

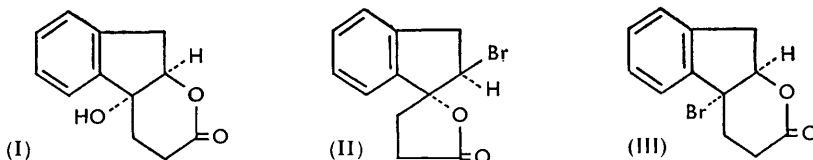
586. *A New Synthesis of 1-Alkylfluorenes.*

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A new preparation of β -3-indenylpropionic acid is described. Some of its reactions have been investigated with a view to the synthesis of fluorene derivatives, and a new synthesis of 1-alkylfluorenes is described.

β -3-(or -1-)INDENYLPROPIONIC ACID, m. p. 120—121°, has been prepared by Clemo, Groves, Munday, and Swan¹ from 2-indenylethanol and in other ways, always in poor yield. We have improved the preparation of the alcohol, by using indenyl-lithium in place of the Grignard derivative, but we were unable to convert the alcohol into the bromide in even the modest yield reported by Clemo and his colleagues. A β -indenylpropionic acid, m. p. 159—160°, has also been obtained in 14% yield by Cromwell and Capps² by the interaction of indenyl-lithium and β -bromopropionic acid. We have obtained the acid, m. p. 120—121°, in good yield as its ethyl ester by addition of ethyl acrylate to indene. Use of acrylonitrile gave a lower yield of the nitrile. The structure of this acid remains uncertain; on the basis of its reactions we consider that it is probably β -3-indenylpropionic acid, while the acid of Cromwell and Capps may be β -1-indenylpropionic acid, or possibly a polymorphic modification.

It was intended to convert this acid into β -(2-oxo-1-indanyl)propionic acid by methods similar to those used in the preparation of indan-2-one.³ β -3-Indenylpropionic acid was oxidised by performic acid to a lactone $C_{12}H_{12}O_3$ to which we assign structure (I). It shows an absorption maximum at 1757 cm^{-1} which we attribute to a six-membered ring. We interpret this reaction as consisting of the epoxidation of the double bond followed by opening of the epoxide ring to give a lactone.



Attempts to dehydrate this lactone have proved unsuccessful. The addition of bromine to ethyl β -3-indenylpropionate emulsified in water³ gave a mixture of two isomeric lactones, A and B, $C_{12}H_{11}O_2Br$, which have respectively absorption at 1770 and 1757 cm^{-1} . This suggests that lactone A contains a five-membered ring and is produced by normal

¹ Clemo, Groves, Munday, and Swan, *J.*, 1951, 863.

² Cromwell and Capps, *J. Amer. Chem. Soc.*, 1952, **74**, 4448.

³ Levin, Graham, and Kolloff, *J. Org. Chem.*, 1944, **9**, 384.

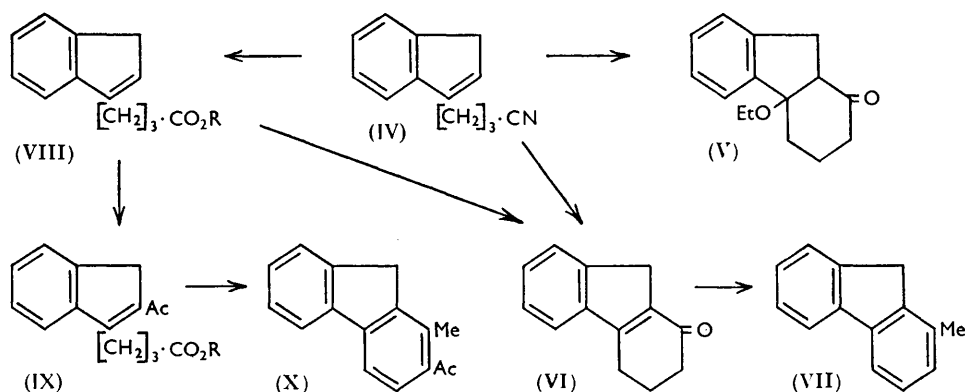
addition of hypobromous acid to the double bond to give ethyl β -(2-bromo-1-hydroxy-1-indenyl)propionate, which is then hydrolysed and lactonised to substance (II). Production of a five-membered lactone ring from β -1-indenylpropionic acid would not be easily possible.

Lactone B, containing a six-membered ring, is produced by initial hydrolysis to the acid which adds bromonium ion and is then lactonised directly to compound (III). Addition of bromine to the free acid was unsatisfactory, probably because of the difficulty of emulsifying it in water. Neither lactone proved of use for further work; lactone A with alkali gave a resin, while lactone B gave a mixture of compound (I) and a smaller amount of an unidentified substance. As the production of (I) in this way involves hydrolysis with retention of configuration, the epoxide may be an intermediate.

It seemed possible that the same method might be used to add a third ring as we⁴ have recently done in the naphthalene series. Indene itself is polymerised under Friedel-Craft conditions, but ethyl β -3-indenylpropionate is much more stable, and gave the 2-acetyl derivative in 60% yield.

γ -3-Indenylbutyronitrile (IV) was then prepared by reduction of ethyl β -3-indenylpropionate with lithium aluminium hydride followed by reaction with phosphorus tribromide and sodium cyanide. Attempted hydrolysis of this nitrile with ethanolic sulphuric acid gave a ketone (V) which with dinitrophenylhydrazine gave the dinitrophenylhydrazone of the corresponding unsaturated ketone (VI).

This prompted investigation of a Hoesch type cyclisation of the nitrile, and on treatment with hydrogen chloride and zinc chloride in ether the unsaturated ketone (VI) was obtained in good yield. Ethanol could not be added to this ketone in the presence of hydrogen chloride. γ -3-Indenylbutyronitrile was hydrolysed with aqueous alkali, and the acid was cyclised to the ketone (VI) by treatment with phosphorus pentachloride. The structure of ketone (VI) as 1:2:3:4-tetrahydrofluoren-1-one was confirmed by reaction with methylmagnesium bromide and dehydrogenation, which gave 1-methylfluorene (VII). This is probably the simplest synthesis of this compound, but the method does not permit introduction of a second substituent.



Ethyl γ -3-indenylbutyrate was acetylated smoothly with acetyl chloride and aluminium chloride in nitrobenzene to yield ethyl γ -(2-acetyl-3-indenyl)butyrate (IX; R = Et). This ester was very unstable to alkali, but could be hydrolysed with dilute aqueous acid. The acid chloride reacted with dimethylcadmium to yield a resin, which with sodium ethoxide gave a small amount of 2-acetyl-1-methylfluorene (X). The low yield is not surprising, in view of the instability of all these 2-acetylindenes to alkali. None of the fluorene was

⁴ Howell and Taylor, *J.*, 1956, 4252.

obtained after acid cyclisation. It is interesting that this reaction gave the fluorene and not its dihydro-derivative (cf. Hückel and Schwen).⁵

Application of this type of synthesis to *Ar*-substituted indenenes is difficult, because of the ambiguity between positions 1 and 3, but if use could be made of the readily-accessible indan-1-ones to prepare γ -3-indenylbutyric acid a useful method would be available. We have prepared 4-methylindan-1-one⁶ but in parallel with the results of Clemo *et al.*¹ find that the Stobbe reaction gives only a very small yield. Other ketonic condensations were equally unsuccessful.

The Friedel-Crafts acetylation of γ -3-indenylbutyronitrile was successful, but the Hoesch reaction between acetonitrile and ethyl β -3-indenylpropionate gave unchanged material.

An attempt to prepare 4-3'-indenylbutan-2-one from dimethylcadmium and the appropriate acid chloride was unsuccessful; only the cyclic ketone 1 : 2 : 3 : 8-tetrahydro-1-oxocyclopent[*a*]indene¹ was obtained.

EXPERIMENTAL

2-Indenylethanol.—To butyl-lithium, prepared from lithium (10.0 g.) and butyl bromide (117 g.) in ether (500 ml.), indene (58 g.) was added with stirring under nitrogen at -10° . After 1 hr. ethylene oxide (44 g.) was added at -30° during $\frac{1}{2}$ hr. The solution was washed with acid and water at room temperature, and distilled. 2-Indenylethanol (47.7 g., 60%), n_D^{20} 1.5604, was collected at 166°/14 mm. (Found: C, 82.15; H, 7.7. Calc. for $C_{11}H_{12}O$: C, 82.5; H, 7.55%).

Ethyl β -3-Indenylpropionate.—Ethyl acrylate (40 ml.) was added to a boiling solution of sodium methoxide (1 g.) [from sodium and methanol (5 ml.)] and indene (120 ml.) during 15 min. The solution was refluxed for a further 40 min. and then distilled under reduced pressure. After a fore-run of unchanged indene, ethyl β -3-indenylpropionate (40.6 g., 47%, based on ethyl acrylate) was collected at 140°/0.05 mm. as a pale yellow oil, n_D^{20} 1.5411.

Hydrolysis with aqueous sodium hydroxide gave the acid (94%), m. p. 124—126° (Found: C, 76.4; H, 6.3. Calc. for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4%). Clemo *et al.* give m. p. 121—122°.

β -3-Indenylpropionitrile.—This was prepared (13% yield) as described for the ethyl ester, except that it was necessary to acidify before distillation. β -3-Indenylpropionitrile had b. p. 123°/0.1 mm., n_D^{20} 1.5703 (Found: C, 85.3; H, 6.3; N, 8.3. Calc. for $C_{12}H_{11}N$: C, 85.2; H, 6.5; N, 8.3%). Alkaline hydrolysis gave the acid, m. p. 126°.

β -(1 : 2-Dihydroxy-1-indanyl)propionic 2-lactone (I).— β -3-Indenylpropionic acid (1.0 g.) in chloroform (30 ml.) was added to hydrogen peroxide (30%; 30 ml.) and formic acid (10 ml.), and the mixture stirred for 12 hr. The organic layer was washed with water and evaporated; the residue gave β -(1 : 2-dihydroxy-1-indanyl)propionic 2-lactone (0.5 g. 46%) as needles, m. p. 122—124° (from benzene) (Found: C, 70.4; H, 6.1. $C_{12}H_{12}O_3$ requires C, 70.6; H, 5.9%), $\nu_{max.}$ (in nujol) 1757 cm^{-1} . The lactone dissolves in alkali and is reprecipitated by acid. Perphthalic acid is without effect on the indenylpropionic acid.

Addition of Bromine to Ethyl β -3-Indenylpropionate.—Ethyl β -3-indenylpropionate (5.0 g.) in water (100 ml.) was stirred vigorously with "Teepol" (5 ml.) at 70°, while a slight excess of a saturated solution of bromine in aqueous sodium bromide was added. On cooling, an oil separated and was extracted with benzene. The extracted material gave lactone A, β -(2-bromo-1-hydroxy-1-indanyl)propiolactone (II) (1.7 g.), as prisms, m. p. 99° (from ethanol) (Found: C, 53.7; H, 4.3. $C_{12}H_{11}O_2Br$ requires C, 53.8; H, 4.1%), $\nu_{max.}$ (in nujol) 1770 cm^{-1} . The material insoluble in benzene gave lactone B, β -(1-bromo-2-hydroxy-1-indanyl)propionic 2-lactone (III), (1.2 g.) as needles, m. p. 148° (from ethanol) (Found: C, 53.9; H, 4.2. $C_{12}H_{11}O_2Br$ requires C, 53.8; H, 4.1%). $\nu_{max.}$ (in nujol) 1757 cm^{-1} .

Hydrolysis of Lactone B.—Lactone B was soluble in boiling aqueous potassium hydroxide; acidification and fractional crystallisation from benzene gave the hydroxy-lactone (I) m. p. and mixed m. p. 124°, and another substance, m. p. 100° (Found: C, 70.7; H, 5.9. $C_{12}H_{12}O_3$ requires C, 70.6; H, 5.9%), $\nu_{max.}$ (in nujol) 1690 cm^{-1} ; no hydroxyl absorption.

⁵ Hückel and Schwen, *Ber.*, 1956, **89**, 481.

⁶ Young, *Ber.*, 1892, **25**, 2104.

Ethyl β -(2-Acetyl-3-indenyl)propionate.—Acetyl chloride (1.6 ml.) and aluminium chloride (3.1 g.) in nitrobenzene (10 ml.) were added to ethyl indenylpropionate (5.0 g.) in nitrobenzene (10 ml.). Next morning water and ether were added, the organic layer was washed and evaporated, and the residue distilled. *Ethyl β -(2-acetyl-3-indenyl)propionate* (3.3 g., 56%) was collected at 168°/0.5 mm.; it formed prisms, m. p. 50—52° [from light petroleum (b. p. 40—60°)] (Found: C, 74.2; H, 6.7. $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.0%). The *semicarbazone* formed needles, m. p. 158° (from ethanol) (Found: C, 64.4; H, 6.4; N, 13.2. $C_{17}H_{21}O_3N_3$ requires C, 64.7; H, 6.7; N, 13.3%).

This ester was very unstable to alkali; the free *acid* was obtained with 2N-aqueous hydrochloric acid, and formed pale yellow needles, m. p. 142—144° (from ethyl acetate) (Found: C, 73.3; H, 6.2. $C_{14}H_{14}O_3$ requires C, 73.0; H, 6.1%).

3-3'-Indenylpropanol.—Ethyl indenylpropionate (21.6 g.) was added dropwise to lithium aluminium hydride (3.0 g.) in ether (200 ml.), and the solution refluxed for 1 hr. After addition of dilute hydrochloric acid, the ether layer was separated and evaporated, and the residue distilled. *3-3'-Indenylpropanol* (15.8 g., 91%) was collected as a pale yellow oil at 120°/0.1 mm. (Found: C, 82.6; H, 8.2. $C_{12}H_{14}O$ requires C, 82.7; H, 8.1%).

3-3'-Indenylpropyl Bromide.—The alcohol (36.0 g.) was dissolved in benzene (150 ml.), and phosphorus tribromide (28 g.) in benzene (30 ml.) added dropwise. The solution was kept at 50° for 7 hr. and then stored overnight. The solution was washed with sodium hydrogen carbonate solution and water, dried, and evaporated. *3-3'-Indenylpropyl bromide* (32.4 g., 66%) was collected at 140°/0.8 mm. as a pale yellow oil, n_D^{20} 1.5851.

γ -3-Indenylbutyronitrile (IV).—Indenylpropyl bromide (9.0 g.), sodium cyanide (3 g.), water (4 ml.), and ethanol (9 ml.) were refluxed for 9 hr., then diluted with water and ether, and the organic layer was distilled. *γ -3-Indenylbutyronitrile* (6.4 g., 92%) had b. p. 126°/0.1 mm. We were unable to obtain this compound free from bromine.

11-Ethoxy-1 : 2 : 3 : 4 : 10 : 11-hexahydrofluoren-1-one (V).—The above nitrile (6.0 g.), sulphuric acid (11 ml.), and ethanol (25 ml.) were refluxed for 2 hr., the solution was worked up with water and ether, and the residue distilled (2 g.; b. p. 120—130°/0.01 mm.). *11-Ethoxy-1 : 2 : 3 : 4 : 10 : 11-hexahydrofluoren-1-one* formed needles, m. p. 149° [from light petroleum (b. p. 80—100°)] (Found: C, 78.1; H, 7.8. $C_{15}H_{15}O$ requires C, 78.2; H, 7.8%). With dinitrophenylhydrazine this ketone gave dark red plates, m. p. 280° (from acetone), of *1 : 2 : 3 : 4-tetrahydrofluoren-1-one 2 : 4-dinitrophenylhydrazone* (Found: C, 62.9; H, 4.5; N, 15.3. $C_{19}H_{16}O_4N_4$ requires C, 62.6; H, 4.4; N, 15.4%).

Ethyl γ -3-Indenylbutyrate (VIII; R = Et).—The nitrile (IV) was hydrolysed with aqueous potassium hydroxide. *γ -3-Indenylbutyric acid* formed crystals, m. p. 91—93°, from light petroleum (b. p. 80—100°) (Found: C, 77.4; H, 7.0. $C_{13}H_{14}O_2$ requires C, 77.2; H, 6.9%). Fischer-Speier esterification gave *ethyl γ -3-indenylbutyrate* (80%, from the nitrile), b. p. 116°/0.02 mm. (Found: C, 78.45; H, 8.3. $C_{15}H_{16}O_2$ requires C, 78.2; H, 7.9%), n_D^{20} 1.5362.

1 : 2 : 3 : 4-Tetrahydrofluoren-1-one (VI).—*Method A.* Powdered zinc chloride (1.0 g.) was added to *γ -3-indenylbutyronitrile* (2.0 g.) in ether (10 ml.). Hydrogen chloride was then passed for 2 hr. and the mixture diluted with water and boiled for $\frac{1}{4}$ hr. *1 : 2 : 3 : 4-Tetrahydrofluoren-1-one* (1.2 g., 60%) was obtained as plates, m. p. 104—106° [from light petroleum (b. p. 80—100°)] (Found: C, 85.0; H, 6.5. $C_{13}H_{12}O$ requires: C, 84.75; H, 6.6%). The dinitrophenylhydrazone formed red plates, m. p. and mixed m. p. 280°.

Method B. Phosphorus pentachloride (1.1 g.) was added to *γ -3-indenylbutyric acid* (1.1 g.) in benzene (20 ml.). After $1\frac{1}{2}$ hour's refluxing the solution was cooled, washed with sodium hydrogen carbonate solution, and evaporated. The residue was crystallised as before, forming pale yellow plates (0.5 g., 45%), m. p. and mixed m. p. 104—106° (Found: C, 84.7; H, 6.3%).

1-Methylfluorene (VII).—*Method A.* The above ketone (0.8 g.) in ether (10 ml.) was added to methylmagnesium bromide (from magnesium; 0.2 g.). After 1 hour's refluxing the complex was decomposed with dilute sulphuric acid, and the ether evaporated. The residue was warmed on the steam-bath for 10 min. with formic acid (5 ml.), the acid removed with sodium hydrogen carbonate from ether solution, and the residue heated with palladised charcoal (30%; 0.1 g.) at 300° for 2 hr. and then at 350° for $\frac{1}{2}$ hr. *1-Methylfluorene* (0.35 g.) formed plates (from methanol), m. p. and mixed m. p. with an authentic specimen obtained by the stepwise reduction of methyl fluorene-1-carboxylate, 85° (Found: C, 93.3; H, 6.7. Calc. for $C_{14}H_{12}$: C, 93.3; H, 6.7%).

Method B. Methyl fluorene-1-carboxylate (183 mg.) in ether (5 ml.) was added to lithium

aluminium hydride (100 mg.) in ether (10 ml.). After 1 hour's refluxing the solution was worked up in the usual way. 1-Hydroxymethylfluorene (60 mg.) had m. p. 148° (from ethyl acetate); Pinck and Hilbert⁷ record m. p. 148° for a specimen obtained differently. Hydrogenation over Adams's catalyst in glacial acetic acid gave 1-methylfluorene, m. p. 85°.

Ethyl γ -(2-Acetyl-3-indenyl)butyrate (IX; R = Et).—Aluminium chloride (6.0 g.) and acetyl chloride (3.1 ml.) in nitrobenzene (25 ml.) were added to ethyl γ -3-indenylbutyrate (10.0 g.) in nitrobenzene (25 ml.). After storage overnight the mixture was worked up with hydrochloric acid and ice, and the organic layer distilled. *Ethyl γ -(2-acetyl-3-indenyl)butyrate* (7.0 g., 59%), b. p. 184°/0.1 mm., formed needles, m. p. 46—48° [from light petroleum (b. p. 40—60°)] (Found: C, 74.8; H, 7.4. C₁₇H₂₀O₃ requires C, 75.0; H, 7.4%). γ -(2-Acetyl-3-indenyl)butyric acid, obtained by hydrolysis with 2N-hydrochloric acid, formed plates, m. p. 138—140° (from ethyl acetate) (Found: C, 73.5; H, 6.4. C₁₅H₁₆O₃ requires C, 73.5; H, 6.6%).

2-Acetyl-1-methylfluorene (X).—The above acid (1.3 g.) was converted into the acid chloride with phosphorus pentachloride (1.1 g.) in toluene (20 ml.). The toluene was removed under reduced pressure and benzene (20 ml.) added. This solution was then added to one of dimethylcadmium prepared from magnesium (0.26 g.), excess of methyl bromide, and cadmium chloride (1.0 g.) in benzene (50 ml.). The solution was refluxed for $\frac{1}{2}$ hr. and then worked up with hydrochloric acid. After extraction with sodium hydrogen carbonate solution, which removed only a very small amount of acid, the neutral residue (1.3 g.) was refluxed for 1 hr. with sodium ethoxide [from sodium (0.2 g.) and ethanol (25 ml.)], and diluted with water and ether. The residue from the ether was a dark brown oil which was extracted repeatedly with light petroleum (b. p. 80—100°). Evaporation gave a residue which crystallised from methanol giving *2-acetyl-1-methylfluorene* (25 mg.), m. p. 132° (Found: C, 86.3; H, 6.4. C₁₆H₁₄O requires C, 86.45; H, 6.35%). The ultraviolet absorption spectrum shows λ_{\max} . 305 m μ (log ϵ 4.36), λ_{\min} . 250 m μ (log ϵ 3.24). 2-Acetylfluorene shows an absorption of the same general form with λ_{\max} . 312 m μ (log ϵ 4.43), λ_{\min} . 250 m μ (log ϵ 3.5).

γ -(2-Acetyl-3-indenyl)butyronitrile.— γ -3-Indenylbutyronitrile (5.0 g.) in nitrobenzene (10 ml.) was treated with aluminium chloride (3.6 g.) and acetyl chloride (2.0 g.) in nitrobenzene (10 ml.). After storage overnight the solution was worked up in the usual manner; γ -(2-acetyl-3-indenyl)butyronitrile (2.4 g., 39%) boiled at 183°/0.5 mm. and formed needles, m. p. 72—73°, from light petroleum (b. p. 60—80°) (Found: C, 79.5; H, 6.7. C₁₅H₁₅ON requires C, 80.0; H, 6.7%).

4-Methylindan-1-one.— β -o-Tolylpropionic acid (64 g.) in benzene (200 ml.) and phosphorus pentachloride (80 g.) were kept for $\frac{1}{2}$ hr. at room temperature. The benzene was evaporated under reduced pressure, the residual acid chloride taken up in light petroleum (600 ml.; b. p. 80—100°) and the solution decanted from phosphorus compounds on to aluminium chloride (52 g.). After 2 hours' refluxing the solution was diluted with water and methylene chloride, the organic layer separated, and the residue after evaporation distilled in steam. Recrystallisation gave *4-methylindan-1-one* (44 g., 77%) as long prisms, m. p. 95° [from light petroleum (b. p. 100—120°)] (Found: C, 82.3; H, 6.9. Calc. for C₁₀H₁₀O: C, 82.2; H, 6.9%).

4-Methyl-3-indenylsuccinic Acid.—To a stirred mixture of sodium hydride (7.4 g.), dry benzene (50 ml.), diethyl succinate (55 g.), and *4-methylindan-1-one* (14.6 g.) was added a few drops of ethanol under nitrogen. After a short while the mixture began to reflux; after 1 hr. acetic acid (20 g.) in ether (200 ml.) was added. The solution was washed with water, and the acidic material extracted with sodium carbonate solution. Acidification gave an oil which was hydrolysed with aqueous potassium hydroxide. After acidification, *4-methyl-3-indenylsuccinic acid* (1.2 g.) formed prisms, m. p. 214° (decomp.) (from ethanol) (Found: C, 67.0; H, 5.3. C₁₃H₁₂O₄ requires C, 67.2; H, 5.2%).

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⁷ Pinck and Hilbert, *J. Amer. Chem. Soc.*, 1946, **68**, 751.