392. *A New Synthetical Route from Indan-1-ones to 3-Oxoindane-1-carboxylic Acids.*

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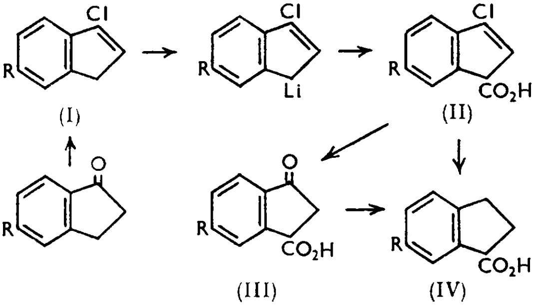
In a new approach to substitution in the 3-position of the indan-1-ones, 3-chloroindene was converted, *via* its lithium derivative, into 3-chloroindene-1-carboxylic acid. From the latter, 3-oxoindane-1-carboxylic acid and indane-1-carboxylic acid were readily obtained. The same sequence applied to 5-methoxyindan-1-one, gave 6-methoxyindane-1-carboxylic acid in small yield. 3-Bromoindene, prepared by an improved method, failed to give an ethylenic Grignard reagent.

THERE is no direct method of substituting the 3-position of indan-1-one. Although this position is relatively unreactive in the keto-form, in the enol it corresponds to the active 1-position of the indene nucleus and may be sufficiently activated to permit substitution under enolising conditions. Indan-1-ones and the related 1-oxotetralins and acetophenones are believed to enolise readily under the influence of sodium acetylide and Grignard reagents, since many of the normal ketonic reactions fail.[1-7] Used in equivalent quantity, the reagent would be expected to be destroyed by the enol; a large excess of reagent has no significant effect, for sodium acetylide fails to condense with 5-methoxyindan-1-one [1] or indan-1-one,[2] and the product is mainly unchanged ketone. However, this does not preclude the possibility of a sodium derivative's having been formed at the reactive methylene position (as in indene), for, since the systems lacked a potential reactant for such a derivative, the original ketone would still have been regenerated on acidification.

The problem is simplified by using, in place of the enol, indene derivatives easily formed from and reconverted into indan-1-one, and the reaction was explored through the 3-halogenoindenes.



The lithium derivative of 3-chloroindene [8] was carbonated under conditions which gave a high yield of carboxylic acid from indene (it is not certain whether this is the indene-1- or -3-carboxylic acid). The acidic product from 3-chloroindene contained at least two acids, one of which was 3-chloroindene-1-carboxylic acid (II; R = H); its ultra-violet absorption closely resembled that of indene-1(or 3)-carboxylic acid. Hydrolysis of 3-chloroindene-1-carboxylic acid with hydrochloric acid gave the known 3-oxoindane-1-carboxylic acid [9] (III; R = H) in quantitative yield. Other hydrolytic reagents were

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[1] Donbrow, Ph.D. Thesis, Univ. of London, 1956, 54.

[2] Mathieson, Ph.D. Thesis, Univ. of London, 1951, 94.

[3] Hertz, *J. Amer. Chem. Soc.*, 1953, **75**, 73.

[4] Wagner-Jauregg, Arnold, and Hüter, *Ber.*, 1942, **75**, 1293.

[5] Wagner-Jauregg and Hippchen, *ibid.*, 1943, **76**, 694.

[6] Campbell, Campbell, and Eby, *J. Amer. Chem. Soc.*, 1938, **60**, 2882.

[7] Dane, Höss, Bindseil, and Schmitt, *Annalen*, 1937, **532**, 39.

[8] von Braun and Ostermayer, *Ber.*, 1937, **70**, 1006.

[9] Speight, Stevenson, and Thorpe, *J.*, 1924, 2185.

unsatisfactory, 80% sulphuric acid causing partial sulphonation, and alkali causing polymerisation.

Hydrogenation of the 3-chloro-acid yielded indane-1-carboxylic acid[10] (IV; R = H). 5-Methoxyindan-1-one was similarly converted into 3-chloro-6-methoxyindene (I; R = OMe), which, because of its instability, was metallated and carbonated without isolation, yielding an amorphous mixture of acids which was hydrogenated, esterified, and separated by chromatography. A fraction, recognised as a 5- or 6-methoxyindane (light absorption maximum at 283 mμ), was hydrolysed, giving the known 6-methoxyindane-1-carboxylic acid[11] (IV; R = OMe). Traces were also obtained of a high-melting acid (pK_a 4), probably a nuclear-substituted carboxylic acid.

An apparently alternative route to indene-3-carboxylic acid is by carboxylation of the ethylenic Grignard reagent from 3-bromoindene. Jacobi[12] reported success but Porter and Suter[13] have shown that he was using 2-bromoindene. In the present work, 3-bromoindene was prepared by a modification of the method of von Braun and Ostermayer[8] in improved yield. Its ultraviolet absorption is similar to that of 3-chloroindene, except that the low-intensity bands at 279, 285, and 289 mμ are replaced by a single strong band at 287 mμ, ε 2160. There was no reaction between 3-bromoindene and magnesium, however, either under the inverse conditions reported by Jacobi to give a " vigorous " reaction or by use of activated magnesium[14] or the usual variants of the Grignard technique. In view of the increased reactivity observed in 3-chloro-6-methoxyindene, it is possible that an ethylenic Grignard could be formed from 3-bromo-6-methoxyindene.

EXPERIMENTAL

*3-Chloroindene-*1*-carboxylic Acid.*—Butyl-lithium (0·04 mole) was prepared by Gilman's method[15] and filtered off under nitrogen. A solution of 3-chloroindene[8] (3·91 g., 0·026 mole; b. p. 57—58°/1 mm.) in dry ether (20 ml.) was added dropwise during 10 min. at $< -10°$. The mixture was kept at room temperature for 10 min. and then carbonated and worked up by the usual method. The aqueous alkaline solution was separated, washed with ether, slightly acidified with dilute sulphuric acid, and extracted with ether. The ether-soluble material, on crystallisation from benzene, gave pale brown needles (1 g.), m. p. 181—182° (decomp.) [Found: C, 61·5; H, 3·6; Cl, 18·4%; equiv., 194 (by rapid direct potentiometric titration in 30% alcohol). $C_{10}H_7O_2Cl$ requires C, 61·7; H, 3·6; Cl, 18·2%; equiv., 195], $\lambda_{max.}$ in water containing 5% of ethanol 225 and 257 mμ (ε 11500 and 4130, respectively). [Indene-1(or 3)-carboxylic acid, prepared from indene and phenyl or *n*-butyl-lithium by the above method, had m. p. 161—162°, $\lambda_{max.}$ in 0·5N-aqueous sulphuric acid 226 and 265 mμ (ε 9600 and 3300, respectively)].

TABLE 1. *Absorption maxima of some indenes and indan-*1*-ones* (*solvent: ethanol*).

Compound	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ) *	ε	Compound	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ) *	ε
Indene	249	9200	279	530	3-Chloro-6-methoxyindene	268	12300	295f	3200
			285f	300				303f	1500
			290f	180	3-Oxoindane-1-carboxylic acid	244·5	11300	286	2020
3-Chloroindene ...	253	9550	279	660				291	2120
			285f	290	Indan-1-one	244	14400	286	3000
			289f	250				291·5	3100
3-Bromoindene ...	253	10100	297	2160					

* f = flat.

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[10] Linnell, Mathieson, and Modi, *J.*, 1953, 3257.
[11] Askam and Linnell, *J.*, 1954, 4691.
[12] Jacobi, *J. prakt. Chem.*, 1931, **129**, 55.
[13] Porter and Suter, *J. Amer. Chem. Soc.*, 1935, **54**, 2022.
[14] Gilman and Kirby, *Rec. Trav. chim.*, 1935, **54**, 577.
[15] Gilman, Beel, Brannen, Bullock, Dunn, and Miller, *ibid.*, 1949, **71**, 1499.

Phenyl-lithium, in place of *n*-butyl-lithium, gave a smaller yield of acids, and the 3-chloroindene-1-carboxylic acid was accompanied by traces of a yellowish-brown amorphous acid, m. p. 195°, sparingly soluble in chloroform and benzene, soluble in ethanol. When phenyl-lithium was used, the main product, on fractionation, gave (*a*) a liquid, b. p. 46°/0·2 mm., and (*b*) traces of diphenyl, b. p. 50°/0·2 mm., m. p. 69°. The main liquid had an absorption maximum at 253 mμ, characteristic of the 3-chloroindene system, and contained chlorine. It decomposed in a few hours at 15° under nitrogen to a green crystalline mass. The tar was removed with boiling benzene and the remainder dissolved in boiling chloroform, from which a tangled skein of white fibres, m. p. 350° (decomp.), axially twisted and birefringent, slowly separated.

3-*Oxoindane*-1-*carboxylic Acid*.—3-Chloroindene-1-carboxylic acid (0·3 g.) was refluxed with hydrochloric acid (10 ml.) for 4 hr. The solution was cooled, nearly neutralised, and extracted with ether. The extract gave pale yellow plates (0·27 g.), m. p. 114—116°. Crystallisation from boiling water gave hydrated 3-oxoindane-1-carboxylic acid in plates, m. p. 83·5° (lit.,[9] m. p. 84°). Stored in a vacuum desiccator (H_2SO_4), this effloresced to the anhydrous acid, m. p. 118° (lit.,[9] m. p. 120°) [Found: equiv., 177 (by semimicro-potentiometric titration). Calc. for $C_{10}H_8O_3$: equiv., 176]. Methyl 3-oxoindane-1-carboxylate 2 : 4-dinitrophenylhydrazone was prepared by boiling the free acid with Brady's reagent in methanol for 3 min.; it formed red plates, m. p. 232° (from glacial acetic acid) (Mathieson[16] gives m. p. 232—233°) (Found: C, 55·0; H, 3·7; N, 15·2. Calc. for $C_{17}H_{14}O_6N_4$: C, 55·1; H, 3·8; N, 15·1%).

When 3-chloroindene-1-carboxylic acid was heated for 4 hr. at 80° with 80% sulphuric acid, cooled, and diluted with water, 50% of starting material was deposited, and the remaining product was highly soluble in water and could not be extracted or precipitated. Alkaline hydrolysis gave a dark brown non-ketonic acid, m. p. 200° (decomp.), resistant to purification.

Indane-1-*carboxylic acid*.—(i) A solution of 3-chloroindene-1-carboxylic acid (0·195 g.) in ethanol (10 ml.) was hydrogenated [catalyst, 5% palladised strontium carbonate (0·6 g.)] to yield a mixture of the acid and ester, which was hydrolysed with 20% sodium hydroxide. Indane-1-carboxylic acid (0·115 g., 71%) was obtained by ether extraction of the acidified solution; it had m. p. 56° (from water containing a trace of dilute hydrochloric acid) (lit.,[10] m. p. 55—56°) [Found: equiv., 162 (by potentiometric titration). Calc. for $C_{10}H_{10}O_2$: equiv., 162]. The *p*-toluidide formed needles, m. p. 162—163° (lit.,[10] m. p. 162—163°) (Found: C, 81·0; H, 6·9; N, 5·5. Calc. for $C_{17}H_{17}ON$: C, 81·3; H, 6·9; N, 5·6%).

(ii) 3-Oxoindane-1-carboxylic acid (0·15 g.) was refluxed for 15 hr. with freshly-prepared zinc amalgam (0·44 g.) and a 1 : 1 mixture of hydrochloric acid and water (1 ml.). The cooled mixture yielded indane-1-carboxylic acid (0·1 g.), m. p. and mixed m. p. 56° (from acidified water) (Found: equiv., 163).

3-*Chloro*-6-*methoxyindene*.—This was prepared from phosphorus pentachloride (16·6 g.) and 5-methoxyindan-1-one (12·2 g.) in benzene (150 ml.) by the method used for 3-chloroindene. After removal of the benzene and phosphorus oxychloride at 12 mm., the liquid was fractionated, yielding (*a*) 3-chloro-6-methoxyindene (main fraction), b. p. 115—116°/1—2 mm., (*b*) b. p. 118—140°/1—2 mm. (containing some unchanged 5-methoxyindan-1-one). The fractions solidified and rapidly became tarry, even under nitrogen, and particularly during isolation after attempted recrystallisation from ether. Analytical data were obtained on samples from the first fraction, freshly recrystallised from ether, dried quickly by aspiration with nitrogen and weighed into tared flasks containing ethanol [Found (by hydrolysis with 50% sulphuric acid, partial neutralisation, and potentiometric titration with silver nitrate): Cl, 19·4. Calc. for $C_{10}H_9OCl$: Cl, 19·6%)]. 5-Methoxyindan-1-one was recovered from the hydrolysate. The ultraviolet absorption, determined on ethanol solutions similarly prepared (Table 1), readily distinguished the chloromethoxyindene from 5-methoxyindan-1-one, which has additional characteristic peaks at 287·5 and 294·5 mμ.

Subsequent preparations were conducted under a stream of dry nitrogen, which was led into a series of potash traps, the contents of which were periodically analysed for chloride content. Evolution of hydrogen chloride was complete, and 95% of theory, after 6 hr. After removal of the benzene and by-products under nitrogen, the absence of 5-methoxyindan-1-one was shown spectrophotometrically, and the chlorine content of a sample checked by reduction with sodium in alcohol and argentometric titration.

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[16] Mathieson, personal communication.

6-*Methoxyindane-1-carboxylic Acid.*—Crude 3-chloro-6-methoxyindene (4·51 g., 0·025 mole), prepared as above, was dissolved in 1 : 1 benzene–ether and treated with a solution of *n*-butyllithium (0·03 mole) at 15°. The solution was carbonated immediately. The crude *acid* (1·2 g.) yielded pale brown needles (0·2 g.), m. p. 170° (decomp.) (Kofler block), from benzene [Found: Cl, 15·6% (by hydrolysis and potentiometric titration with silver nitrate); equiv., 231 (by hydrolysis). $C_{11}H_9O_3Cl$ requires Cl, 15·8%; equiv., 225].

The crude chloro-acids (0·7 g.) were hydrogenated (5% palladised strontium carbonate) in ethanol, and gave a partially esterified product. The separated ester (0·23 g.) had the ultraviolet absorption of a 5- or 6-methoxyindane ($\lambda_{max.}$ 283 mμ, ε 3200, calc. as $C_{13}H_{16}O_3$). The free acids were esterified with diazomethane, dissolved in the minimum of benzene, and a solution in light petroleum separated on alumina, from which the indane fraction (0·2 g.) was eluted with light petroleum. The combined indane fractions were hydrolysed by boiling 20% hydrochloric acid, giving a near-quantitative yield of 6-methoxyindane-1-carboxylic acid, m. p. 109·5—110° (from boiling water) (Found: C, 68·5; H, 6·4%; equiv., 195. Calc. for $C_{11}H_{12}O_3$: C, 68·7; H, 6·3%; equiv., 192). A mixture with a sample prepared by Dr. V. Askam by Clemmensen reduction of 6-methoxy-3-oxoindane-1-carboxylic acid[11] had the same m. p.

Several amorphous non-volatile fractions were obtained on elution of the alumina column with benzene and benzene–ethanol. On hydrolysis the largest fraction gave an acid, traces of which crystallised from benzene (Found: equiv., approx. 155); it had pK_a 4 (approx.) in 30% ethanol and gave a brown precipitate with ferric chloride solution.

3-*Bromoindene.*—To a stirred suspension of phosphorus pentabromide (46·2 g., 0·106 mole) in benzene (50 ml.) was added a solution of indan-1-one (13·2 g., 0·1 mole) in benzene (25 ml.) followed by benzene (10 ml.), the temperature being kept below 5°. The solution was stirred for 2 hr. at 5° and the bulk of the hydrogen bromide removed at 20°/12 mm. The benzene solution was added to crushed ice (500 g.) and the benzene was separated immediately upon liquefaction, washed with ice-cooled water, 5% sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4). Evaporation and storage over solid carbon dioxide gave pale brown crystals (5·4 g.) of 3-bromoindene. The residual liquid gave two fractions (*a*) b. p. 120—130°/1—2 mm. (indan-1-one) and (*b*) b. p. >140°/1—2 mm. (mainly 3-bromoindene). The yield of 3-bromoindene was 6·8 g. (35%); the yield from the method of von Braun and Ostermayer[8] was 10%. Recrystallised from ether–light petroleum (b. p. 40—60°) 3-bromoindene formed pale yellow prisms (5 g.), m. p. 37° (lit.,[8] m. p. 42°) (Found: C, 55·5; H, 3·6; Br, 40·5. Calc. for C_9H_7Br: C, 55·4; H, 3·6; Br, 41·0%). When refluxed with hydrochloric acid for 6 hr., 3-bromoindene yielded indan-1-one, m. p. and mixed m. p. 42°.

When the reaction mixture was kept for some time before being worked up, the yield of 3-bromoindene was lower and there was also formed a *dibromide*, m. p. 174° (Found: Br, 56·8. $C_9H_7Br_2$ requires Br, 58·0%).

Some of the microanalyses were carried out in the microanalytical laboratory (Mr. Crouch) of the University of London School of Pharmacy. I thank Professor W. H. Linnell for his interest.

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