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Reactions of Ethyl 2-(1-Indanylidene)cyanoacetate Anion with Alkylating Agents and Aldehydes

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Ethyl 2-(1-indanylidene)cyanoacetate (I) was treated with phenylmagnesium bromide and the resultant ambident anion (II) was reacted with a few alkylating agents and aldehydes. Interestingly, the alkylation reactions of the alkylidenecyanoacetate system were accompanied by γ-alkylation to a significant extent together with the preferred α-alkylation. The anion was also formed by the use of sodium hydride and subjected to the alkylation reactions. It seems that the alkylation reactions are dependent upon metal counterions yielding α- and γ-substituted products in a different proportion. Reactions of the anion with aldehydes afforded a diene (VI) and lactone (VII) which were formed as the result of an exclusive reaction at the γ-position.

Keywords——indan derivatives; Grignard reagent; γ-alkylation; regioselectivity; metal counterion; reaction with aldehyde

Enolate anions derived from α,β-unsaturated carbonyl systems are ambident in their behavior toward carbon alkylation. Although conceptually an alkylating agent may form a C–C bond either at the α- or γ-carbon, C-alkylation occurs almost exclusively at the α-carbon of the highest electron density.[2] For this reason the γ-alkylation of α,β-unsaturated carbonyl systems has been a subject of considerable interest.[3] During synthetic studies on indan derivatives, as part of a search for drugs active on the central nervous system, we found that γ-alkylation occurred in a significant amount along with the preferred α-alkylation in alkylation reactions of the anion formed by treatment of ethyl 2-(1-indanylidene)cyanoacetate (I) with a Grignard reagent. This paper reports the alkylation reactions and, in addition, the reaction of the anion II with aldehydes which may provide a synthetic method for the preparations of certain indan derivatives.

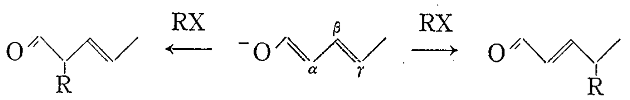

Chart 1

Alkylidenemalonates and -cyanoacetates are known to undergo conjugate addition reaction with a Grignard reagent, especially in the presence of cuprous ion.[4] With the aim of preparing an indan derivative bearing a diphenylmethane structure, I was subjected to reaction with phenylmagnesium bromide. The Grignard reaction did not afford the desired

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2) M.W. Rathke and D. Sullivan, *Tetrahedron Lett.*, **1972**, 4249; J.L. Herrmann, G.R. Kieczykowski, and R.H. Schlessinger, *Tetrahedron Lett.*, **1973**, 2433; H.O. House, "Modern Synthetic Reactions," 2nd ed., W.A. Benjamin, Menlo Park, Calif., 1972, pp. 536—537.

3) *a*) J.A. Katzenellenbogen and A.L. Crumrine, *J. Am. Chem. Soc.*, **96**, 5662 (1974); *b*) J.A. Katzenellenbogen and A.L. Crumrine, *J. Am. Chem. Soc.*, **98**, 4925 (1976); *c*) L.S. Melvin and B.M. Trost, *J. Am. Chem. Soc.*, **94**, 1790 (1972); *d*) B.S. Pitzele, J.S. Baran and D.H. Steinman, *J. Org. Chem.*, **40**, 269 (1975); *e*) P.E. Pfeffer, L.S. Silbert, and E. Kinsel, *Tetrahedron Lett.*, **1973**, 1163.

4) *a*) H.O. House, "Modern Synthetic Reactions," 2nd ed., W.A. Benjamin, Menlo Park, Calif., 1972, p. 534; *b*) A.C. Cope, H.L. Holmes, and H.O. House, "Organic Reactions," Vol. 9, ed. by R. Adams, John Wiley and Sons, Inc., New York, 1957, p. 107.

1,4-addition product, but resulted in the recovery of the starting material from the deeply red-colored reaction mixture. This result suggested that the Grignard reagent acted on I as a base[5] and the resultant colored anion was reversed to I after the usual work-up. In order to examine the reactivity of the anion, alkylating agents such as methyl iodide, benzyl bromide and allyl bromide were reacted with the anion. Benzylation of the anion with benzyl bromide gave rise to a mixture of the α- and γ-benzylated derivatives (IIIb and IVb) in a ratio of *ca.* 3:1 which were separated as crystals by fractional recrystallization from ethanol. The structures of IIIb and IVb were determined on the basis of elementary analysis ($C_{21}H_{19}NO_2$), mass (MS) (*m/e* 317 (M^+)), infrared (IR), ultraviolet (UV) and nuclear magnetic resonance (NMR) spectra. The NMR spectrum of IIIb exhibited an AB-quartet (J=14.5 Hz) at 3.58 and 3.69 ppm due to the benzylic methylene protons, a triplet (J=2.0 Hz) at 6.65 ppm due to one olefinic proton and a doublet (J=2.0 Hz) at 3.38 ppm due to the indene ring methylene protons. The non-conjugated cyano and ester carbonyl groups were indicated by the IR spectrum showing absorption bands at 2260 and 1743 cm^{-1}, respectively. On the other hand, in the NMR spectrum of IVb the benzylic methylene protons appeared as a double doublet at 2.83 ppm (J=3, 18 Hz) and 2.93 ppm (J=6, 18 Hz). The conjugated ester carbonyl band occurred at a lower frequency (1723 cm^{-1}) compared with that of IIIb. The UV spectrum of IVb exhibited absorption maxima at 306 and 327 nm which were similar to that of I, indicating the presence of the indanylidenecyanoacetate structure in IVb.

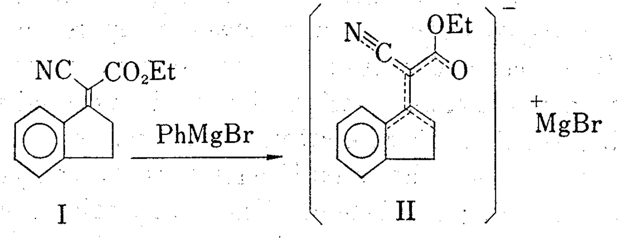
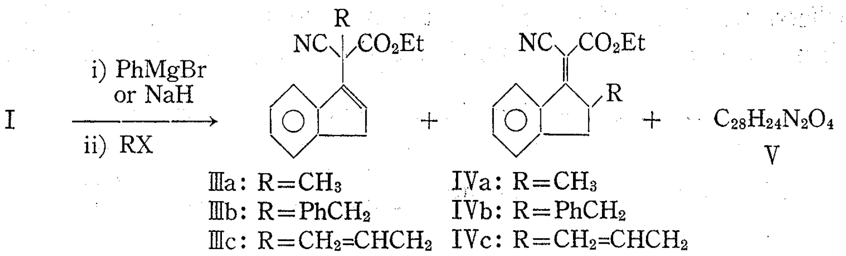


Chart 2



IIIa: R=CH_3 IVa: R=CH_3
IIIb: R=$PhCH_2$ IVb: R=$PhCH_2$
IIIc: R=CH_2=$CHCH_2$ IVc: R=CH_2=$CHCH_2$

Chart 3

Similarly, the anion II was treated with methyl iodide to yield approximately a 3:1 mixture of α- and γ-methylated compounds (IIIa and IVa). The two isomeric products could not be separated, but the proportion of the two isomers was determined by gas chromatography and NMR spectrum.

The above two alkylation reactions yielded a small amount of an uncharacterized by-product (V) formulated as $C_{28}H_{24}N_2O_4$ by the mass spectrum and elementary analysis. The minor product was, however, shown by NMR spectrum not to be an alkylation product, but to be derived from two molecules of I.

Treatment of the anion II with allyl bromide also afforded α- and γ-allylated products (IIIc and IVc). On heating at 130° the α-isomer IIIc readily underwent a Cope rearrangement to the γ-allyl isomer IVc which was identical with the minor product formed in the alkylation reaction.[5b] Ingold's[6] and Cope's groups[5b] previously performed the alkylation of the indanylidenecyanoacetate I by the use of sodium ethoxide as a base to obtain only the α-isomer.

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[5] *a*) G. Stork and S.R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963); *b*) A.C. Cope and L. Field, *J. Am. Chem. Soc.*, **71**, 1589 (1949).

[6] C.K. Ingold and J.F. Thorpe, *J. Chem. Soc.*, **115**, 143 (1919).

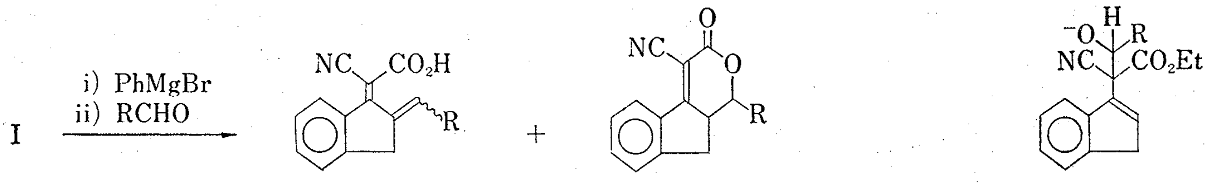
Recently Katzenellenbogen and co-workers[3b)] have reported that lithium dienolate dianions derived from α,β-unsaturated carboxylic acids underwent almost exclusive α-alkylation, but γ-alkylation took place regioselectively when the dicopper anions were alkylated. Copper dienolates generated from α,β-unsaturated esters also underwent γ-alkylation, although the regioselectivities were lower compared with the corresponding α,β-unsaturated acids.[3a)] However, γ-alkylation in that system proceeded by the S_N2' mechanism involving allylic transposition and γ-alkylation products could not be obtained in the alkylation using alkylating agents such as methyl iodide and benzyl bromide. Therefore, it is interesting that the alkylations of the anion II with these two alkylating agents are accompanied by a considerable amount of γ-alkylation. The γ-alkylation appears to be partly responsible for the presence of the benzene ring which may participate in the stabilization of the anion. It should be also pointed out that a counterion, such as the magnesium bromide ion, may effect the γ-alkylation, since the proportion of γ-/α-alkylation was lowered considerably when sodium hydride was utilized in place of phenylmagnesium bromide for these alkylation reactions (Table I). Each metal counterion seems to have almost an equal influence on the regioselectivities of the two alkylation reactions. In these reactions the γ-/α-isomer ratio was practically the same as long as the same metal ion is present as a counterion. Further investigation is needed for clarification of the relation between the structure of the anion and the γ-alkylations.

TABLE I. Regioselectivity in the Alkylation of Cyanoester (I)

Alkylating agent	Metal ion[a)]	Ratio of α : γ alkylated product[b)]	Yield (%)
CH_3I	Mg^{2+}	3 : 1	72
	Na^+	7 : 1	53
$PhCH_2Br$	Mg^{2+}	3 : 1	73
	Na^+	7 : 1	86

a) Mg^{2+}: Phenylmagnesium bromide was used as a base.
Na^+: Sodium hydride was used as a base.
b) The ratio of α-alkylated products to γ-alkylated products was determined by ^1H NMR spectrum.

The anion II also underwent reaction with aldehydes such as acetaldehyde and benzaldehyde. Reaction of the anion with acetaldehyde afforded both diene (VIa) and lactone (VIIa) in yields of 47 and 25%, respectively. The NMR spectrum of VIa in $CDCl_3$ showed a broad singlet centered at 10.42 ppm for the carboxylic acid proton, a broad singlet at 3.72 ppm for the indan CH_2 and a doublet (J=7 Hz) at 2.03 ppm for methyl protons. The IR spectrum revealed absorption bands at 2210 and 1700 cm^{-1} due to the CN and COOH group, respectively. The diene could be cyclized to the lactone derivative VIIa by heating at 110°. The presence of the conjugated lactone was shown by the IR spectrum exhibiting an absorption band at 1720 cm^{-1}. The methyl protons of the lactone resonate at a higher field (1.55 ppm) compared with those of the diene. The anion II when reacted with benzal-



VIa : R=CH_3
VIb : R=Ph

VIIa : R=CH_3
VIIb : R=Ph

VIII

Chart 4

dehyde yielded only the diene derivative (VIb). The diene was similarly converted into the lactone derivative (VIIb) either by refluxing in ethanol or by treatment with an acid. It is interesting that the reactions of the anion with the aldehydes were not accompanied by the α-substituted prodoct (VIII) corresponding to III. It can be assumed that the kinetically controlled product (VIII) is, if formed, labile and isomerizes to the thermodynamically stable γ-substituted isomer VI or VII.

Experimental

Melting points were obtained on a Yanagimoto micro melting point apparatus and uncorrected. Infrared spectra were taken using a Jasco A-2 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60D or HA-100 spectrometer using tetramethylsilane as an internal standard. The chemical shifts of various compounds are given in δ units.

Benzylation of II with Benzyl Bromide——To a solution of phenylmagnesium bromide prepared from bromobenzene (2.59 g), Mg (0.40 g) and a small amount of I_2 in tetrahydrofuran (THF) (20 ml) was added in one portion with cooling at 0° the cyanoester (I, 3.41 g).[5b,6] The colored solution was stirred for 10 min at room temperature, cooled to 0° and benzyl bromide (2.82 g) was added dropwise. The mixture was stirred for 12 hr and extracted with CH_2Cl_2. The extract was washed with H_2O and saturated brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil. The residual oil was chromatographed on a column of silica gel with benzene, affording 2.6 g (73%) of a mixture of IIIb and IVb (3: 1), along with 0.87 g of the starting material (I). The mixture was recrystallized from EtOH, affording 1.83 g of IIIb, mp 120° and 0.08 g of IVb as needles, mp 120°. α-Substituted compound (IIIb), NMR ($CDCl_3$) δ: 1.13 (t, $J=7.5$ Hz, 3H, $C\underline{H}_3CH_2-$), 3.38 (d, $J=2.0$ Hz, 2H, allylic protons of indene), 3.58, 3.69 (AB-q, $J=14.5$ Hz, 2H, $C\underline{H}_2Ph$), 4.21 (q, $J=7.5$ Hz, 2H, $CH_3C\underline{H}_2-$), 6.65 (t, $J=2.0$ Hz, 1H, olefinic proton). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 2260 (CN), 1743 (ester). UV $\lambda_{\max}^{\text{EtOH}}$ nm: 253. MS *m/e*: 317 (M^+ for $C_{21}H_{19}NO_2$). *Anal.* Calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.54; H, 5.96; N, 4.51.

γ-Substituted compound (IVb), NMR in 100 MHz ($CDCl_3$) δ: 1.41 (t, $J=7.0$ Hz, 3H, $C\underline{H}_3CH_2-$), 2.19 (d-d, $J=9$, 13 Hz, 1H, C_3–H_2 of indan), 2.83 (d-d, $J=3$, 18 Hz, 1H, CH_2Ph), 2.93 (d-d, $J=6$, 18 Hz, 1H, $C\underline{H}_2Ph$), 3.12 (d-d, $J=3.5$, 13 Hz, 1H, C_3–H_2 of indan), 4.37 (q, $J=7.0$ Hz, 2H, $CH_3C\underline{H}_2-$), 4.5 center (m, 1H, C_2–H of indan), 7.2—7.6 (m, 8H, aromatic protons), 8.5—8.7 (m, 1H, C_7–H of indan). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 2240 (CN), 1723 (ester). UV $\lambda_{\max}^{\text{EtOH}}$ nm: 306, 327. MS *m/e*: 317 (M^+ for $C_{21}H_{19}NO_2$). *Anal.* Calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.44; H, 5.97; N, 4.30. In addition to the above products a trace amount of V was detected on thin layer chromatography.

Methylation of II with Methyl Iodide——According to the above procedure, a THF solution of the anion (II) was prepared from the cyanoester (I, 3.41 g) and 1.1 equimolar amounts of phenylmagnesium bromide in THF (20 ml). To this solution was added dropwise with stirring and cooling at 0° methyl iodide (6.39 g). After stirring for 12 hr at room temperature, the reaction mixture was cooled in ice-water, treated with 10% NH_4Cl and extracted with CH_2Cl_2. The extract was washed with H_2O and saturated brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residual oil was chromatographed on a column of silica gel with benzene–AcOEt (4: 1), affording 2.6 g (72%) of a 3: 1 mixture of IIIa and IVa as an oil and 35 mg of V as a solid, mp 228—231°. MS *m/e*: 452 (M^+ for $C_{28}H_{24}N_2O_4$). *Anal.* Calcd. for $C_{28}H_{24}N_2O_4$: C, 74.32; H, 5.34; N, 6.19. Found: C, 74.27; H, 5.23; N, 6.23. The oil was distilled to give a mixture of IIIa and IVa (3: 1) boiling at 125—130° (bath temperature)/1×10^{-3} mmHg. MS *m/e*: 241 (M^+ for $C_{15}H_{15}NO_2$). *Anal.* Calcd. for $C_{15}H_{15}NO_2$: C, 74.69; H, 6.22; N, 5.81. Found: C, 74.86; N, 6.40; N, 6.01. NMR ($CDCl_3$) δ: α-substituted compound (IIIa), 1.24 (t, $J=7$ Hz, 9/4H. $CH_2C\underline{H}_3$), 2.01 (s, 9/4H, CH_3), 3.43 (d, $J=2$ Hz, 6/4H, allylic protons of indene), 4.28 (q, $J=7$ Hz, 6/4H, $C\underline{H}_2CH_3$), 6.70 (t, $J=2$ Hz, 3/4H, olefinic protons), 7.2—7.8 (m, aromatic protons); γ-substituted compound (IVa), 1.26 (t, $J=7$ Hz, 3/4H, $CH_2C\underline{H}_3$), 4.36 (q, $J=7$ Hz, 1/2H $C\underline{H}_2CH_3$), 7.2—7.8 (m, aromatic protons), 8.5—8.7 (m, 1/4H, C_7–H of indan).

Allylation of II with Allyl Bromide——Allyl bromide (3.63 g) was reacted with the anion (II) similarly prepared from cynoester (I, 4.54 g) and 1.1 equimolar amounts of phenylmagnesium bromide in THF (20 ml). The crude product was chromatographed on a column of silica gel with benzene, affording 2.45 g of IIIc and 0.78 g of a mixture of IIIc and IVc (59%). On heating IIIc at *ca.* 130°, Cope rearrangement occurred and IIIc was converted to IVc completely after 3 hr.

α-Substituted compound (IIIc), mp 58—61° (from ether, lit.[5b] 59—60°). NMR ($CDCl_3$) δ: 1.22, (t, $J=7$ Hz, 3H, $C\underline{H}_3CH_2-$), 3.11 (bd, $J=6.5$ Hz, 2H, $CH_2{=}CH{-}C\underline{H}_2-$), 3.42 (d, $J=2$ Hz, 2H, allylic protons of indene), 4.26 (q, $J=7$ Hz, 2H, $CH_3C\underline{H}_2-$), 5.1—6.4 (m, 3H, $C\underline{H}_2{=}C\underline{H}-$), 6.73 (t, $J=2$ Hz, 1H, olefinic proton of indene), 7.2—7.8 (m, 4H, aromatic protons). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 2250 (CN), 1745 (ester), 1642 (olefin). UV $\lambda_{\max}^{\text{EtOH}}$ nm: 253.

γ-Substituted compound (IVc), mp 64—65°. NMR ($CDCl_3$) δ: 1.38 (t, $J=7$ Hz, 3H, $C\underline{H}_3CH_2-$), 4.36 (q, $J=7$ Hz, 2H, $CH_3C\underline{H}_2-$), 4.8—6.1 (m, 3H, $CH_2{=}CH-$), 7.2—7.6 (m, 3H, aromatic protons), 8.5—8.7 (m, 1H, C_7–H of indan). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 2240 (CN), 1720 (ester), 1645 (olefin). UV $\lambda_{\max}^{\text{EtOH}}$ nm: 306, 328. MS *m/e*: 267 (M^+ for $C_{17}H_{17}NO_2$). *Anal.* Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.10; H, 6.42; N, 5.45.

Benzylation of I Using NaH as a Base——To a suspension of NaH (120 mg) in anhydrous (THF) (20 ml) was added in one portion with cooling at 0° the cyanoester (I, 1.135 g). The solution was stirred for 1 hr at 50°, cooled to 0° and benzyl bromide (941 mg) in THF (3 ml) was added dropwise. The reaction mixture was stirred overnight at room temperature and poured into ice-AcOEt. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on a column of silica gel with benzene to give 1.16 g of a 7: 1 mixture of IIIb and IVb, along with 0.17 g of the starting material (I).

Methylation of I Using NaH as a Base——According to the above procedure, a THF solution of the anion of I was prepared from the cyanoester (I, 454 mg) and NaH (53 mg). To this solution was added dropwise with stirring and cooling at 0° methyl iodide (848 mg). After stirring overnight at room temperature, the reaction mixture was poured into ice-AcOEt. The extract was washed with H_2O, and dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by preparative thin-layer chromatography (benzene) to give 253 mg of a 7: 1 mixture of IIIa and IVa.

Reaction of II with Acetaldehyde——To an ice-cooled THF solution of the anion (II) prepared from cyanoester (I, 4.5 g) and 1.1 equimolar amounts of phenylmagnesium bromide was added dropwise with stirring acetaldehyde (0.88 g). After stirring for 1 hr at room temperature, the reaction mixture was cooled again in an ice-bath, 10% NH_4Cl was added and the mixture was extracted with CH_2Cl_2. The extract was washed with H_2O and saturated brine, dried over anhydrous $MgSO_4$ and freed of the solvent *in vacuo*. The residual oil was chromatographed on a column of silica gel with CH_2Cl_2, affording 1.1 g (25%) of VIIa. mp 185° (from EtOH) (dec.). NMR ($CDCl_3$) δ: 1.55 (d, $J=6$ Hz, 3H, CH_3), 4.40 (d-q, $J=6$, 11.5 Hz, 1H, CH_3-$C\underline{H}$-), 2.6—3.5 (m, 3H, C_2-H and C_3-H_2 of indan), 7.4—7.7 (m, 3H, aromatic protons), 8.25—8.42 (m, 1H, C_7-H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2230 (CN), 1720 (lactone).

The aqueous layer was acidified to pH=5 with 10% HCl and extracted with AcOEt. The extract was washed with H_2O and aq. NaCl, dried over $MgSO_4$ and evaporated *in vacuo*. Trituration of the residual oil with ether and pet. ether gave VIa as a solid (2.1 g, 47%), mp 109—110° (from ether-pet. ether) (converted into VIIa). NMR ($CDCl_3$) δ: 2.03 (d, $J=7$ Hz, 3H, CH_3), 3.72 (bs, 2H, C_3-H_2 of indan), 7.3—7.8 (m, 4H, olefinic and aromatic protons), 8.3—8.6 (m, 1H, C_7-H of indan), 10.42 (bs, 1H, COOH). IR ν_{max}^{Nujol} cm^{-1}: 2210 (CN), 1700 (COOH).

Reaction of II with Benzaldehyde——To an ice-cooled THF solution of the anion (II) prepared from 3.405 g of cyanoester (I) and 1.1 equimolar amounts of phenylmagnesium bromide in THF (20 ml) was added dropwise with stirring 1.59 g of benzaldehyde. Stirring was continued for 1.5 hr at room temperature, then the mixture was cooled again in ice-H_2O and 10 ml of 10% NH_4Cl was added and the reaction mixture was extracted with CH_2Cl_2. The extract was cooled to separate out the precipitate, to which H_2O was added. The aq. solution was adjusted to pH 5 with 5% HCl and extracted with AcOEt. The extract was washed with H_2O and aq. NaCl, dried over $MgSO_4$ and evaporated to give crude carboxylic acid (VIb). NMR (DMSO-d_6): 3.92 (bs, 2H, C_3-H_2 of indan), 7.3—7.9 (m, 9H, aromatic and olefinic protons), 8.3—8.6 (m, 1H, C_7-H of indan). IR ν_{max}^{Nujol} cm^{-1}: 2190 (CN), 1670 (COOH). The above crude carboxylic acid (VIb) was heated in EtOH and cooled in ice-bath. The precipitate was filtered off to give 0.90 g of VIIb as crystals. The filtrate was evaporated *in vacuo* and the residual oil was chromatographed on a column of silica gel eluting with benzene-AcOEt (9: 1) to give 1.95 g (67%) of VIIb, mp 194—195°. NMR (DMF-d_7): 2.96 (d, $J=7$ Hz, 2H, C_3-H_2 of indan), 3.99 (d-t, $J=7$, 12 Hz, 1H, C_2-H of indan), 5.73 (d, $J=12$ Hz, 1H, $PhC\underline{H}$), 7.4—7.9 (m, 8H, aromatic protons), 8.2—8.5 (m, 1H, C_7-H of indan). IR ν_{max}^{Nujol} cm^{-1}: 2220 (CN), 1715 (lactone). *Anal.* Calcd. for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.48; H, 4.68; N, 5.16.