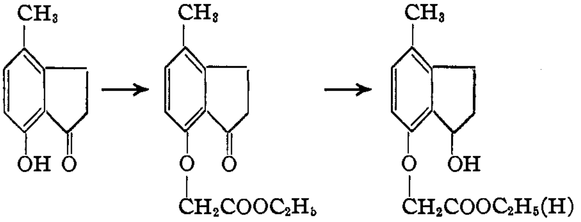
When the acid (4.8 g.) was heated for one hour at 220–240° in quinoline (25 ml.) containing copper acetate (0.2 g.), it was converted into **3-benz[e]indene** in yields of 40–85%. The hydrocarbon formed colorless crystals from ligroin, m. p. 48.5–50°; b. p. 173° at 33 mm.

Anal. Calcd. for $C_{13}H_{10}$: C, 94.0; H, 6.0. Found: C, 93.5; H, 6.0.

The **picrate** separated from benzene in the form of pale red needles, m. p. 125–127°.

Anal. Calcd. for $C_{19}H_{13}N_3O_7$: C, 57.7; H, 3.3. Found: C, 58.0; H, 3.4.

C. The following synthesis failed to produce an indene of the desired type because dehydration of the final product illustrated always resulted in the formation of a resinous polymer.



7-Hydroxy-4-methylindanone was obtained in yields of 61–74% (reported[12] 60%) from *p*-cresyl β-bromopropionate (170 g.) with aluminum chloride. Attempts to reduce the carbonyl group using sodium and ethyl or amyl alcohol, or hydrogen and copper chromite were unsuccessful; the benzoate of the phenol also resisted catalytic reduction. With the calculated amounts of sodium ethoxide and ethyl bromoacetate in alcohol, the phenol (45 g.) yielded (70–85%) **ethyl 1-keto-4-methylindanyl-7-oxyacetate,** colorless needles from dilute alcohol, m. p. 124.5–125.5°.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.7; H, 6.5. Found: C, 67.5; H, 6.6.

The corresponding **acid,** flat needles from acetic acid, m. p. 200–203°, was obtained in nearly quantitative yields by saponification with aqueous potassium hydroxide. It was not changed by treatment with sodium in ethyl or amyl alcohol.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.5; H, 5.5; neut. equiv., 220. Found: C, 65.2; H, 5.5; neut. equiv., 227.

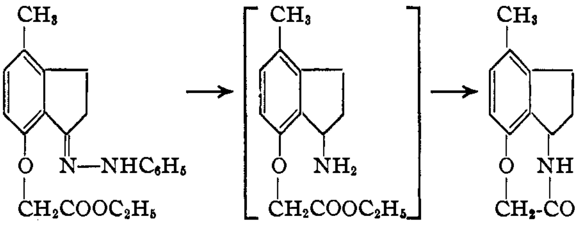
When the keto ester was reduced with Raney nickel and hydrogen at 100 atm. in alcohol at 175° or at 140° during seventy-five minutes, it yielded an oily product. Saponification of this with 10% potassium hydroxide gave only **4-methylindanyl-7-oxyacetic acid,** thin colorless needles from alcohol, m. p. 191–192°; yields, 36–41%.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.9; H, 6.8. Found: C, 70.2; H, 7.0.

However, when the keto ester was reduced in the same way but at 100°, it was partly unchanged, partly converted into the desoxy compound, and partly converted into the corresponding hydroxy ester. Saponification and fractional crystallization from ligroin and ether gave **1-hydroxy-4-methylindanyl-7-oxyacetic acid,** m. p. 122–123° with decomposition; yield, 46–56%.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.9; H, 6.3. Found: C, 65.2; H, 6.6.

D. The following synthesis failed to produce an indene of the desired type because the formation of a stable lactam containing a seven-membered ring took place spontaneously, preventing the introduction of the required double bond.



The **oxime** of ethyl 1-keto-4-methylindanyl-7-oxyacetate was obtained in 92% yield by boiling a mixture of the ester with hydroxylamine hydrochloride and sodium acetate in alcohol for ten minutes. It formed colorless needles, m. p. 186–187° (gas evolution), and it was not changed by treatment with hydrogen in dioxane in the presence of platinum black.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.9; H, 6.5. Found: C, 63.9; H, 6.7.

The corresponding **phenylhydrazone** of the ester (96–98% yields) formed pale yellow needles from alcohol, m. p. 163–166°.

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 71.0; H, 6.5. Found: C, 71.5, 70.9; H, 6.2; 5.7.

A solution of the phenylhydrazone in alcohol containing Raney nickel was subjected to the action of hydrogen at 100 atm. and at 100° for seventy-five minutes. The only products that could be isolated were aniline and **2a,3-dihydro - 9 - methyl[1,4]oxazep[5,6,7-cd]indan - 4(5) - one,** yield 36%. The lactam formed long flat colorless needles from alcohol, m. p. 241–241.5°. It sublimed unchanged when it was heated above its melting point.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.4. Found: C, 71.0; H, 6.4.

Summary

The synthesis of indenyl-5-oxyacetic acid and of indenyl-6-oxyacetic acid is reported. The existence of these two substances indicates that the non-benzenoid double bond of an indene is in a

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(10) Mayer and Sieglitz, *Ber.*, **55**, 1853 (1922).

(11) Thielepape and Fulde, *ibid.*, **66**, 1454 (1933).

(12) Krollpfeiffer and Schultze, *ibid.*, **57**, 600 (1924).

fixed position, even when (and this is contrary to previous conclusions) the indene has no substituent group in its five-membered ring.

A number of compounds prepared incidentally in exploratory syntheses are also reported.

MINNEAPOLIS, MINNESOTA RECEIVED AUGUST 17, 1943

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Synthesis of Compounds Related to the Sex Hormones

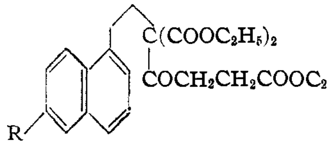
BY W. E. BACHMANN, R. A. GREGG AND E. F. PRATT[1]

In the preparation of an intermediate in the synthesis of estrone-a,[2] cyclization of the triethyl ester of 5-keto-6,6-dicarboxy-8-*m*-anisyloctanoic acid was effected by means of 100% phosphoric acid; cyclization took place to the benzene ring in a position para to a methoxy group. We were interested in determining how readily a similar cyclization would occur to the beta position of the naphthalene nucleus. Such a cyclization would offer a route to norequilenin and related compounds.

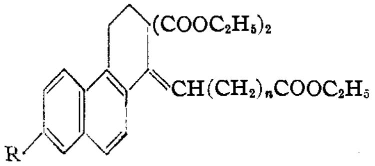
Condensation of the sodio derivative of β-1-naphthylethylmalonic ester with the acid chloride of ethyl hydrogen succinate gave the triethyl ester of 4-keto-5,5-dicarboxy-7-α-naphthylheptanoic acid (I) It was found that cyclization to II could be effected by means of 100% phosphoric acid provided that a higher temperature and a longer time were employed than were required for the anisyl derivative. Hydrolysis of the unsaturated triester yielded the corresponding tricarboxylic acid, which was decarboxylated in hot water to an unsaturated dicarboxylic acid, probably 2-carboxy-3,4-dihydrophenanthrene-1-β-propionic acid (III), although the position of the double bond has not been established. The acid was obtained in 15–23% over-all yields from I.

The dimethyl ester of III is the key compound from which the three cyclic ketones IV, V and VI were prepared. These differ in the degree of unsaturation in the C ring. By dehydrogenation of the dimethyl ester of III by means of palladium-charcoal at 310°, the dimethyl ester of 2-carboxyphenanthrene-1-β-propionic acid was obtained which was converted to 3′-keto-1,2-cyclopentenophenanthrene (IV) through Dieckmann cyclization followed by hydrolysis and decarboxylation of the resulting product. The cyclic ketone was identical with the compound which had been prepared previously by cyclization of β-1-phenanthrylpropionic acid.[3]

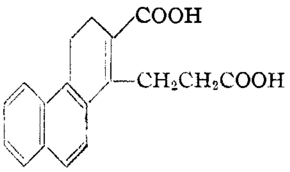
When the dimethyl ester of III was cyclized by the Dieckmann method and the resulting cyclic β-keto ester hydrolyzed and decarboxylated, 3′-keto-3,4-dihydro-1,2-cyclopentenophenanthrene (V) was produced. The position of the double bond in the compound has not been established. The compound is probably identical with the cyclic ketone obtained by Bardhan[4] by treatment of the unsaturated dicarboxylic acid (III) with acetic anhydride followed by distillation of the product and with the compound prepared by Robinson and Thompson.[5]



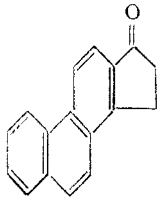
I R = H
Ia R = OCH$_3$



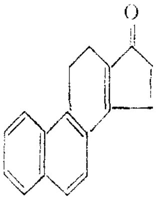
II R = H; n = 1
IIa R = OCH$_3$; n = 1
IIb R = H; n = 2
IIc R = OCH$_3$; n = 2



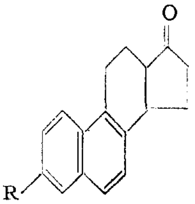
III



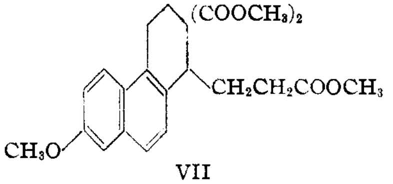
IV



V



VI R = H
VIa R = OH



VII

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[1] From the Ph. D. dissertations of R. A. Gregg and E. F. Pratt.

[2] Bachmann, Kushner and Stevenson, THIS JOURNAL, **64**, 974 (1942).

[3] Bachmann and Kloetzel, *ibid.*, **59**, 2207 (1937).

[4] Bardhan, *J. Chem. Soc.*, 1848 (1936).

[5] Robinson and Thompson, *ibid.*, 1739 (1939).