Tetrahedron Vol. 42, No. 2, pp. 609 to 616, 1986
Printed in Great Britain.

0040-4020/86 $3.00 + .00

CYCLIZATION OF ETHYL YLIDENECYANOACETATES TO CARBOCYCLIC o-AMINOESTERS. AN EFFICIENT SYNTHESIS OF 1,2,3,6,7,8-HEXAHYDRO-as-INDACENE DERIVATIVES

JANUSZ SEPIOŁ

Department of Organic Chemistry, Jagiellonian University,
30-060 Krakow, Karasia 3, Poland

(*Received in UK 22 October* 1985)

Abstract - Ethyl ylidenecyanoacetates 2 undergo cyclization in cold sulfuric acid to give the lactone 3 and o-aminoester 4. The key o-aminoester 4 is used to the synthesis of a variety of as-hydrindacene derivatives including o-aminocarboxylic acid 5, o-hydroxyester 8, o-hydroxycarboxylic acid 9, or the ester 11.

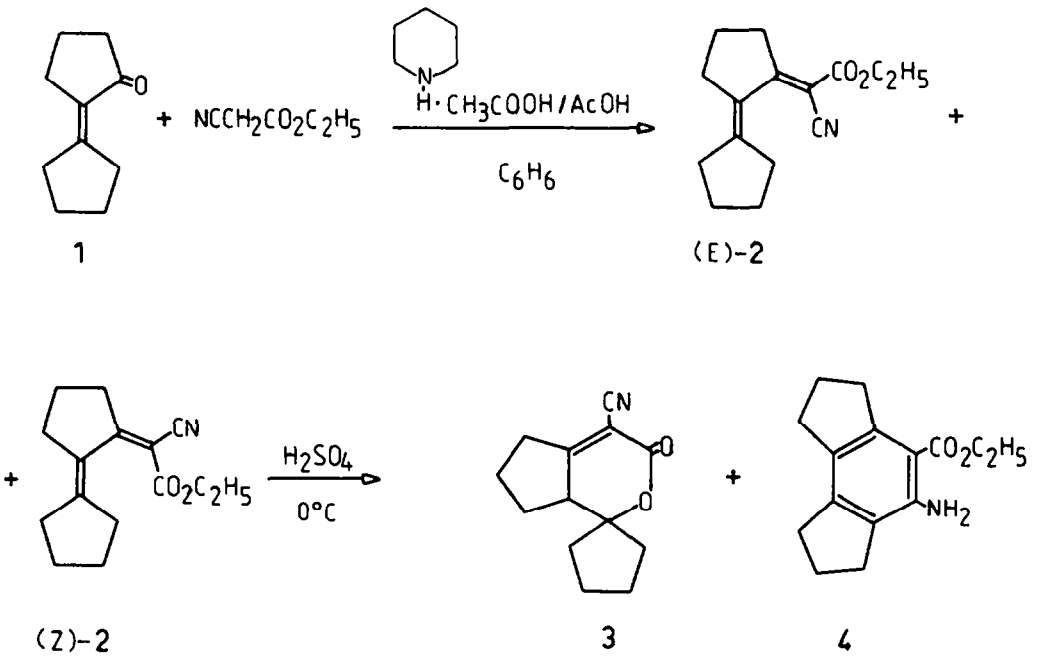
Condensation of unsymmetrical ketones with ethyl cyanoacetate affords mixtures of (E) and (Z) isomers of ethyl ylidenecyanoacetates, and the cyclization of some ylidenecyanoacetates to carbocyclic o-hydroxynitriles has also been relatively well documented in the literature.[1,2] During such cyclization the ethoxycarbonyl group of the (Z) isomer of the starting ylidenecyanoacetate acts as an electrophile attacking the appropriately positioned aromatic ring or the olefinic system. The cyclization is usually carried out under mildly protic conditions but occurs spontaneously on heating an ylidenecyanoacetate. The cyano group remains inactive in the cyclization step. Until recently this mode of ring closure of ylidenecyanoacetates had found little synthetic application mainly because of very low reactivity of the cyano group of o-hydroxynitriles to further transformations. Theoretically, some ethyl (alkyl) ylidenecyanoacetates can be considered as synthetic precursors to carbocyclic o-aminoesters. In such cases, the cyclization step would involve the cyano group, usually of the (E) isomer, as the active agent in the ring closure leading to carbocyclic o-aminoester, whilst the ester function would remain inactive. This type of cyclization of alkyl ylidenecyanoacetates, especially obtained from α,β or β,γ-unsaturated ketones, is potentially an attractive and simple route to carbocyclic o-aminoesters which otherwise are difficult to synthesize by classical methods.

In continuing our studies on the application of ethyl ylidenecyanoacetates to the synthesis of aromatic carbocyclic systems, we describe herein a convenient and efficient preparation of as-hydrindacene system from 2-cyclopentylidenecyclopentanone 1. The majority of synthetic routes to 1,2,3,6,7,8-hexahydro-as-indacene 7 and its derivatives are based on the Diels-Alder reaction of 1,1'-dicyclopentenyl with a variety of dienophiles.[3] The reaction of 1,1'-dicyclopentenyl with maleic anhydride[4-10] and methyl acetylenedicarboxylate[6] has been investigated. A derivative of this diene has been generated *in situ* from 2-cyclopentylidenecyclopentanone 1 and treated with methyl acetylenedicarboxylate,[11]

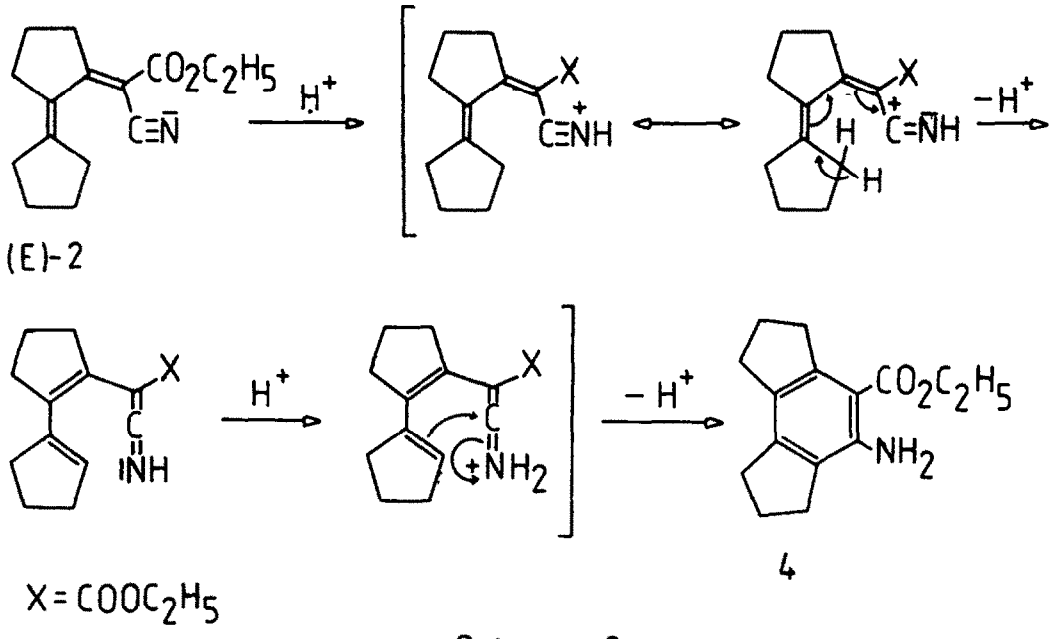
and maleic,[12] or chloromaleic anhydride.[11] An earlier rather elaborate route [13] to as-hydrindacene 7 has been recently modified.[14] The dienic synthesis of as-hydrindacene system although extensively employed, has several drawbacks. The functional groups introduced into the 4 and 5 positions of as-hydrindacene system are limited to those borne by the dienophilic reagent, e. g. the ester, carboxylic or cyano groups. The removal of functional groups from the 4 and 5 positions of as-hydrindacene is difficult and usually gives poor yields of the hydrocarbon or involves the rearrangement of the carbocyclic skeleton.[8,10]

RESULTS AND DISCUSSION

We have reported previously the synthesis of (E)/(Z)-2 by condensation of 2-cyclopentylidenecyclopentanone 1 with ethyl cyanoacetate catalyzed by ammonium acetate/acetic acid.[2] This condensation proceeds with difficulty and usually after 1-2 hours of heating of benzene solution of 1 and ethyl cyanoacetate, the catalyst become ineffective as indicated by the cessation of water separation in a Dean-Stark water separator. In order to obtain satisfactory yields of 2, fresh portions of ammonium acetate are added; this procedure is often repeated several times with the need to cool the reaction mixture. This inconvenience is now avoided by using piperidine acetate/acetic acid as catalyst, although the condensation proceeds very slowly and the reaction mixture has to be continuously heated for 36 hours. The ^{1}H-NMR spectrum of the condensation product confirms the presence of isomers (E)-2 and (Z)-2 in the ratio 8 : 2. We have found previously that heating of (E)/(Z)-2 in boiling acetamide affords 5-hydroxy-1,2,3,-6,7,8-hexahydro-as-indacene-4-carbonitrile in moderate yield.[2] In this report we describe the results of cyclization of (E)/(Z)-2 under strongly acidic conditions (Scheme 1).



Scheme 1

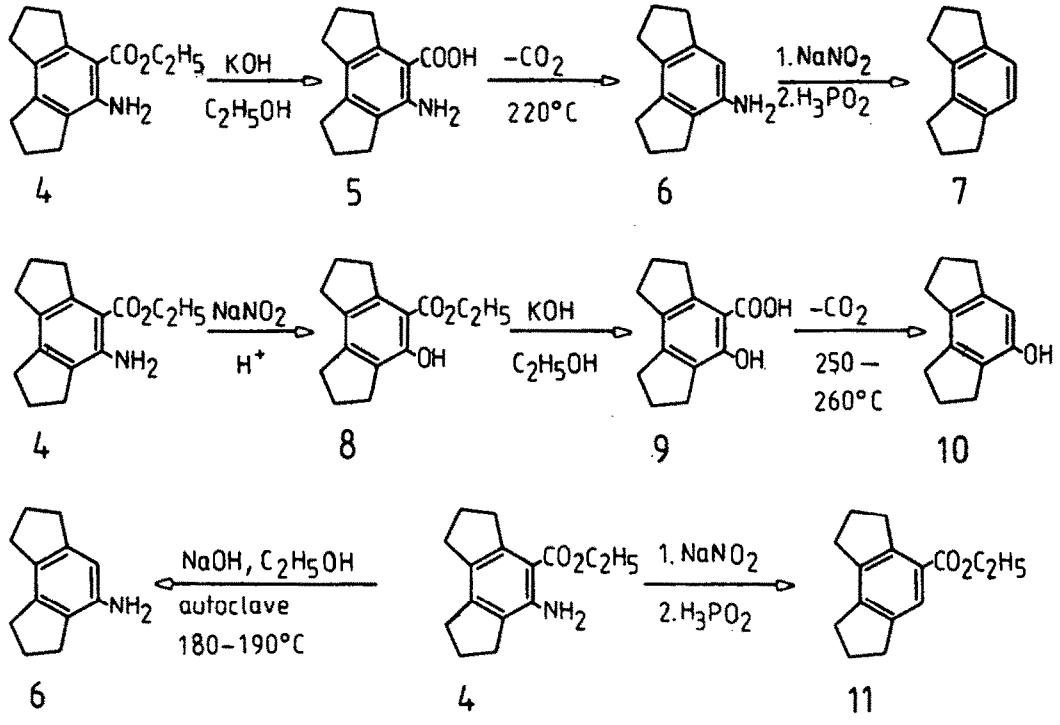


Scheme 2

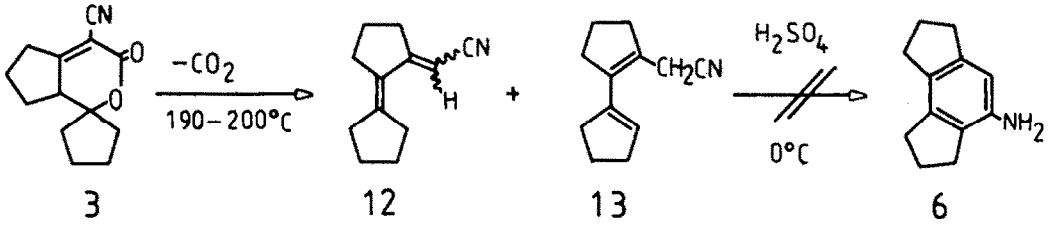
When an ice-cold concentrated sulfuric acid solution of (E)/(Z)-2 is allowed to stand for a few hours and then quenched with ice the spirolactone 3 is isolated in 14% yield. The lactone 3 is presumably formed by cyclization of the isomer (Z)-2. Neutralization of the acidic solution affords the o-aminoester 4 in 35% yield. This dissolves in dilute sulfuric acid and can consequently be simply separated from the precipitated lactone 3. It appears that the formation of 4 involves cyclization of the isomer (E)-2. The presumed mechanism of this cyclization is outlined in Scheme 2. Ring closure of (E)-2 in concentrated sulfuric acid evidently involves the interaction of the protonated nitrile group and the olefinic bond of the cyclopentene ring.

We have already investigated the synthesis of as-hydrindacene 7 which involved condensation of 1 with malonodinitrile and cyclization of obtained 2-cyclopentylidene-cyclopentylidenemalonodinitrile in sulfuric acid.[15] However, the yield of 5-amino-as-hydrindacene-4-carbonitrile was poor and the o-aminonitrile was difficult to separate from by-products formed during cyclization in concentrated sulfuric acid.[15,16] We now report a simple two-step synthesis of the key o-aminoester 4 from the ketone 1 which has opened several routes to other useful derivatives of as-hydrindacene (Scheme 3). Some of these compounds are not available or are difficult to obtain by the dienic synthesis from 1,1'-dicyclopentenyl.

The hydrolysis of 4 in ethanolic potassium hydroxide solution gives o-aminocarboxylic acid 5 in 95% yield. This acid may be smoothly decarboxylated to the amine 6 in 91% yield by heating at 220°C. The amine 6 is also obtained directly from o-aminoester 4 by heating 4 in an autoclave in ethanolic sodium hydroxide solution; this reaction involves the elimination of the ethoxycarbonyl group from 4. A similar method was employed earlier for eliminating of the cyano or carbamoyl functions from carbocyclic o-aminonitriles or o-aminoamides, respectively.[15,17] The amine 6 can be easily deaminated as described previously to yield as-hydrindacene 7.[15] Heating of the diazonium solution obtained from 4 with dilute sulfuric acid gives the o-hydroxyester 8 which then affords on hydrolysis the o-hydroxycarboxylic acid 9 in 91% yield. Decarboxylation of 9 by the usual method gives as-hydrindacenol 10 in moderate yield, and diazotization



Scheme 3



Scheme 4

of 4 in 50% hypophosphorous acid affords the ester 11 [18] in 94% yield.

Infrared spectrum of the spirolactone 3 shows absorption of the cyano group at 2222 cm^{-1}, of the carbonyl group at 1710 cm^{-1}, and of the double bond at 1640 cm^{-1}. The structure of 3 is supported by the results of thermal decarboxylation of the lactone. Heating 3 at 190-200°C at normal pressure is accompanied by vigorous evolution of carbon dioxide. Infrared spectrum of colorless oil obtained in this reaction reveals a conjugated and unconjugated cyano group at 2202 and 2243 cm^{-1}, respectively. These bands are assigned to nitriles 12 and 13. The ^{1}H-NMR spectrum of the mixture confirms the presence of 12 and 13 in 1 : 1 ratio. Separation of 12 and 13 has not been attempted. It is assumed that cyclization of this mixture, especially of the nitrile 13, could furnish the amine 6. However, dissolving 12 and 13 in concentrated sulfuric acid followed by the usual work-up gives only untractable high-melting product which fails to to afford the expected amine 6.

The efficient synthesis of as-hydrindacene system involving the cyclization of (E)/(Z)-2 in sulfuric acid encouraged us to investigate further the scope of this reaction. Ring closure of certain ylidenecyanoacetates obtained from unsaturated ketones is currently under investigation.

EXPERIMENTAL SECTION

All b.ps and m.ps are uncorrected. Elemental analyses were performed by the Regional Laboratory of Physico-Chemical Analyses, Krakow. The IR spectra were obtained on a Perkin-Elmer 1320 IR instrument. The ^{1}H-NMR spectra were obtained on a Perkin-Elmer R-12 A (60 MHz) spectrometer and chemical shifts are reported in parts per million downfield from Me_4Si. The coupling constant of methylene cyclopentene protons of as-hydrindacene derivatives in ^{1}H-NMR spectra was in the range of 7.0-7.5 Hz. 2-Cyclopentylidenecyclopentanone 1 (Aldrich Europe) and ethyl cyanoacetate were redistilled under reduced pressure immediately before use.

(E)/(Z)-Ethyl 2-Cyclopentylidene-cyclopentylidenecyanoacetate 2 A solution of 1 (100.0 g, 0.66 mol) and ethyl cyanoacetate (80.0 g, 0.71 mol) in 300 ml of dry benzene was mixed with a catalyst prepared by dissolving piperidine (7.0 g) in glacial acetic acid (14.0 g). The reaction mixture was magnetically stirred and heated for 36 hr under vigorous reflux in a 1000 ml flask equipped with a Dean-Stark water separator. The solution was washed with water and saturated sodium hydrogen carbonate solution and then dried with anhydrous magnesium sulfate. Benzene was distilled off on a rotary evaporator and the product was fractionated under reduced pressure to afford 83.0 g (51%) of (E)/(Z)-2 as yellowish oil, b.p. 134-136°/0.01 mm, lit.[2] b.p. 147-150°/3.0 mm; IR (neat) cm^{-1} 2955, 2846, 2223, 1723, 1617, 1567, 1450, 1370, 1268, 1203, 1097, 1038, 776; ^{1}H-NMR ($CDCl_3$) (E)-2 δ, ppm 1.30 (t, 3H, J=8 Hz, OCH_2CH_3), 1.80 (m, 6H, CH_2), 2.30 (m, 6H, CH_2), 3.03 (t, 2H, CH_2), 4.23 (q, 2H, J=8 Hz, OCH_2CH_3); (Z)-2 δ, 1.27 (t, 3H, J=8 Hz, OCH_2CH_3), 1.80 (m, 6H, CH_2), 2.30 (m, 6H, CH_2), 3.00 (t, 2H, CH_2), 4.19 (q, 2H, J=8 Hz, OCH_2CH_3). The (E)-2 : (Z)-2 ratio estimated from this spectrum was 8 : 2.

Cyclization of (E)/(Z)-Ethyl 2-Cyclopentylidene-cyclopentylidenecyanoacetate 2 in Concentrated Sulfuric Acid The cyanoester (E)/(Z)-2 (12.3 g, 50 mmol) was slowly dissolved in ice-cold concentrated sulfuric acid (60 ml) under stirring with a magnetic stirrer. The solution was kept in ice-bath for 2 hr and then at room temp. for 4 hr. The brown solution was poured onto 400 g of crushed ice causing the precipitation of a semi-solid product. The mixture was left overnight at room temp. and then the solid was filtered off on a Büchner funnel, washed with water and dried. Recrystallization from methanol followed by sublimation in vacuo and final recrystallization from methanol afforded 1.5 g (14%) of 4'-cyano-3'-oxo-3',5',6',7'-tetrahydro-spiro[cyclopentane-1,1'(7a H)-cyclopenta[c]pyran] 3 as colorless rods, m.p. 107-108°; IR (KBr) cm^{-1} 2960, 2878, 2222, 1710, 1640, 1363, 1297, 1172, 1136, 1095, 973, 967, 901, 764; ^{1}H-NMR ($CDCl_3$) δ, ppm 1.5-2.3 (m, 12H, CH_2), 2.7-3.2 (m, 3H). (Found: C, 71.65; H, 6.99; N, 6.47. Calc for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45%.)

The acidic filtrate obtained on isolation of the lactone 3 was cooled in ice-bath and neutralized under stirring with ammonium hydroxide solution. The brown precipitate was filtered off on a Büchner funnel, washed with water, and sublimed in vacuo. Recrystallization from n-hexane afforded 4.3 g (35%) of ethyl 5-amino-1,2,3,6,7,8-hexahydro-as-indacene-4-carboxylate 4 as slightly yellow crystals which usually form colorless fluffy needles on sublimation in vacuo, m.p. 80°; IR (KBr) cm^{-1} 3484, 3373, 2962, 2840, 1665, 1604, 1567, 1366, 1292, 1257, 1195, 1090, 798; ^{1}H-NMR ($CDCl_3$) δ, ppm 1.34 (t, 3H, J=7 Hz, OCH_2CH_3), 2.05 (quintet, 4H, CH_2), 2.67 (t, 6H, CH_2), 3.05 (t, 2H, CH_2), 4.30 (q, 2H, J=7 Hz, OCH_2CH_3), 5.25 (br.s, 2H, NH_2). (Found: C, 73.37; H, 7.87; N, 5.60. Calc for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71%.)

5-Amino-1,2,3,6,7,8-hexahydro-as-indacene-4-carboxylic Acid 5 o-Aminoester 4 (1.226 g, 5 mmol) was dissolved in a solution of potassium hydroxide (2.0 g) in 20 ml of ethanol. The solution was refluxed for 1.5 hr, then diluted with 100 ml of water and neutralized with hydrochloric acid in such manner that the pH of the solution was in the range 7.0-7.1. The precipitated white solid was isolated, washed with water, dried, and sublimed in vacuo at 180-190°/0.05 mm. Recrystallization from ethanol furnished 1.032 g (95%) of 5 as yellowish crystals, m.p. 213° (dec.), lit.[16] m.p. 205°; IR (KBr) cm^{-1} 3493, 3370, 2900(br.), 2838, 1635, 1598, 1554, 1430, 1296, 1252, 1203; ^{1}H-NMR (Me_2SO-d_6) δ, ppm 1.95 (quintet, 4H, CH_2), 2.60 (m, 6H, CH_2), 3.05 (t, 2H, CH_2), 8.00 (br.s, 2H, NH_2).(Found: C, 71.72; H, 6.92; N, 6.45. Calc for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45%.)

4-Amino-1,2,3,6,7,8-hexahydro-as-indacene 6 Method a : Thoroughly powdered and dry o-aminocarboxylic acid 5 (869 mg, 4 mmol) was placed in a 20 cm tube. The tube was fitted with a cold finger to prevent vapours of the product from escaping during the process of decarboxylation. The apparatus was heated at atmospheric pressure on a silicone oil bath to 220° and maintained at this temperature for 20 min. Melting of the acid was accompanied by vigorous evolution of carbon dioxide. The black oil was then purified by distillation/sublimation at 50°/0.05 mm. Recrystallization from petroleum ether (b.p. 35-50°) followed by sublimation in vacuo afforded 633 mg (91%) of 6 as colorless needles, m.p. 45-46°, lit.[15] m.p. 45-46°; IR (neat) cm^{-1} 3440, 3353, 3209, 2946, 2838, 1618, 1478, 1453, 1359, 1300, 843; ^{1}H-NMR (CCl_4) δ, ppm 2.00 (m, 4H, CH_2), 2.60 (m, 8H, CH_2), 3.12 (s, 2H, NH_2), 6.11 (s, 1H, Ar-H).

Method b : The o-aminoester 4 (981 mg, 4 mmol) and sodium hydroxide (1.0 g) were dissolved in 60 ml of ethanol. The solution was heated in a 250 ml autoclave at 180-190° for 4 hr. The mixture was diluted with 50 ml of water and ethanol was distilled off. The precipitated black oil solidified on standing at room temperature. The solid was isolated, washed with water, and recrystallized from petroleum ether (b.p. 35-50°). Sublimation in vacuo afforded 401 mg (58%) of 6 as colorless needles, m.p. 45-46°. Spectral properties of 6 obtained by this method were identical with the above reported spectral data for the amine 6.

Ethyl 5-Hydroxy-1,2,3,6,7,8-hexahydro-as-indacene-4-carboxylate 8 The o-aminoester 4 (981 mg, 4 mmol) was dissolved in 10 ml of 25% sulfuric acid. The solution was cooled in ice-bath and diazotized with saturated solution of sodium nitrite (420 mg, 6 mmol). The diazonium solution was poured slowly into 75 ml of boiling and magnetically stirred 5% sulfuric acid and the mixture was heated for additional 5 min. The precipitated yellow oil solidified on cooling to room temp. The solid was filtered off, washed with water, and sublimed in vacuo. Recrystallization from n-hexane furnished 890 mg (90%) of 8 as yellow needles, m.p. 82°; IR (KBr) cm^{-1} 3052, 2960, 1648, 1623, 1398, 1373, 1317, 1254, 1203, 1090, 1037, 1018, 803, 762; ^{1}H-NMR ($CDCl_3$) δ, ppm 1.38 (t, 3H, J=7 Hz, OCH_2CH_3), 1.8-2.3 (m, 4H, CH_2) 2.5-2.9 (m, 6H, CH_2), 3.12 (t, 2H, CH_2), 4.36 (q, 2H, J=7 Hz, OCH_2CH_3).(Found: C, 73.03; H, 7.27. Calc for $C_{15}H_{18}O_3$: C, 73.15; H, 7.36%.)

5-Hydroxy-1,2,3,6,7,8-hexahydro-as-indacene-4-carboxylic Acid 9 The o-hydroxyester 8 (246 mg, 1 mmol) and potassium hydroxide (0.5 g) were dissolved in 7 ml of ethanol. The solution was refluxed for 80 min. and then diluted with 60 ml of water. The solution was neutralized by the addition of hydrochloric acid and the pH was adjusted to 5.0. The precipitated gelly white solid was isolated by suction, washed with water and sublimed in vacuo. Recrystallization from ethanol afforded 198 mg (91%) of 9 as yellowy crystals, m.p. 242° (dec.) ; IR (KBr) cm^{-1} 2940, 2580, 1624, 1445, 1293, 1254, 1206, 1087, 908; ^{1}H-NMR (Me_2SO-d_6) δ, ppm

1.7-2.2 (m, 4H, CH_2), 2.4-2.8 (m, 6H, CH_2), 3.05 (t, 2H, CH_2).(Found: C, 71.56; H, 6.39. Calc for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46%.)

4-Hydroxy-1,2,3,6,7,8-hexahydro-as-indacene 10 The o-hydroxycarboxylic acid 9 (109 mg, 0.5 mmol) was placed in a tube fitted with a cold finger. The tube was heated at normal pressure at 250-260° for 30 min. Since the hydrindacenol 10 cosublimed with the starting acid 9, the product was removed from cold finger and the decarboxylation procedure was repeated two more times. Final sublimation in vacuo and recrystallization from n-hexane furnished 46 mg (53%) of 10 as colorless needles, m.p. 110°, lit.[2] m.p. 107-108°; IR (KBr) cm^{-1} 3300, 2920, 1592, 1453, 1350, 1318, 1269, 1157, 1068, 849; ^{1}H-NMR ($CDCl_3$) δ, ppm 1.9-2.3 (m, 4H, CH_2), 2.72 (t, 4H, CH_2), 2.82 (t, 4H, CH_2), 4.97 (s, 1H, OH), 6.54 (s, 1H, Ar-H).

Ethyl 1,2,3,6,7,8-Hexahydro-as-indacene-4-carboxylate 11 The o-aminoester 4 (245 mg, 1 mmol) was dissolved in 6.0 ml of 50% hypophosphorous acid. The solution was cooled in ice-bath and diazotized with sodium nitrite (140 mg, 2 mmol) dissolved in a small amount of water. The reaction mixture was kept overnight in a refrigerator and was then diluted with 20 ml of water. The precipitated solid was separated, washed with water, and sublimed in vacuo. Recrystallization from petroleum ether (b.p. 35-50°) afforded 217 mg (94%) of 11 as colorless long needles, m.p. 50-51°, lit.[18] m.p. 50-50.5°; IR (KBr) cm^{-1} 2947, 2838, 1710, 1368, 1286, 1262, 1227, 1183, 1157, 1050, 780; ^{1}H-NMR ($CDCl_3$) δ, ppm 1.37 (t, 3H, J=6 Hz OCH_2CH_3), 2.04 (quintet, 4H, CH_2), 2.77 (t, 6H, CH_2), 3.23 (t, 2H, CH_2), 4.32 (q, 2H, J=6 Hz, OCH_2CH_3), 7.70 (s, 1H, Ar-H).

The Decarboxylation of the Lactone 3 The lactone 3 (652 mg, 3 mmol) was placed in a long test tube and heated on an oil bath at 190-200° for 30 min. Vigorous decarboxylation began at 150-160°. The dark oil was distilled in a micro-distillation apparatus to afford 446 mg (86%) of a mixture of 12 and 13 as colorless oil, b.p. 80-82°/0.05 mm; IR (neat) cm^{-1} 3044, 2950, 2846, 2243, 2202, 1642, 1591, 1443, 1418, 1030, 957, 805; ^{1}H-NMR ($CDCl_3$) 12 δ, ppm 1.5-2.1 (m, CH_2), 2.2-2.8 (m, CH_2), 5.66 (t, 1H, C=C(CN)H); 13 δ, ppm 1.5-2.1 (m, CH_2), 2.2-2.8 (m, CH_2), 3.32 (s, 2H, CH_2CN), 5.19 (m, $1H_{vinylic}$). The ratio of 12 and 13 estimated from the ^{1}H-NMR spectrum was 1 : 1. The microanalysis was carried out for the mixture of 12 and 13.(Found: C, 83.09; H, 8.79; N, 7.98. Calc for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.08%.)

Acknowledgment - The author gratefully acknowledges the support of this research by Jagiellonian University.

REFERENCES AND NOTES

1. P. Bagchi, F. Bergmann and D. K. Bannerjee, J. Am. Chem. Soc. 71, 989 (1949).
2. J. Sepioł and J. Mirek, Synthesis 290 (1979); and references cited therein.
3. For an earlier review of synthetic routes to as-hydrindacene 7 and its derivatives see: G. Le Guillanton, Bull. Soc. Chim. Fr. 611 (1963).
4. E. de Barry Barnett and C. A. Lawrence, J. Chem. Soc. 1104 (1935).
5. V. R. Skvarchenko, R. Ya. Levina and O. Yu. Okhlobystin, Dokl. Akad. Nauk SSSR 99, 789 (1954); Chem. Abstr. 49, 5414 d (1955).
6. D. S. Greidinger and D. Ginsburg, J. Org. Chem. 22, 1406 (1957).
7. G. Le Guillanton, Bull. Soc. Chim. Fr. 620 (1963).

8. R. H. Wightman, R. J. Wain and D. H. Lake, Can. J. Chem. 49, 1360 (1971).
9. M. E. Isabelle, D. H. Lake and R. H. Wightman, Can. J. Chem. 55, 3268 (1977).
10. R. P. Thummel and W. Nutakul, J. Org. Chem. 42, 300 (1977).
11. J. Wolinsky and R. B. Login, J. Org. Chem. 35, 3205 (1970).
12. J. Wolinsky and R. B. Login, J. Org. Chem. 37, 121 (1972).
13. H. Rapoport and G. Smolinsky, J. Am. Chem. Soc. 82, 1171 (1960).
14. M. E. Isabelle, R. H. Wightman, H. W. Avdovich and D. E. Laycock, Can. J. Chem. 58, 1344 (1980).
15. J. Sepioł, B. Kawałek and J. Mirek, Synthesis 701 (1977).
16. R. P. Thummel and T. Fuchigami, J. Org. Chem. 46, 5217 (1981).
17. J. Sepioł, Synthesis 559 (1983).
18. G. Le Guillanton, Bull. Soc. Chim. Fr. 630 (1963).