

Structure of the Indene-3-acetic Acids. Part II.¹ Reformatsky Reactions of 6-Benzyloxy-, 5,6-Dimethoxy-, and 6-Methoxy-indan-1-ones

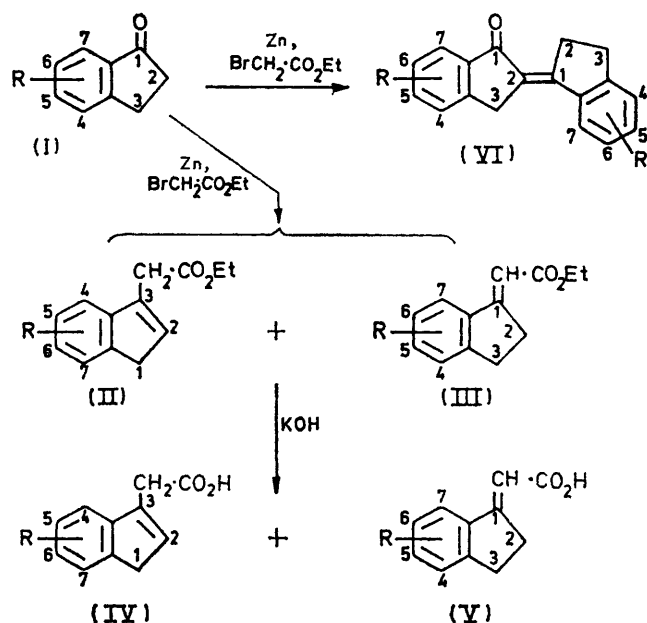
By K. Brewster, R. A. Chittenden, R. M. Pinder,* and M. Skeels, Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire

Reformatsky reactions of ethyl bromoacetate with indan-1-ones usually gave mixtures of the *endo*- and *exo*-unsaturated esters, but the reaction with 5,6-dimethoxyindan-1-one gave solely the *exo*-isomer. Hydrolysis of the esters from the title indan-1-ones gave mixtures of the isomeric acids, except in the last case, when 5-methoxyindene-3-acetic acid alone was obtained. It is concluded that the functional role of the aryl substituent in providing an extended conjugated system favours *exo*-unsaturation.

OUR continuing interest^{1,2} in the use of indene-3-acetic acids as synthetic intermediates involved a study of the Reformatsky reaction of a number of indan-1-ones. Previous experience^{1,3} had demonstrated that the position of the double bond (*endo* or *exo*) in the ester and in the acid subsequently obtained by hydrolysis is not qualitatively predictable in such systems. Indan-1-one (I; R = H) gives a 70 : 30 mixture of *endo*- (II; R = H) and *exo*- (III; R = H) unsaturated esters in a Reformatsky reaction with ethyl bromoacetate, and the mixture is hydrolysed to give only the *endo*-unsaturated acid, indene-3-acetic acid (IV; R = H). In contrast, 5-methoxyindan-1-one (I; R = 5-OMe) gives a 50 : 50 mixture of the esters, which is hydrolysed to an 85 : 15 mixture of *endo*- and *exo*-unsaturated acids, the greater proportion of the *exo*-isomer being attributed to the effect of the methoxy-group in providing an extended conjugated system.³ However, both 6-methoxy-2-methylindan-1-one^{4,5} and 6,7-dimethoxyindan-1-one⁶ are reported to give only the *endo*-unsaturated esters in Reformatsky reactions. We now report the Reformatsky reactions of 6-benzyloxy-, 5,6-dimethoxy-, and 6-methoxy-indan-1-ones with ethyl bromoacetate.

Separation of the mixture of isomeric esters (II) and (III) from the self-condensation products (VI) was readily achieved by making use of the solubility of the

former and the insolubility of the latter in hexane. We² and others^{7,8} have commented upon the ready



formation of the latter compounds whenever indanones or other alicyclic ketones^{9,10} are condensed with a

¹ Part I, R. M. Pinder, *Chem. and Ind.*, 1970, 719.

² R. M. Pinder, *J. Chem. Soc. (C)*, 1970, 114.

³ R. D. Hoffsommer, D. Taub, and N. L. Wendler, *J. Org. Chem.*, 1969, **34**, 4182.

⁴ T. Y. Shen, *Chim. Thérap.*, 1967, **2**, 181.

⁵ T. Y. Shen, R. L. Ellis, B. E. Witzel, and A. R. Matzuk, Abstracts 152nd Amer. Chem. Soc. Meeting, New York, 1966, p. 3P.

⁶ E. C. Horning and G. N. Walker, *J. Amer. Chem. Soc.*, 1954, **76**, 1700.

⁷ F. Bell and J. Spanswick, *J. Chem. Soc. (C)*, 1966, 1887.

⁸ S. K. Dasgupta, S. R. Ghosh, and A. S. Sarma, *Tetrahedron Letters*, 1969, **28**, 2331.

⁹ R. L. Shriner, *Org. Reactions*, 1947, **1**, 1.

¹⁰ G. Jones, *Org. Reactions*, 1967, **15**, 204.

variety of reactants. They are readily identified by their i.r. and n.m.r. spectra,² showing *inter alia* a strong carbonyl band at 1675 cm⁻¹ and a singlet at δ ca. 3.8 p.p.m. for the C-3 methylene protons of the indan-1-one system. Thin-layer and gas-liquid chromatography failed to resolve the isomeric esters, but samples of most of them were obtained by various techniques. Thus, the 50:50 mixture of ethyl 5-benzyloxyindene-3-acetate (II; R = 5-O·CH₂Ph) and ethyl 6-benzyloxyindan-1-ylideneacetate (III; R = 6-O·CH₂Ph) was equilibrated to a 10:90 mixture upon distillation or treatment with ethanolic sodium ethoxide. Recrystallization of the equilibrated mixture from low-boiling petroleum afforded the pure *exo*-unsaturated ester, the *endo*-isomer being subsequently obtained from the mother liquors. Both mixtures, and the pure isomeric esters, were hydrolysed to a mixture of *endo*- and *exo*-unsaturated acids in the same proportions (85:15); the solubility of the former and the insolubility of the latter in diethyl ether facilitated isolation of the two isomers.

In contrast, Reformatsky reaction of 6-methoxyindan-1-one (I; R = 6-OMe) gave an equilibrium mixture containing mainly *endo*-unsaturated ester (70%), obtained by distillation or acidic treatment of the original mixture of 44% *endo*- and 56% *exo*-isomer. Hydrolysis gave solely 5-methoxyindene-3-acetic acid (IV; R = 5-OMe), and re-esterification of this acid with ethanolic hydrogen chloride gave once more a mixture closely corresponding to that obtained by equilibration. 5,6-Dimethoxyindan-1-one [I; R = 5,6-(OMe)₂] gave solely

methoxycarbonylmethylenetriphenylphosphorane, and this is not therefore a route applicable to direct synthesis of the *exo*-unsaturated esters.

Our results confirm other work^{1,3} and tentatively demonstrate that substituents such as 6-methoxy [structure (III)], which provide for extended conjugation with the carbonyl function, favour *exo*-unsaturation. However, it might be expected on this basis that 6-methoxy- and 6-benzyloxyindan-1-ones would behave similarly in Reformatsky reactions. They do not, and it is clear that the position of the double bond in the esters obtained in such reactions, and in the acid hydrolysis products, is not at present qualitatively predictable.

EXPERIMENTAL

M.p.s were recorded with an Electrothermal capillary apparatus. I.r. spectra were measured with a Perkin-Elmer Infracord. N.m.r. spectra were measured for solutions in [2H]chloroform with a JEOL JNM-4H-100 spectrometer at 100 MHz, with tetramethylsilane as internal standard. Microanalyses were performed by Mr. A. C. Thomas of these laboratories.

Activated zinc wire for use in Reformatsky reactions was prepared by boiling a mixture of zinc wire (10 g), concentrated sulphuric acid (300 ml), and concentrated nitric acid (5 ml) for 20 min. The hot mixture was filtered, and the metal washed thoroughly with water, ethanol, acetone, and diethyl ether, before being dried (P₂O₅) under reduced pressure.

Isomer ratios and physical constants for *endo*- and *exo*-3-acetic acids, indan-1-ylideneacetic acids, and their esters

Structure	R *	M.p. (°C)	Total % yield of <i>endo</i> - <i>exo</i> mixture	% in <i>endo</i> - <i>exo</i> mixture †	ν_{CO} /cm ⁻¹	δ (p.p.m.)		Formula	Calc. (%)		Found (%)	
						$\text{=CH}\cdot\text{CO}_2\text{R}$	2-CH_2		C	H	C	H
(II)	5-O·CH ₂ Ph	41—43	56	50(10)	1740	3.50	6.40	C ₂₀ H ₂₀ O ₃	77.9	6.5	77.7	6.3
(III)	6-O·CH ₂ Ph	104—105	56	50(90)	1695	6.20	2.95	C ₂₀ H ₂₀ O ₃	77.9	6.5	77.8	6.2
(IV)	5-O·CH ₂ Ph	107—108	74	85	1710	3.50	6.47	C ₁₈ H ₁₆ O ₃	77.1	5.75	77.2	5.75
(V)	6-O·CH ₂ Ph	188—189	74	15	1685	6.22	2.95	C ₁₈ H ₁₆ O ₃	77.1	5.75	77.5	5.8
(II)	5-OMe	†	48	44(70)	1725	3.50	6.40	C ₁₄ H ₁₆ O ₃	72.4	6.9	72.1	7.0
(III)	6-OMe	78—79	48	56(30)	1690	6.24	2.97	C ₁₄ H ₁₆ O ₃	72.4	6.9	72.2	6.9
(IV)	5-OMe	127—128	78	100	1700	3.60	6.45	C ₁₂ H ₁₂ O ₃	70.6	5.9	70.3	6.0
(III)	5,6-(OMe) ₂	105—106	43	100	1690	6.10	2.95	C ₁₂ H ₁₂ O ₄	68.7	6.9	68.4	6.9
(IV)	† (Me) ₂	146—147	82	58	1700	3.60	6.35	C ₁₂ H ₁₄ O ₄	66.7	6.0	67.2	6.1
(V)	† (Me) ₂	202—203	82	42	1665	6.05	2.90	C ₁₂ H ₁₄ O ₄	66.7	6.0	67.0	6.0

* Numbering refers to the formula specified in the first column and to the structures shown in the Scheme. † These figures refer to mixtures produced under kinetic control; the figures in parentheses refer to those obtained under thermodynamic control. ‡ B.p. 150—153° at 1.0 mmHg.

the *exo*-unsaturated ester, ethyl 5,6-dimethoxyindan-1-ylideneacetate [III; R = 5,6-(OMe)₂], in a Reformatsky reaction; the product did not equilibrate to an *endo*-*exo* mixture. This ester subsequently hydrolysed to a mixture of 42% of the *exo*- and 58% of the *endo*-unsaturated acid. In contrast to experience with benzaldehydes¹¹ and with other alicyclic ketones^{12,13} our indanones did not undergo the Wittig reaction with

Indene-3-acetates (II) and *Indan-1-ylideneacetates* (III).—Typically, a solution of the indan-1-one (0.1 mol) and ethyl 5-oxoacetate (16.7 g, 0.1 mol) in dry benzene (50 ml) was added during 15 min to activated zinc wire (6.5 g, 0.1 mol) covered with dry benzene (50 ml). The mixture was stirred and heated under reflux for 3—4 h until all of the zinc had disappeared. The cooled solution was poured into 10% sulphuric acid (100 ml), and the benzene layer was washed with water and saturated brine, dried (MgSO₄), and

¹¹ F. Bohlmann, *Chem. Ber.*, 1957, **90**, 1519.

¹² M. P. Cava and R. J. Pohl, *J. Amer. Chem. Soc.*, 1960, **82**, 5242.

¹³ A. W. Johnson, 'Ylid Chemistry,' Academic Press, London, 1966, p. 140.

evaporated. The residual oil was extracted for 5–10 min with boiling hexane and the extract was filtered. The filtrate contained the isomeric esters (see later); the residue, consisting of the self-condensation products (VI), was recrystallized from benzene.

6-Benzoyloxy-2-(6-benzoyloxyindan-1-ylidene)indan-1-one (VI; R = 6-O-CH₂Ph) had m.p. 147–148° (lit.,³ 148–149°); yield 14%.

6-Methoxy-2-(6-methoxyindan-1-ylidene)indan-1-one (VI; R = 6-OMe) had m.p. 169–170°; yield 12% (Found: C, 77.9; H, 5.8. C₂₀H₁₈O₃ requires C, 78.4; H, 5.9%).

5,6-Dimethoxy-2-(5,6-dimethoxyindan-1-ylidene)indan-1-one [VI; R = 5,6-(OMe)₂] had m.p. 142–143°; yield 7% (Found: C, 72.0; H, 6.2. C₂₂H₂₂O₅ requires C, 72.1; H, 6.05%).

The hexane filtrate was evaporated to dryness and the residue submitted to spectroscopic analysis; the proportions of *endo*- and *exo*-isomers were calculated from the integrals of the n.m.r. signals for -CH₂·CO₂Et and =CH·CO₂Et (Table).

Ethyl 5-benzoyloxyindene-3-acetate (II; R = 5-O-CH₂Ph), which formed 50% of the mixture in hexane and 10% of the equilibrium mixture (from 2 h reflux with sodium ethoxide³) was obtained by recrystallization of the latter from light petroleum (b.p. 40–60°). The mother liquors contained 85% of this compound, the crystals being pure ethyl 6-benzoyloxyindan-1-ylideneacetate (III; R = 6-O-CH₂Ph), and two more recrystallizations sufficed to separate the

endo-unsaturated isomer, which was recrystallized from hexane. Physical constants are recorded in the Table.

Ethyl 5-methoxyindene-3-acetate (II; R = 5-OMe), which formed 44% of the original mixture and 70% of the equilibrium mixture (from distillation or warming with ethanolic formic acid³) was obtained from the mother liquors as a liquid, b.p. 150–153° at 1 mmHg, after complete crystallization of ethyl 6-methoxyindan-1-ylideneacetate (III; R = 6-OMe) from light petroleum (b.p. 40–60°).

Ethyl 5,6-dimethoxyindan-1-ylideneacetate [III; R = 5,6-(OMe)₂] was the sole product from the Reformatsky reaction of 5,6-dimethoxyindan-1-one, and was recrystallized from hexane.

Indene-3-acetic Acids (IV) and Indan-1-ylideneacetic Acids (V).—Typically, the total product from the Reformatsky reaction was dissolved in ethanol (100 ml), to which potassium hydroxide pellets (1.4 equiv.) were added under nitrogen. The solution was stirred under reflux for 4 h, then diluted with water (200 ml), and the aqueous solution was decolourised with charcoal. The cooled solution was acidified with 10% hydrochloric acid, and the precipitated solid was filtered and dried. Extraction with diethyl ether followed by filtration afforded the ether-soluble indene-3-acetic acids (IV) and the ether-insoluble indan-1-ylideneacetic acids (V). The former were recrystallized from cyclohexane and the latter from toluene.

[1/2061 Received, 5th November, 1971]