

orated to dryness under vacuum leaving a residue which after two crystallizations from ethanol weighed 2.0 g. (12%) and melted at 210–211°.

Anal. Calcd. for $C_{13}H_{19}N_5O_3$: C, 53.23; H, 6.53; N, 23.90. Found: C, 53.58; H, 6.35; N, 23.87.

WARNER-CHILCOTT RESEARCH LABORATORIES
113 WEST 18TH STREET
NEW YORK 11, NEW YORK

Syntheses in the Indene Series¹

BY JOHN KOO²

RECEIVED DECEMBER 19, 1952

In connection with a projected synthesis of colchicine analogs, various substituted indenenes were prepared as model compounds. Attempts were made to introduce substituents which, by cyclization, might yield tricyclic systems. The present note describes the synthesis of some of those indene derivatives.

Veratraldehyde and piperonal were condensed with ethyl acetoacetate by an extension of Knoevenagel's method,³ and the resulting benzylideneacetoacetic esters (Ia,b) hydrogenated to the benzylacetoacetic esters (IIa,b).⁴ Acid-catalyzed cyclodehydration of IIa and IIb produced the indene esters IIIa and IIIb, in addition to small amounts of the corresponding carboxylic acids, which resulted from hydrolysis accompanying the cyclization. Analogously, veratrylacetone (IIc)⁵ and veratrylaceto-phenone (IId)⁶ were cyclized to the indene derivatives IIIc and IIId. The indene ester IIIa and the phenylindene IIId condensed with ethyl oxalate to form IVa and IVd in 85 and 76% yields, respectively, while the methylindene IIIc failed to yield an oxalyl derivative. Apparently, activation by an aryl group in the 3- or by an ester group in the 2-position is required for formation or sufficient resonance stabilization of the carbanion which must be an intermediate in the condensation with ethyl oxalate. Since IVa and IVd form enol acetates, it is believed that they exist, at least partly, in the tautomeric enolic forms (Va,d). Attempts to reduce the carbonyl group in IVa to a methylene group by catalytic hydrogenation with palladium-carbon or by chemical reduction with aluminum amalgam failed or yielded inseparable mixtures. It was possible, however, to hydrogenate the indene ester IIIa to the indane ester VIa in 77% yield.

Experimental⁷

Ethyl Veratrylideneacetoacetate (Ia).—A homogeneous mixture of 182.6 g. of veratraldehyde, 130 g. of ethyl aceto-

(1) Supported in part by a grant-in-aid from the American Cancer Society recommended by the Committee on Growth of the National Research Council.

(2) American Cancer Society Postdoctoral Fellow, 1948–1950; Special Research Fellow of the National Cancer Institute, National Institutes of Health.

(3) E. Knoevenagel, *Ber.*, **29**, 172 (1896); **31**, 730 (1898).

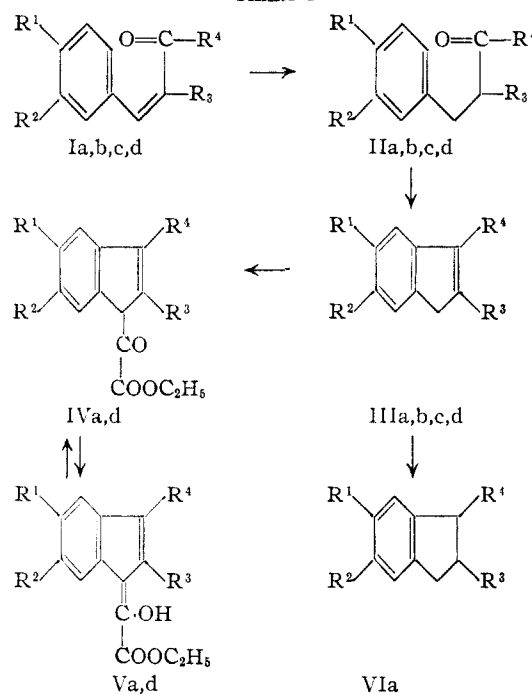
(4) R. H. Barry, A. M. Mattocks and W. H. Hartung, *THIS JOURNAL*, **70**, 693 (1948), prepared IIb from piperonal via piperonyl alcohol and piperonyl chloride.

(5) A. Kaufmann and R. Radosević, *Ber.*, **49**, 675 (1916).

(6) P. Pfeiffer, E. Kalckbrenner, W. Kunze and K. Levin, *J. prakt. Chem.*, [2] **119**, 109 (1928).

(7) Melting points are corrected and boiling points uncorrected. Analyses were carried out by Mrs. S. M. Woods of the University of Pennsylvania, and by Dr. W. C. Alford and his associates of the National Institutes of Health.

CHART 1



Series a: $R^1 = R^2 = OCH_3$; $R^3 = CO_2C_2H_5$; $R^4 = CH_3$
Series b: $R^1 = R^2 = -OCH_2O-$; $R^3 = CO_2C_2H_5$; $R^4 = CH_3$
Series c: $R^1 = R^2 = OCH_3$; $R^3 = H$; $R^4 = CH_3$
Series d: $R^1 = R^2 = OCH_3$; $R^3 = H$; $R^4 = C_6H_5$

acetate and 70 ml. of benzene was refluxed with 3.4 g. of piperidine and 12.2 g. of glacial acetic acid. Water liberated in the reaction was collected in a moisture trap. The reaction was completed in two hours, at which time 25 ml. of water had been collected. The solution was then cooled, diluted with 300 ml. of ether, washed twice with 100 ml. each of very dilute acetic acid and once with water, and dried over magnesium sulfate. After removal of solvents, the product was distilled to yield 175 g. (63%) of a pale yellowish oil, b.p. 190–192° (1 mm.), which solidified after standing for two days and then melted at 75–81°.

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 64.73; H, 6.25. Found: C, 64.60; H, 6.60.

Ethyl Piperonylideneacetoacetate (Ib).—This compound was obtained from piperonal in 62% yield by the procedure used for the preparation of Ia. The pale yellow oil, b.p. 179° (1.6 mm.), solidified on standing and remelted at 74–77°.

Anal. Calcd. for $C_{14}H_{14}O_6$: C, 64.11; H, 5.37. Found: C, 63.78; H, 5.49.

Ethyl Veratrylacetoacetate (IIa).—A solution of 139 g. of IIa in 150 ml. of ethyl acetate was hydrogenated with 9 g. of 5% palladium-carbon catalyst at room temperature and 45 lb. pressure for two hours. Removal of catalyst and solvent, followed by vacuum distillation, provided 100 g. (70%) of colorless oil, b.p. 169° (1 mm.).

Anal. Calcd. for $C_{16}H_{20}O_6$: C, 64.27; H, 7.19. Found: C, 64.27; H, 7.01.

The 2,4-dinitrophenylhydrazone formed yellowish crystals (from dilute ethanol), m.p. 116–117°.

Anal. Calcd. for $C_{21}H_{24}O_8H_4$: C, 54.78; H, 5.28. Found: C, 54.74; H, 5.36.

Ethyl Piperonylacetoacetate (IIb).—Hydrogenation of Ib by the above procedure gave a 52% yield of colorless oil, b.p. 151–153° (0.8 mm.) (reported⁴ 160–161° (4 mm.)).

Veratrylacetone (IIc).—This compound was similarly obtained in 83% yield by reducing 69 g. of veratrylideneacetone (Ic),⁵ m.p. 84–86° (reported⁵ 91–92°,⁸ 84–85°⁹), with 5 g. of palladium-carbon catalyst in 150 ml. of glacial acetic acid for 35 minutes. The colorless material had b.p. 127–129° (0.5 mm.) and m.p. 53–56° (reported⁵ b.p. 181° (14 mm.), m.p. 55°).

(8) C. F. Van Duin, *Rec. trav. chim.*, **45**, 345 (1926).

Veratrylacetophenone (IIId).—Veratrylideneacetophenone (Id), m.p. 90–92° (reported 85°, 88°⁹) was hydrogenated with palladium-carbon catalyst in ethyl acetate for four hours to give a 93% yield of solid, m.p. 68–70° (reported⁹ 67.5–68.5°) which crystallized from dilute ethanol in colorless scales, with no change in m.p.

Ethyl 5,6-Dimethoxy-3-methylindene-2-carboxylate (IIIa).—A solution of 56 g. of IIa in 45 ml. of 85% phosphoric acid was added slowly with vigorous stirring to a mixture of 90 ml. of concd. sulfuric acid and 45 ml. of 85% phosphoric acid at 0–5°. The reaction mixture became rapidly red, then bluish, and solidified. It was stirred into ice-water almost immediately. The white precipitate was collected, washed with cold water, dissolved in ether, and the solution washed with 10% sodium bicarbonate. Evaporation of the solvent gave 24 g. (46%) of a colorless solid, which after recrystallization from 70% ethanol formed large colorless crystals, m.p. 136–136.5°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.54; H, 6.92.

Acidification of the sodium bicarbonate washings with concd. hydrochloric acid yielded 5 g. (10%) of 5,6-dimethoxy-3-methylindene-2-carboxylic acid as a heavy white solid, which after recrystallization from acetone melted at 228–230°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 66.65; H, 6.02. Found: C, 66.49; H, 5.85.

Ethyl 5,6-Methylenedioxy-3-methylindene-2-carboxylate (IIIb).—A solution of 1 g. of IIb in 3 ml. of sulfuric and 3 ml. of phosphoric acid was prepared and kept at 0° for 40 minutes, at which time the color had changed from yellow to greenish-blue. The pale green crude solid (0.79 g.), obtained as above after treatment with bicarbonate, was recrystallized from dilute ethanol, but the product was still quite impure. It was, therefore, dissolved in ether-ethyl acetate, and the solution shaken exhaustively with 2% aqueous sodium hydroxide, then with water. Drying and evaporating the solvent yielded 0.443 g. (48%) of a solid, m.p. 105–107°, which was recrystallized from 70% ethanol to give tiny colorless needles, m.p. 107–108°.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.72. Found: C, 68.08; H, 5.71.

From the sodium bicarbonate washings, there was obtained 0.032 g. (3.6%) of 5,6-methylenedioxy-3-methylindene-2-carboxylic acid, which separated from ethyl acetate-70% ethanol in small colorless crystals, m.p. 280–281° (dec.).

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.04; H, 4.62. Found: C, 66.27; H, 4.61.

5,6-Dimethoxy-3-methylindene (IIIc).—This compound was obtained from 21 g. of IIc in 42 ml. of phosphoric acid and 42 ml. of sulfuric acid at 10–15° by the method used for preparing IIIa, except that the crude product (10 g., 52%) was obtained directly by pouring the reaction mixture into 400 ml. of ice-water after 0.5 hour, with omission of the bicarbonate treatment. The product formed small colorless scales (from dilute ethanol), m.p. 132–133°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.60; H, 7.63.

5,6-Dimethoxy-3-phenylindene (IIId).—A 91% yield of crude material was obtained similarly from IIc, except that the reaction mixture was heated at 60–70° for 30 minutes. Recrystallization from dilute ethanol gave small colorless scales, m.p. 112–113.5°. The yield dropped to 10% when the reaction was carried out below 25°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.75; H, 6.25.

Ethyl 1-Ethoxalyl-5,6-dimethoxy-3-methylindene-2-carboxylate (IVa).—To a still warm solution of 1.15 g. of sodium in 50 ml. of absolute ethanol was added rapidly with vigorous swirling 7.5 g. of ethyl oxalate, then a suspension of 18 g. of IIIa in 100 ml. of hot absolute ethanol. The mixture was shaken for another two minutes, the yellowish paste stirred into cold water, and the mixture acidified with dilute hydrochloric acid. The solid was collected, washed with water and purified from 70% ethanol to yield 19 g. (77%) of yellowish crystals, m.p. 143–146°.

Anal. Calcd. for $C_{18}H_{20}O_7$: C, 62.97; H, 6.12. Found: C, 62.92; H, 5.99.

The 2,4-dinitrophenylhydrazone formed small yellow crystals (from ethyl acetate), m.p. 180–182°.

Anal. Calcd. for $C_{22}H_{20}O_{10}N_4$: C, 55.35; H, 4.83. Found: C, 55.20; H, 4.73.

The deep yellow crystalline enol acetate, m.p. 132–133°, was prepared by refluxing IVa with acetic anhydride and pyridine, followed by diluting with ice-water and recrystallization from dilute ethanol.

Anal. Calcd. for $C_{21}H_{24}O_8$: C, 62.37; H, 5.98. Found: C, 62.36; H, 6.03.

1-Ethoxalyl-5,6-dimethoxy-3-phenylindene (IVd).—This compound was obtained in 76% yield from 0.46 g. of sodium, 15 ml. of ethanol, 3 g. of ethyl oxalate and 4.2 g. of IIId, and formed deep red needles, m.p. 122–124°.

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 71.50; H, 5.75. Found: C, 71.46; H, 5.57.

The enol acetate crystallized from ethanol in orange-colored cottony needles, m.p. 165–167°.

Anal. Calcd. for $C_{23}H_{22}O_6$: C, 70.03; H, 5.62. Found: C, 69.88; H, 5.86.

Ethyl 5,6-Dimethoxy-3-methylindane-2-carboxylate (VIa).—Hydrogenation of 1 g. of IIIa in 15 ml. of glacial acetic acid with 0.5 g. of 5% palladium-carbon catalyst at 60° and 40 lb. pressure for 2.5 hr. yielded 0.95 g. of oil, which was crystallized from ether-ethyl acetate-pentane to give 0.85 g. (85%) of small colorless crystals, m.p. 48–49°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 68.15; H, 7.62. Found: C, 68.03; H, 7.57.

Saponification of VIa provided 5,6-dimethoxy-3-methylindane-2-carboxylic acid as small colorless crystals (from dilute ethanol), m.p. 176–177°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 66.08; H, 6.82. Found: C, 65.85; H, 6.77.

Acknowledgment.—The author wishes to express his appreciation to Dr. E. C. Horning for many helpful suggestions during the course of this work at the University of Pennsylvania.

JOHN HARRISON LABORATORY
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA., AND
LABORATORY OF CHEMICAL PHARMACOLOGY
NATIONAL CANCER INSTITUTE
BETHESDA 14, MD.

Non-additivity of Polarographic Diffusion Currents with Mixtures of Certain Reducible Species

BY STANLEY L. MILLER¹ AND EDWIN F. ORLEMANN

RECEIVED DECEMBER 17, 1952

Under certain conditions we have found that the polarographic diffusion currents of two species are not additive. This effect has been studied for mixtures of Ce(IV) and O_2 and for mixtures of Fe(III) and Cr(VI) in 1 *M* H_2SO_4 and 1 *M* $HClO_4$. The results show that non-additivity of diffusion currents to give either a larger or smaller current than expected can occur as a result of very fast reactions in the diffusion layer when the species have significantly different diffusion coefficients. The effect is of some theoretical interest and its occurrence must be recognized in connection with a limited number of analytical applications.

Experimental

The polarograms were recorded on a Sargent model XII polarograph. The drop time was about three seconds, and the temperature was $25.00 \pm 0.05^\circ$. Runs were made with both an internal anode and with an external calomel cell

(9) R. Dickinson, I. M. Hellbron and F. Irving, *J. Chem. Soc.*, 1888 (1927).

(1) Department of Chemistry, University of Chicago, Chicago, Ill., National Science Foundation Predoctoral Fellow, 1952–1953.