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Synthesis and Structure of 1,5- and 1,7-Dihydro-*s*-indacenes

LARS TROGEN and ULF EDLUND

Department of Organic Chemistry, University of Umeå, S-901 87 Umeå, Sweden

The synthesis of 1,5- and 1,7-dihydro-*s*-indacenes starting from 1,2,4,5-tetrakis(bromomethyl)benzene and ethyl acetoacetate is reported. The ratio between the two isomers was found to be 5:4 using quantitative ^{13}C NMR. Furthermore, the chemical shifts indicated a very similar electronic structure for the two species.

The "saturation" of substituent electronic effects has been a subject of much concern partly because of the failure of finding systems and experimental methods sufficiently sensitive to probe the proposed effects. So far the most convincing support for the concept of "saturation" has been found in conjugated systems having π-electron acceptor or donor groups while the importance of polar saturation effects has been assumed to be minor.[1] If we only consider ^{13}C NMR characterizations the most thoroughly investigated compounds are the 1,4-disubstituted benzenes, 1-X-4-Y-Ph, and they also constitute the only class of polysubstituted structures where the data matrix is sufficiently large to make any interpretation worthwhile. Taft *et al.* reported a non-additive behaviour for *para*-carbons and they analysed the influence of a Y substituent on the 4-carbon by a dual substituent approach.[2] Their results were interpreted to indicate that the σ-charge density at the 4-carbon regulates the ease of π-polarization due to the remote *para*-X substituent (Y fixed). This approach has recently been criticized by Lynch.[3] He shows quite clearly that measured data for the 4-position are well reproduced by linear proportionality relationships with ^{13}C substituent shifts (SCS) from monosubstituted benzenes, while those for the C-1 and C-2 positions were explained by simple additivity.

In order to assess the different modes of action of substituents in unsaturated systems we are currently studying ^{13}C NMR substituent effects in several 2-substituted indenes. The rigid indene framework is an ideal model system to probe such effects since the remote C4 – C7 carbon positions have the capacity to separate field and π-alternating effects.[4] As an extension of this study we were looking for a rigid bifunctional system where the substituents should be sufficiently far apart to avoid proximate effects at studied carbons. Moreover, we wanted a system where assignment of the carbon signals could be made unambigously. The dihydro-*s*-indacene system (*6* and *7*, Scheme *1*) was found to fulfil most of our demands in this respect and the protonated aromatic carbons should be reliable probes for substituent effects in 2,6-disubstituted derivatives. It would also be interesting to study the substituent influence on the ratio of the isomeric 1,5- and 1,7-dihydro-*s*-indacenes.

In this first paper we report the total synthesis and structure of the parent unsubstituted hydrocarbon starting from 1,2,4,5-tetrakis-(bromomethyl)benzene (*1*). To our knowledge this is the first reported synthetic route for the preparation of the 1,5- and 1,7-dihydro-*s*-indacene isomers. However, in a review article [5] the synthesis of the 1,5-isomer was briefly mentioned. This sole isomer was said to be prepared by reduction of (the labile) *s*-indacene, either catalytically or through protonation of the dianion obtained in a Birch-reduction.

The synthetic steps involved in the preparation of the dihydro-*s*-indacene system are shown in Scheme *1*. Starting with *1* it was quite natural to test the "extractive alkylation" reaction [6] (*1*→*2*), thus forming both five-membered rings in one single step.

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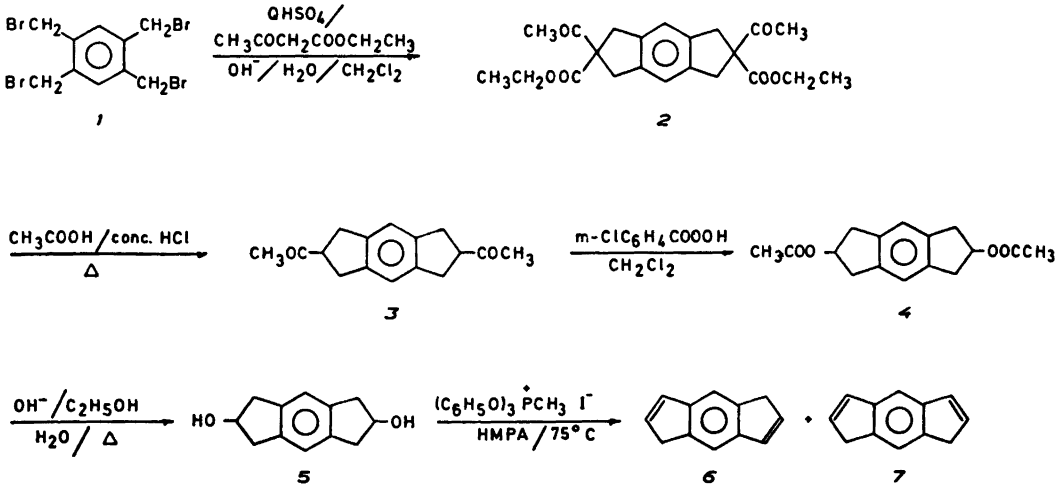
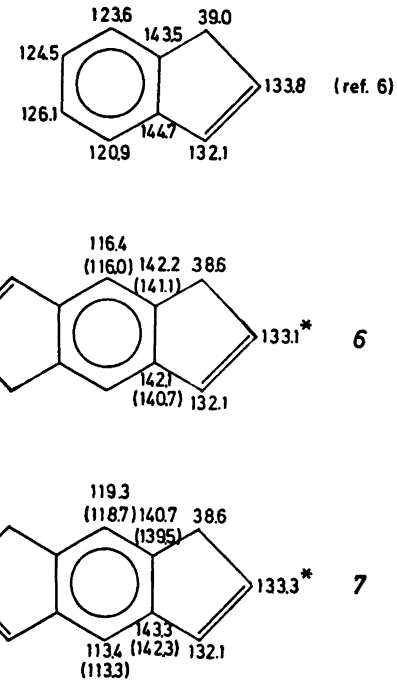


Scheme 1.

First all synthetic steps, except the alkaline hydrolysis, were checked using the indan system. The choice of this model was rationalized by the assumption that reactivity characteristics would be very similar for the remote, isolated substituents in the *s*-hydrindacene system and for the corresponding substituents in the model species. When testing the synthetic routes using the indan model, difficulties were met with in two of the steps, *viz.* those corresponding to (*2*→*3*) and (*5*→*6,7*). A decarbethoxylation procedure like heating 2-acetyl-2-carbethoxyindan in wet dimethyl sulfoxide containing sodium chloride [7] only led to a very incomplete reaction. However, a smooth conversion to the ketone was accomplished by heating the β-keto ester in a mixture of acetic acid and concentrated hydrochloric acid.[8]

Similarly we failed in the dehydration step using conventional methods such as heating the alcohol with potassium bisulfate, hexamethylphosphoric triamide (HMPA), diphosphorus pentoxide/benzene or *p*-toluenesulfonic acid/benzene. However, heating 2-indanol with methyltriphenoxyphosphonium iodide in HMPA [9] gave indene in a satisfactory yield.

In order to keep substance losses at a minimum and to achieve a good overall yield of *6* and *7*, only two of the intermediate products (*3* and *5*) were purified. Purification of *3* was brought about by simple column chromatography (CC) using chloroform as eluting solvent,



Scheme 2. ^{13}C NMR chemical shifts observed for the dihydro-*s*-indacenes (*6* and *7*) in $CDCl_3$ (*ca.* 1 M, 27 °C). The chemical shifts for indene are given for comparative purposes. Shift values within brackets represent calculated shifts using $\Delta\delta$ (indene − benzene) values, assuming additivity. Signals marked with an asterisk may be interchanged.

while the diol *5* was isolated by continuous extraction with diethyl ether. In the final step we obtained, together with the dihydro-*s*-indacene isomers, a small amount (*ca.* 10 % from *5*) of 2-iodo-1,2,3,5-tetrahydro-*s*-indacene, a by-product which could be removed by CC.

No specific attempts were made to prove that the intermediates *2* – *5* were obtained as mixtures of geometrical isomers. The ^{1}H NMR spectra of these compounds are very similar to those of their bicyclic counterparts but the signals arising from protons attached to the five-membered rings were less well-resolved. This fact together with observed elongated melting intervals for purified material strengthened the assumption of the presence of spatial isomers.

Although the ^{1}H NMR spectrum of the dihydro-*s*-indacenes indicated the presence of two geometrical isomers, the better resolved ^{13}C NMR spectrum was much more helpful not only to confirm an isomeric mixture but also to probe the actual isomeric ratio. Since both isomers can be assumed to have the same rotational correlation time, the signal areas of the dipole-dipole relaxed carbons were used to determine the ratio of *6* and *7*. We found isomer *6* to be slightly perferred in solution. The observed ratio *6* to *7* (5:4) was confirmed to be the one thermodynamically determined by adding a small amount of 1,4-diazabicyclo-octane (DABCO) to a benzene solution. (Sauter *et al.*[10] have reported the triethylamine catalyzed equilibration of dihydro-*as*-indacene double-bond isomers). Most interestingly we found a good correlation between observed ^{13}C chemical shifts and those calculated using the indene chemical shift data (Scheme 2). The fact that simple additivity prevails and that the ^{13}C NMR shift data for the vinylic carbons are the same for both structures clearly indicates that the vinylic group is electronically neutral[11] and that the electron distribution is very similar for the *6* and *7* structures.

EXPERIMENTAL

Measurements. The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL PFT-60 NMR instrument. The FT spectra were measured at 27 °C and the decays were sampled using 8K data points over a spectral width of 4000 Hz. In the quantitative study, however, we used a more narrow spectral window and 16K data points. The FID was, in this case, multiplied with a large negative exponential weighing function. $CDCl_3$ was used as solvent for all substances except the diol *5* where dimethyl sulfoxide-d_6 was used. Assignments of ^{13}C NMR signals were made by comparison with the indene shift data[4] and by standard decoupling procedures. For the assignment of the non-protonated carbons we utilized the intensity differences and the expected similarity to the calculated values. Mass spectra were obtained on an LKB 9000 instrument. Gas chromatographic analyses were performed on a PYE M64 instrument, 5 % QF1 on Chromosorb W AW-DMCS 100 – 120 mesh (210 cm, 4 mm i.d.) with N_2 as carrier.

Materials. Ethyl acetoacetate (Merck) was vacuum distilled before use and the tetrabutylammonium hydrogen sulfate ($QHSO_4$, LAB-KEMI) was recrystallized from isobutyl methyl ketone as suggested.[6] Dichloromethane, used in the rearrangement step (*3*→*4*), was dried by distillation from diphosphorus pentaoxide. The HMPA was purified by treatment with calcium hydride and vacuum distilled from this reagent to a receiver containing pre-dried molecular sieve 4A. CC was done throughout on Merck silica gel 60, 230 – 400 mesh.

2,6-Diacetyl-s-hydrindacene (3). The synthesis of *2* was performed in a flask mounted for magnetic stirring and equipped with a dropping funnel and a reflux condenser. In the reaction flask 68.0 g (0.2 mol) $QHSO_4$ in water (50 ml) was neutralized by dropwise addition of a solution of 8.0 g (0.2 mol) sodium hydroxide in water (50 ml). *1*[12] (22.5 g, 50 mmol) was dissolved in dichloromethane (160 ml) by gentle heating. Ethyl acetoacetate (13.0 g, 0.1 mol) in dichloromethane (35 ml) was added. The mixture was transferred to the reaction flask using an additional amount of dichloromethane (35 ml). To the vigorously stirred two-phase system, aqueous sodium hydroxide (8.0 g, 0.2 mol in 50 ml of water) was added during 15 min. The exothermic reaction caused the solvent to boil gently. After the alkali solution had been added, the mixture was boiled for another 20 min, whereafter it was cooled to room temperature. The water phase was extracted once with dichloromethane. The combined extracts gave, after evaporation of solvent, a viscous, light yellow oil. The product was taken up in diethyl ether and washed with water and brine. After drying ($MgSO_4$) and evaporation of solvent 18.2 g (94 %) of a very viscous, colourless oil was obtained. Judged from the ^{1}H NMR spectrum the oil mainly consisted of the desired product (*2*). CC (diethyl ether) of a sample yielded a low-melting (*ca.* 85 – 95 °C) solid which showed high purity according to ^{1}H NMR. ^{1}H NMR: δ 6.97 (s, 2 H), 4.19 (q, 4 H), 3.44 (s, 8 H), 2.20 (s, 6 H), 1.24 (t, 6 H).

Crude *2* (14.3 g) was dissolved in glacial acetic acid (72 ml) and concentrated hydro-

chloric acid (75 ml) was added. The stirred mixture was refluxed gently overnight (14 h),[8] allowed to cool off and poured into a separatory funnel containing diethyl ether (*ca.* 450 ml) and water (*ca.* 1300 ml). Extraction with diethyl ether was repeated twice (2 × 250 ml) and the combined extracts washed with water, 10 % sodium hydrogen carbonate, water and brine. The slightly yellow solution was filtered through a layer of anhydrous sodium sulfate before drying with $MgSO_4$. Evaporation of solvent left 6.5 g (72.4 %) of a pale yellow crystalline material for which the ^1H NMR spectrum indicated only minor impurities. Recrystallization from acetone or CC using chloroform, (the diketone was transferred to the column as a concentrated dichloromethane solution) afforded the desired *3*, m.p. 142–150 °C. (Found: C 78.2; H 7.3. Calc. for $C_{16}H_{18}O_2$ (242.3): C 79.31; H 7.49). ^1H NMR: δ 6.97 (s, 2 H), 3.6–2.5 (m, 10 H), 2.17 (s, 6 H).

*2,6-Dihydroxy-*s*-hydrindacene (5).* The transformation of purified *3* into the diacetate (*4*) was achieved by treating 4.55 g (18.8 mmol) of *3* with 85 % *m*-chloroperbenzoic acid (11.50 g) in dry dichloromethane (70 ml). The solution was magnetically stirred for 48–50 h at ambient temperature in a sealed flask. The proceeding of the reaction could be conveniently followed by GLC. The reaction mixture was diluted to about five times its original volume with chloroform and then washed with 4 % sodium bisulfite, 0.3 M sodium hydroxide, water and brine. Filtration through anhydrous sodium sulfate, drying ($MgSO_4$) and evaporation of solvent gave a quantitative yield (5.2 g) of *4* as a faintly yellow solid. ^1H NMR: δ 7.08 (s, 2 H), 5.7–5.3 (m, 2 H), 3.6–2.7 (m, 8 H), 2.0 (s, 6 H).

The diacetate (3.54 g, 12.9 mmol) was hydrolyzed by dissolving it in warm 99.5 % ethanol (96 ml) and then adding 87.2 % potassium hydroxide (4.6 g) in water (20 ml). The stirred mixture was kept at 80 °C for 2 h and then at room temperature for another 26 h. All ethanol was removed by evaporation and the remaining material was transferred to a liquid-liquid extractor using a small amount of water. During the extraction (diethyl ether) magnetic stirring of the water phase facilitated the dissolution of the precipitated diol. Removal of solvent furnished 1.72 g (70.1 % yield from *4*) highly pure (^1H NMR) *5* m.p. 197–203 °C. Anal. $C_{12}H_{14}O_2$: C, H. ^1H NMR: δ 6.98 (s, 2 H), 4.84 (d, 2 H), 4.7–4.2 (m, 2 H), 3.3–2.4 (m, 8 H).

*1,5- and 1,7-Dihydro-*s*-indacenes (6,7).* In a one-necked flask equipped with an air-cooler and a drying tube 1.43 g (7.5 mmol) of *5* was heated with methyltriphenoxyphosphonium iodide[13] (14.7 g) in dry HMPA (45 ml).[9] The stirred mixture was kept at 75 °C for 3 h, whereupon, after cooling it was diluted with 2 M potassium hydroxide (350 ml). Repeated extraction with cyclohexane, washing with water and brine gave, after drying ($MgSO_4$) and evaporation of solvent, 1.19 g of a crystalline, pale yellow product which, to *ca.* 90 %, consisted of the expected dihydro-*s*-indacenes (*6* and *7*). The pure mixture of *6* and *7* could be isolated as colourless crystals (m.p. 113–120 °C, sealed capillary) by CC (hexane). The remaining part of the product (*ca.* 10 %) proved (^1H NMR and MS) to be 2-iodo-1,2,3,5-tetrahydro-*s*-indacene. Thus the combined yield of *6* and *7* was ca. 86 %.

According to quantitative ^{13}C NMR the isomeric ratio was 5:4. The dihydro-*s*-indacenes turned out to be rather sensitive to air oxidation even in the solid state and therefore should be stored in the cold under an inert atmosphere. Anal. $C_{12}H_{10}$: C, H. MS (70 eV): *m/e* 154 (M, 100 %). From signals due to protons attached to the five-membered rings ^1H NMR indicated two overlapping AKX_2 systems. ^1H, NMR: δ 7.4–7.2 (m, 2 H), 6.8–6.6 (m, 2 H (A)), 6.4–6.2 (m, 2 H (K)), 3.24 (s, (broad) 4 H (X_2)).

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