The Base-Catalyzed Reaction of Fluorene and Indene with Lactones and Hydroxy Acids

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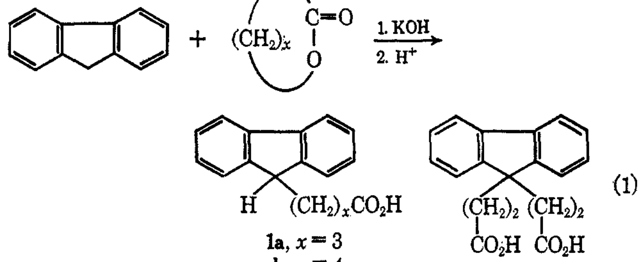
The alkylation of fluorene and indene[2] with alcohols gives 9-alkylfluorenes and 1,3-dialkylindenes in high yield. The reaction has been extended to cover reactions of hydroxy acid salts with indole[3] to form 3-indolealkanoic acids. This Note reports the base-catalyzed reaction of hydroxy acid salts with fluorene to give 9-fluorenylalkanoic acids and with indene to give 3-indenylalkanoic acids and 1,3-indenedialkanoic acids. The hydroxy acid salts were normally generated *in situ* by the reaction of strong base, such as potassium hydroxide, with lactones. Most of the compounds synthesized by this technique were unreported prior to this work.

Treatment of fluorene with γ-butyrolactone, δ-valerolactone, and ε-caprolactone in the presence of potassium hydroxide at 200–220° produced 9-fluorenylalkanoic acids 1a–c in yields of 33, 83, and 96%, respectively (eq 1). Similarly, reaction of fluorene with propiolactone gave diacid 2, while glycolic acid afforded 9-fluorenylacetic acid in 10% yield. Bachmann and Sheehan[4] have previously synthesized 9-fluorenylacetic acid using a four-step process. The acid products from these reactions were normally isolated as the methyl esters for analytical evaluation. A summary of these reactions is found in Table I and the properties of the products are found in Table II.



1a, $x = 3$
b, $x = 4$
c, $x = 5$

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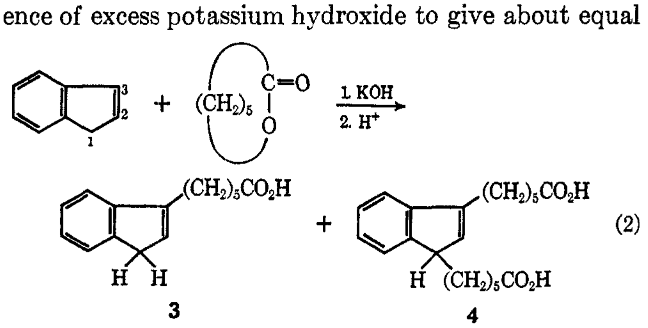
(1)

Indene also reacted with ε-caprolactone in the presence of excess potassium hydroxide to give about equal amounts of 6-(3-indenyl)caproic acid, **3**, and 1,3-bis(carboxypentyl)indene, **4**. These products were isolated and identified as their methyl esters.



3 **4**

(2)

TABLE I

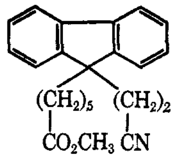
BASE-CATALYZED REACTIONS OF FLUORENE WITH LACTONES AND HYDROXY ACIDS[a]

Lactone, x	Temp, °C	Time, hr	Yield of 1, %	Efficiency on fluorene, %
2[b]	220	20	18	67
3	220	22	33	67
4	220	20	83	91
5[c]	220	20	96	100
1[d]	250	20	10	20

[a] All runs in stainless steel rocker autoclave unless otherwise noted. [b] Product was the diacid 9,9-bis(carboxyethyl)fluorene, **2**. [c] Run at atmospheric pressure at reflux of reaction mixture. [d] Glycolic acid used as starting material.

Other substrates which were tried in this general reaction of hydroxy acid salts with active methylene-containing compounds were diphenylmethane, 9,10-dihydroanthracene, 9,10-dihydrophenanthrene, and 9-methylfluorene. Only 9,10-dihydroanthracene gave a product and that was only a 5% yield of acidic material containing an anthracene, rather than dihydroanthracene, nucleus. The failure of these compounds to react can be rationalized on mechanistic grounds which will be discussed below.

The structure proof of the fluorene and indene derivatives was provided by a combination of nmr, infrared, and ultraviolet spectroscopy along with elemental analysis, and comparison of properties with those of identical compounds in the literature, when available. For example, the nmr spectrum of fluorene contains a sharp singlet of δ 3.8 representing the methylene protons of carbon 9. The fluorene compounds which were disubstituted on the 9 position showed no resonance in this area. The eight protons of the aromatic rings were observed in a complex multiplet between δ 7.0 and 7.8. Fluorene derivatives singly substituted at carbon 9, such as 9-fluorenylacetic acid and methyl 6-(9-fluorenylcaproate), gave triplets representing single protons centered at δ 4.38 and 3.80, respectively. When methyl 6-(9-fluorenyl)caproate was cyanoethylated by the method of Bruson[5] to form **5** this triplet disappeared.



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In all cases, the number of aromatic protons stayed constant at eight.

The nmr spectrum of indene showed peaks centered at δ 3.20 for the two protons of the carbon 1 methylene groups and peaks centered at δ 6.35 and 6.75, representing one proton each, for the 2 and 3 position protons, respectively. The nmr spectrum of methyl 6-(3-indenyl)caproate, **6**, showed no proton at carbon 3 and absorption at δ 6.07 for the carbon 2 proton and a quartet at δ 3.2 representing two protons. The disubstituted indene showed a single proton at carbon 1 (δ 3.2) as well as a single proton at carbon 2 (δ 6.10). In both cases,

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(1) To whom inquiries should be addressed.

(2) (a) H. E. Fritz, D. W. Peck, M. A. Eccles, and K. E. Atkins, *J. Org. Chem.*, **30**, 2540 (1965); (b) K. L. Schoen and E. I. Becker, *J. Amer. Chem. Soc.*, **77**, 6030 (1955).

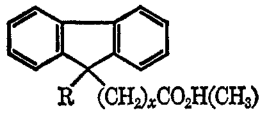
(3) (a) H. E. Fritz, *J. Org. Chem.*, **28**, 1384 (1963); (b) H. E. Johnson and D. G. Crosby, *ibid.*, **28**, 1246 (1963).

(4) W. E. Bachmann and J. C. Sheehan, *J. Amer. Chem. Soc.*, **62**, 2687 (1940).

(5) H. A. Bruson, *ibid.*, **64**, 2457 (1942).

TABLE II

PROPERTIES OF 9-FLUORENYL ACIDS AND METHYL ESTERS[a]

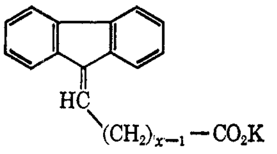


	x	Acid or ester mp, °C	Methyl ester bp (mm), °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Sapon equiv Calcd	Sapon equiv Found
Acid[b]	2	282–284[c]	. . .	73.53	5.85	73.72	6.05	. . .	. . .
Ester	2	83–84[d]	196–200 (0.4)	74.50	6.60	74.50	6.60	169	170
Acid	3	133–133.5[d]	. . .	80.92	6.39	81.10	6.48	. . .	. . .
Ester	3	52[c]	166–170 (0.4)	81.21	6.78	81.29	6.95	266	263
Acid[e]	4	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Ester	4	39[f]	212 (3)	81.43	7.14	81.52	7.41	280	277
Ester[g]	4	. . .	270 (10)	82.49	9.06	82.46	8.91	378	377
Acid	5	66[d]	. . .	81.40	7.19	81.61	7.25	. . .	. . .
Ester	5	43–44[c]	195–197 (1)	81.60	7.70	81.66	7.53	284	294
Acid[h]	1	131–132[i]	. . .	80.30	5.40	80.20	5.50	. . .	. . .

[a] R = H except where $x = 2$, then it is –$(CH_2)_2CO_2H(CH_3)$. [b] Neut equiv, 153 (calcd 155). [c] Recrystallized from methanol. [d] Recrystallized from cyclohexane. [e] Acid only isolated as methyl ester. [f] Recrystallized from hexane. [g] 2,2,4-Trimethylpentyl ester. [h] Neut equiv, 229 (calcd 224). [i] Lit.[4] mp 131–132°.

the aromatic pattern remained consistent with that of indene and represented four protons.

The proposed mechanism for the reaction of both fluorene and indene with lactones is analogous to that relayed by Schoen and Becker[2] for the alkylation of fluorene with alcohols. The first step is the reaction of lactone with potassium hydroxide to yield the salt of the hydroxy acid. Next the alcohol function is oxidized or dehydrogenates to the corresponding aldehyde and this aldehyde condenses with a fluorenyl anion to form an alkylidene compound, 7, which is reduced either by



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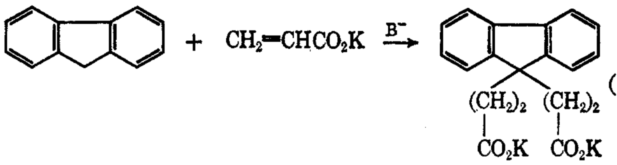
hydrogen present from dehydrogenation of the alcohol group or by alkoxide to yield product.

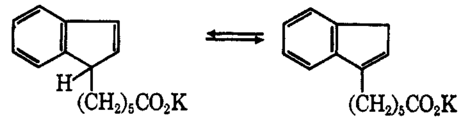
This mechanism explains why no product is formed when 9-substituted fluorenes are used as substrates since both methylene hydrogens are needed to yield the intermediate alkylidene compound. The failure of diphenylmethane to react can be rationalized by the fact that its pK_a is 35[6] while those of indene[5] and fluorene[5] are 21 and 25, respectively. The acidity of these methylene protons could determine whether an anion would be formed under the reaction conditions.

This mechanism also explains why only monosubstituted fluorenes are obtained, except in the case of propiolactone. When this lactone is opened with potassium hydroxide it forms a hydroxy acid salt which upon dehydration could yield an acrylate salt. Acrylate esters[7] are known to condense with compounds containing activated methylene groups under basic catalysis (Michael reaction), but the use of acrylate salts is not reported. It is thought that this sequence is followed in the propiolactone experiments to yield 9,9-disubstituted fluorenes just as occurs when fluorene is cyanoethylated[5] with acrylonitrile under basic catalysis. The use of acrylate salts in the Michael reaction has been studied and will be reported in the following communication.



(3)

The reaction of indene with ε-caprolactone also fits this mechanistic sequence. Indene would first be attacked at the methylene group and then the double bond isomerized to provide another methylene group for reaction, thus explaining the disubstituted product observed (eq 4 and 5).



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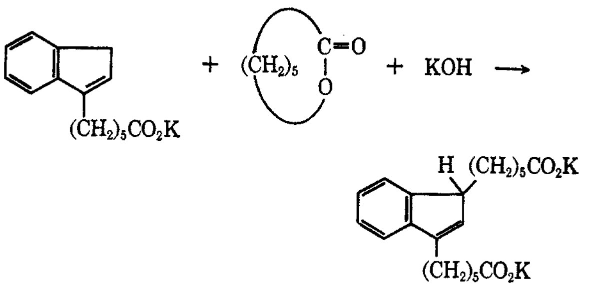

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Experimental Section

Melting points were obtained on a Fisher-Johns melting point block. Infrared spectra were recorded by a Beckman IR-4, ultraviolet spectra by a Cary Model 21 spectrophotometer, and nuclear magnetic resonance spectra by a Varian Associates Model A-60 spectrometer. Elemental analysis was performed by the UCC Chemicals and Plastics Division R and D analytical group.

General Procedure for the Reaction of Lactones with Fluorene. Autoclave Preparation.—To a stainless steel rocker autoclave were charged fluorene (1.0 mol), lactone or hydroxy acid (1.1 mol), and potassium hydroxide (1.3 mol). In the case of propiolactone, a higher yield was obtained if 2.1 mol were used. This mixture was heated to 220° and held for 20 hr. The cooled reaction mixture was treated with water and extracted with isopropyl ether to remove any unreacted fluorene. The aqueous layer was acidified with concentrated hydrochloric acid to release

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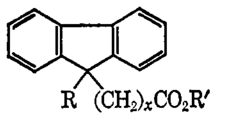
(6) W. K. McEwen, *J. Amer. Chem. Soc.*, **58**, 1124 (1936).

(7) E. B. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

TABLE III

INFRARED SPECTRA[a] OF 9-FLUORENYLALKANOIC ACIDS AND METHYL ESTERS



R	R'	*x*	Primary absorption bands,[b] μ									
H	H	1	3.0–3.9 (b)	5.84 (s)	6.9, 7.0, 7.1 (t)	7.82 (m)	8.10 (m)	10.70 (m)	13.52 (s)			
H	H	3	3.0–4.0 (b)	5.85 (s)	6.9–7.09 (d)	7.75 (m)	8.05 (m)	10.70 (m)	13.53 (s)			
H	H	4	3.0–4.0 (b)	5.84 (s)	6.9–7.05 (d)	7.80 (m)	8.10 (m)	10.70 (m)	13.54 (s)			
H	H	5	3.0–4.0 (b)	5.88 (s)	6.9–7.08 (d)	7.80 (m)	8.18 (m)	10.75 (m)	13.60 (s)			
$(CH_2)_2$ CO_2H	H	2[c]	3.0–4.0 (b)	5.80 (s)	6.91–6.99 (d)	7.72 (m)	8.22 (m)	10.70 (m) 10.90	13.65 (s)			
H	CH_3	3	3.25	3.39	3.45	5.71 (s)	8.10 (m)	8.35 (m)	8.55 (m)	8.71 (m)	13.0 (w)	13.50 (s)
H	CH_3	4	3.22	3.42	3.51	5.78 (s)	8.05 (m)	8.20 (m)	8.41 (m)	8.58 (m)	13.05 (w)	13.54 (s)
H	CH_3	5	3.29	3.42	3.51	5.79 (s)	8.03 (m)	8.41 (m)	8.60 (s)	8.88 (w)	13.09 (w)	13.60 (s)
$(CH_2)_2$ CO_2CH_3	CH_3	2	3.30	3.40	3.50	5.72 (s)	8.02 (m)	8.39 (s)	8.55 (s)		13.15 (m)	13.55 (s)

[a] Unless otherwise designated, spectra were recorded in CCl_4 from 2.0 to 7.5 μ and in CS_2 from 7.5 to 15.0 μ. [b] b = broad, s = strong, m = medium, w = weak, d = doublet, t = triplet. [c] KBr pellet.

the organic acid product. The carboxylic acid was either recrystallized or converted into the methyl ester by refluxing in excess methanol with a catalytic amount of *p*-toluenesulfonic acid. The ester was then distilled under reduced pressure and, if the cuts solidified, was recrystallized.

Atmospheric Pressure Procedure.—The same molar ratios as used above were employed in these reactions. A stainless steel flask rather than a glass flask was used because of the deleterious effect of alkali hydroxides on glassware at high temperatures. The reaction mixture was stirred and heated at reflux and the water formed in the reaction collected in a trap. Some exothermicity was observed during the reaction and care was taken to leave plenty of empty space in the reaction flask. The workup technique used was the same as that outlined above.

The structures of the products from the above reactions were elucidated by nmr, ir, and uv spectroscopy, elemental analysis, neutralization equivalents, and saponification equivalents. Most of these properties are found in Tables II and III and in the discussion section. The uv spectra of these materials are very similar to that of fluorene with about the only significant change being a bathochromic shift of 2–3 mμ for each additional substituent in the 9 position.

9-Carbmethoxypentyl-9-cyanoethylfluorene (5).—A solution of 109 g (0.37 mol) of methyl 6-(9-fluorenyl)caproate and 1000 ml of dioxane was charged to a reaction flask and 10 g of 32% Triton B (benzyltrimethylammonium hydroxide) in methanol was added. Acrylonitrile, 50 g (0.94 mol), was added over 5 min without any sign of reaction; therefore, the mixture was heated to reflux and stirred for 6 hr. About halfway through an additional 10 g of Triton B was added. After cooling to room temperature, the reaction mixture was treated with 2 l. of water and extracted twice with 500-ml portions of benzene. The benzene layers were combined and washed with water several times. After removal of the solvent, the solid product was recrystallized once from cyclohexane and once from methanol to yield 42 g of the methyl ester of 9-carboxypentyl-9-cyanoethylfluorene, **5** (mp 95–96°). The ir spectrum (CS_2 and CCl_4) exhibited primary absorption at 3.28, 3.41, 3.50, 4.43 (C≡N), 5.76 (C=O), 6.9, 7.45, 8.35, 8.58, 12.9, 13.2, and 13.60 μ (fluorene ring); nmr ($CDCl_3$), δ 4.58 for the methyl group, δ 7.32 and 7.70 for the ring protons, and two groups from δ 1.20 to 1.70 and from 1.85 to 2.55 representing the other protons. The integrated areas were consistent with the structure assignments.

Anal. Calcd for $C_{23}H_{25}O_2N$: C, 79.50; H, 7.69; N, 4.23. Found: C, 79.70; H, 7.49; N, 4.04.

Methyl 6-(3-Indenyl)caproate (6) and 1,3-Bis(carbomethoxypentyl)indene (8).—There were charged to a 3-l. stainless steel rocker autoclave 129 g (1.1 mol) of indene, 139 g (1.2 mol) of ε-caprolactone, and 100 g (1.5 mol) of 85% potassium hydroxide pellets and this mixture was heated to 200° for 20 hr. The solid reaction product was treated with water and extracted with isopropyl ether to remove any unreacted indene. The aqueous layer was cooled with ice and acidified with concentrated hydrochloric acid releasing 191 g of an oil which became semisolid on standing. This material was esterified by refluxing for 20 hr with 2 l. of methanol and 5 g of *p*-toluenesulfonic acid. The reaction mixture was treated with 1 l. of water and extracted twice with 250-ml portions of isopropyl ether. The combined ether layers were washed once with 100 ml of 5% sodium hydroxide solution and with water until neutral. The ether was removed and the ester mixture distilled under reduced pressure giving 42 g (15.7%) of methyl 6-(3-indenyl)caproate (**6**) [bp 145° (0.45 mm); $n^{20}D$ 1.5327] and 61 g (27%) of the dimethyl ester of 1,3-bis(carboxypentyl)indene (**8**) [bp 222° (0.4 mm); $n^{20}D$ 1.5250]. The ir (CS_2 and CCl_4) of both **6** and **8** exhibited bands at 5.73 μ (C=O); nmr of **6** (CCl_4), δ 1.4–1.85 (m, six protons), 2.1–2.58 (m, four protons), 3.2 (q, two protons), 4.55 (s, three protons), 6.08 (one proton), and 7.05–7.38 (m, four protons).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.36; H, 8.37.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66; mol wt, 372.5. Found: C, 74.47; H, 8.51; mol wt (by freezing point depression of benzene), 372.

Registry No.—Fluorene, 86-73-7; indene, 95-13-6; 9-fluorenylacetic acid, 6284-80-6; **1a**, 16425-43-7; **1a** methyl ester, 16425-44-8; **1b**, 16425-45-9; **1b** methyl ester, 16425-46-0; **1b** 2,2,4-trimethylpentyl ester, 16425-47-1; **1c**, 16425-48-2; **1c** methyl ester, 16425-49-3; **2**, 4425-95-0; **2** dimethyl ester, 13098-97-0; **5**, 16605-83-7; **6**, 16425-52-8; **8**, 16452-33-8.

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The Michael Reaction of Acrylate Salts

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The Michael reaction[2] has been well reviewed and is an important synthetic tool. Briefly, it consists of the reaction of a carbanion with an electron-deficient unsaturated system.

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(1) To whom inquiries should be addressed.

(2) E. B. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).