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Thiophene Analogues of Indenes

II. The Synthesis, Tautomerism, and Metalation of the Thiophene Analogues of 2-Methylindene

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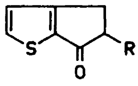
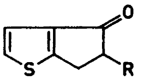
The synthesis of both thiophene analogues of 2-methylindene are described. The rate of the base-catalysed (triethylamine) tautomerisation of 5-methyl-6H-cyclopenta[b]thiophene (IV) into 5-methyl-4H-cyclopenta[b]thiophene (III) in pyridine solution has been followed by NMR-technique. At equilibrium, III in which the double bond is conjugated through the 2-position, is the dominating tautomer. Metalation of III and IV with butyllithium has been undertaken. 1-Indenecarboxylic acid has been synthesised.

In an earlier paper[1] we investigated various routes to the ketones I and II. In this publication the conversion of these ketones into the corresponding alcohols and subsequent dehydration to the indene analogues III and IV is considered. The tautomeric and chemical properties of these compounds are also discussed.



I



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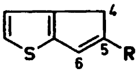
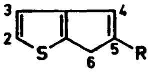


III



IV

Because of their more ready preparation we chose first to examine the 5-methyl ketones (I and II; R = CH_3). The reduction of one of these compounds (I; R = CH_3) has already been reported by Sam and Thompson[2] using sodium borohydride. However, the same workers were not able to obtain the isomeric alcohol from the ketone (II; R = CH_3). We have found that the alcohols may

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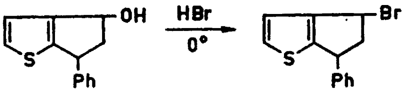
be rapidly and readily obtained in virtually quantitative yields by reduction at 0° with lithium aluminium hydride. Because of the ready acid catalysed dehydration of these alcohols it is essential to maintain basic conditions during the work-up procedure, otherwise the yield falls drastically and the otherwise colourless products rapidly turn brown in colour. No attempts were made to separate the diastereomeric forms, which could be formed.

The dehydration of indanols to indenes has been accomplished by treatment with such reagents as sulphuric acid, phosphorus pentoxide in benzene, and distillation over potassium bisulphate[3] or oxalic acid. In the thiophene series, these reagents are too drastic, and only minute quantities of very impure product results. Various other milder acids were tried and all consistently gave a dark brown fluorescent oil which rapidly resinified. Acheson and coworkers,[4] while attempting to prepare the bromo compound (VI) made a similar observation.



V VI

However, the required dehydration was readily accomplished by heating the alcohol in benzene solution under nitrogen atmosphere with a trace of *p*-toluenesulphonic acid.[5] The dehydration occurred rapidly at 60° and the water of reaction was removed azeotropically (a strong nitrogen stream maintains reflux at this temperature).

The dehydration, however, was complicated by dimer formation. The dimer was in one case isolated in the pure form and its structure determined by NMR- and mass spectrometry. The structure determination will most conveniently be discussed after discussion of the NMR-spectra of the indene analogues.

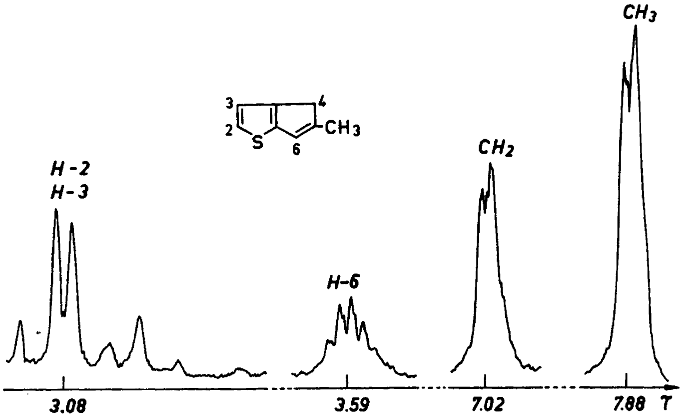


Fig. 1. NMR-spectrum at 60 Mc/s of 5-methyl-4H-cyclopenta[b]thiophene in $DCCl_3$ solution.

The purification of the products was best accomplished chromatographically and we found that rapid elution with light petroleum through acidic aluminium oxide gave the indene analogues (III and IV; R = Me) as colourless oils with correct analytical and spectral (IR and NMR) properties. The indenes proved to be very sensitive to air and acids, and rapidly became brown on standing. However under nitrogen below 0° they were stable for several weeks. The NMR spectra (Figs. 1 and 2) of the two compounds were partic-

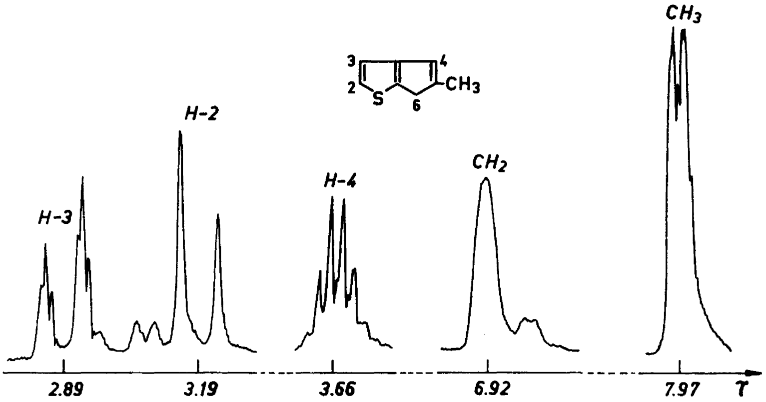


Fig. 2. NMR-spectrum at 60 Mc/s of 5-methyl-6H-cyclopenta[b]thiophene in $DCCl_3$ solution.

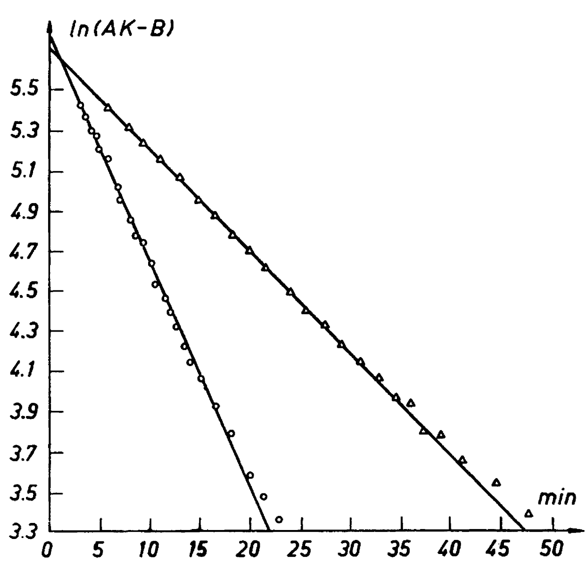


Fig. 3. Rate of tautomerisation of 5-methyl-6H-cyclopenta[b]thiophene (A) to 5-methyl-4H-cyclopenta[b]thiophene (B). ○ 0.179 M TEA; △ 0.0715 M TEA.

ularly revealing. The significant difference lay in the CH_2-absorption peak ($\tau_{\mathrm{CDCl_3}}$ 7.02 in III and $\tau_{\mathrm{CDCH_3}}$ 6.92 in IV). In the indene, IV, 13 % of the isomeric indene (III) was shown to be present, while in the case of III the tautomer was also present to a small extent. In the aromatic region the thiophenic protons appear as a quartet with second order splitting in the low field band of compound IV (triplet, $J_{2,6} = 0.7$ cps).

If the coupling pattern and mechanism of this coupling is the same as in 2-methylthiophenes,[6] long-range coupling to the 3-hydrogen is expected. The theory of the straightest zig-zag path [7] leads to the same assignment. In the NMR-spectrum of III, broadening of the high field doublet was observed indicating a very small long-range coupling to this hydrogen. In both cases the olefinic protons appear as a sextet of relative peak intensities in accord with that expected (1:5:10:10:5:1) from an overlapping quartet (coupling with the methyl group) and triplet (coupling with the methylene group, both of the same order of coupling (1.6 cps)). The methyl and methylene peaks are broadened due to their small mutual coupling.

When the crude reaction product from the preparation of III was allowed to stand at 0° for several days, crystals appeared which on recrystallisation

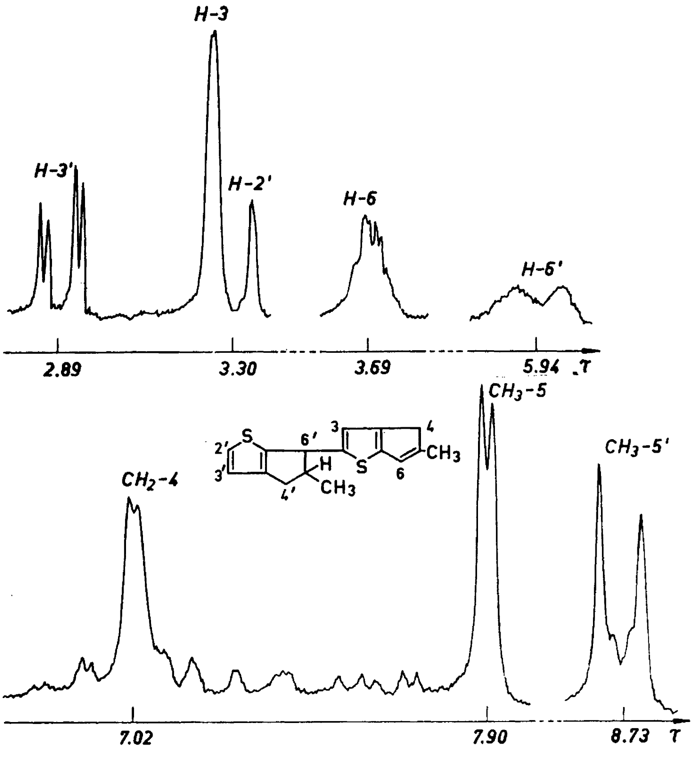
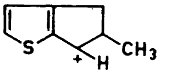
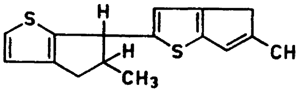


Fig. 4. NMR-spectrum at 60 Mc/s of 2-(5-methyl-5,6-dihydro-4H-cyclopenta[b]thiophene-6-yl)-5-methyl-4H-cyclopenta[b]thiophene in $DCCl_3$ solution.

from light-petrol melt at 72—73°. Molecular weight determination by mass spectrometry indicated it to be dimeric. Its NMR-spectrum (Fig. 4) suggests the compound to be 2-(5-methyl-5,6-dihydro-4H-cyclopenta[b]thiophene-6-yl)-5-methyl-4H-cyclopenta[b]thiophene (VIII).



VII



VIII

The resonances at 2.89 τ and 3.30 τ are assigned to hydrogen 3′ and 2′, respectively. The latter resonance is partly overlapped by the resonance from hydrogen 3 in $DCCl_3$. However, in acetone solution (Fig. 5) these peaks are separated. The coupling constant of 5.0 c/s characteristic of 2,3-disubstituted thiophenes[6] is observed in the 2′- and 3′-hydrogen bands. The low-field band shows additional splitting into a quartet due to long-range coupling (1.2 c/s) to the 6′-hydrogen. The assignment of the 2.89 τ band to hydrogen 3′ is based on this long-range coupling. The resonance of the ethylenic hydrogen 6 occurs at the same position and with similar coupling pattern as the corresponding resonance of III. The band at 5,94 τ is ascribed to hydrogen 6′ and is split into a doublet (6.8 c/s) due to coupling to the 5′-hydrogen. The resonance position is similar to that of dithienylmethane derivatives. The resonance of the CH_2 group in the 4-position and the methyl group in the 5 have the same τ-values as the corresponding resonances of III. The resonance of the CH_3 group in position 5′ occurs as expected as a doublet (J = 6.6 c/s) at 8.73 τ, while the resonances of the 4′-CH_2 and the 5′-CH give rise to a complex pattern between 6.8—7.8 τ partly overlapping the 4-CH_2 resonance. Integration of the different bands gives correct relative intensities.

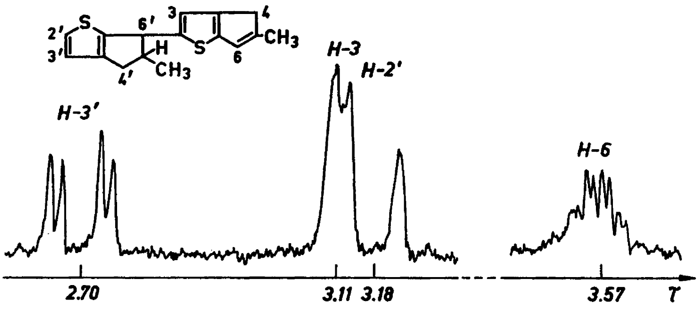


Fig. 5. Part of NMR-spectrum at 60 Mc/s of 2-(5-methyl-5,6-dihydro-4H-cyclopenta[b]-thiophene-6-yl)-5-methyl-4H-cyclopenta[b]thiophene in acetone solution.

A reasonable mechanism for the dimer formation might be suggested. The carbonium ion intermediate (VII) in the E 1 elimination, electrophilically attacks the thiophenic ring. It is suggested that substitution occurs in the α-position as is normal in thiophene itself. However, we are aware that alkylation of thiophene occurs both in the α- and β-position,[8] and that the substitution pattern of III might be different from that of thiophene (*cf.* thianaphthene), so that the connection between the two rings must be considered as tentative at present.

It is interesting to note that for the dimers formed on acid treatment of indene another type of structure is suggested in which the two five-membered carbocyclic rings are connected.[9,10] However, these structures cannot be considered as definitely proven.

The tautomerism of indenes has been shown to be a base-catalysed, pseudo first-order reaction,[11,12] and we therefore decided to observe the course of tautomerism in our systems by following the change in area under the methylene peaks. Bergson and Weidler [11,12] have shown that indenes tautomerise stereospecifically in pyridine solution with aliphatic bases such as triethylamine (TEA) as catalyst. Consequently we used the same conditions in our work. From the first order plot (Fig. 3) the rate of equilibration ($k + k'$) of a 2 M pyridine solution was calculated to be 8.55×10^{-4} sec^{-1} (0.0715 M triethylamine) and 1.91×10^{-3} sec^{-1} (0.179 M triethylamine) at 32°C.

The equilibrium mixture was composed of 76 % of the indene III. This was as expected, as it has been shown by different methods that an unsaturated substituent conjugates more effectively through the 2- than the 3-position of thiophene.[13] It is also noteworthy that pyridine itself very slowly brings about tautomerism (which was not observed with the indenes themselves [11]), suggesting a more ready tautomerisation of the thiophene analogues. In fact, comparison with Bergson and Weidler's results indicates that the thiophene analogues tautomerise faster than indenes by a factor of about ten. The slight deviation from first order kinetics towards the end of the tautomerism is possibly due to some decomposition, since the solution rapidly becomes pink in colour. First order kinetics in respect to the catalyst is also roughly observed. The rate of tautomerism in ethanol solution, followed in the same manner* was slower than in pyridine ($k + k'$) = 5.15×10^{-4} sec^{-1} (0.358 M triethylamine) by a factor of approximately 7—8. This could be due to the difference in basic strength of the catalyst in the two different media. It appears that the prototropy is intramolecular in both pyridine and ethanol solution, since the equilibration in the presence of triethylamine, in either deuteroethanol (EtOD) or in 10 % deuterium oxide in pyridine, occurs without incorporation of deuterium into the indene analogues as shown by NMR spectroscopy.

In order to compare the acidity of the indene system with its thiophene analogue (III and IV) we investigated the metalation of the latter compounds with butyllithium. Indene itself has been metalated by refluxing it for 2 h with butyllithium in ether.[14,15] However, under reflux, our compounds rapidly resinified and no simple products could be isolated on carbonation, However, when the temperature of the reaction was reduced to —20°, —40°, or —70° complete metalation occurred with both compounds III and IV within 15

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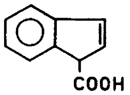
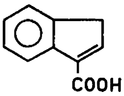
* Some small spinning side band peaks of the ethanol protons appear under the methylene proton peaks of the thiophene compounds under investigation. These render the results slightly less accurate than in the case of the pyridine solution.

min and solid products were obtained in high yield on carbonation. This unexpected result led us to reexamine the metalation of indene itself and again we found that the reaction with butyllithium was rapid and complete, even at −70°.[16]

It has been shown recently that the product obtained when indenylmetal compounds were carbonated and acidified was in every case the 3-acid (X) which was produced by rapid tautomerism of the 1-acid (IX).[17] As this tautomerism would, by analogy with the present work, be base-catalysed and thus probably occur when the metal salt, formed by carbonation,was warmed, we considered that low-temperature acidification would give the unstable 1-acid.* This was in fact the case and the hitherto unknown indene-1-carboxylic acid was obtained in high yield. This compound rapidly tautomerised to the 3-acid (X) in the presence of base. The NMR spectrum of indene-1-carboxylic acid is recorded in Fig. 6.


IX


X

The resonances of hydrogens 2 and 3 occur as quartets due to coupling to each other (5.7 c/s) and to hydrogen 1 (1.9 c/s). The latter hydrogen resonance at 5.58 τ occurs as a 1:2:1 triplet due to its similar couplings to the 2- and 3-hydrogen. In addition a small splitting (0.7 c/s) is observed in the triplet lines due to long-range coupling. Assuming the straightest zig-zag path [7] this coupling is probably to the 4-hydrogen. Another long-range coupling (0.7 c/s) is observed in the 3.08 τ band, which on this basis and on chemical shift considerations is assigned to hydrogen 3. This long-range coupling is probably to hydro-

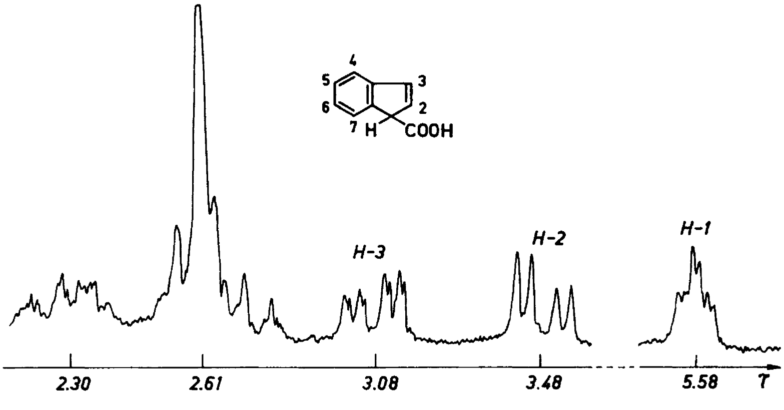


Fig. 6. NMR-spectrum at 60 Mc/s of 1-indenecarboxylic acid in $DCCl_3$ solution.

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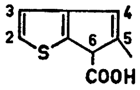
* It is possible but difficult to consider prototropy occurring with the metal derivative of indene. However, when indene is metalated by refluxing for 2 h in ether with butyllithium the 1-acid is still the major product on low temperature acidification of the carbonated compound.

gen 7 in accord with the findings of Elvidge and Foster[5] who observed a similar coupling in the methyl indenes. The COOH resonance occurs at -2.15 τ. NMR-data for the 3-acid are given in Ref. 17.

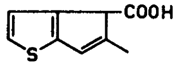
The metalation of the thiophene analogues (III and IV) could conceivably occur at both the aromatic 2-position or the allylic 6-position. We considered that investigation of the carbonated product from such a metalation experiment might help in deciding the relative acidities of the two positions and also give information on the binding conditions in indenyllithium derivatives.

If the indenyllithium derivatives are covalent and do not tautomerise before metalation different acids would be expected from III and IV upon allylic metalation. On the other hand if the lithium derivatives, due to quasi-aromatic stabilisation, are salt-like a mixture of products could be formed.

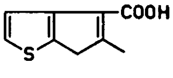
Preliminary experiments indicate that, when the compounds III or IV are metalated under the same reaction conditions at -40° and the product carbonated and acidified at low temperature (as for the preparation of indene-1-carboxylic acid), virtually the same mixture of acids is obtained, as indicated by infrared and NMR spectroscopy. The mixture seems to be predominately composed of the two compounds XI and XII. The NMR spectrum in dimethylsulphoxide (DMSO) shows an olefinic peak 3.55 τ (*cf.* 3.57 τ and 3.59 τ in compounds III and IV in $CDCl_3$) and an absorption at 5.91 τ which we assign to the aliphatic proton adjacent to the carboxylic group in compounds XI (proton 6) and XII (proton 4) (*cf.* 5.47 τ ($CDCl_3$) for the aliphatic proton of indene-1-carboxylic acid). Also methyl (7.86 τ and 7.56 τ), aromatic and carboxylic acid (-0.10 τ) protons are shown, the aromatic absorptions being complex. We observed, during our investigation of the tautomerism of indene-1-carboxylic acid, that addition of triethylamine to a strong solution of the acid in chloroform caused immediate precipitation of the isomeric 3-acid. When we repeated this experiment on the acids obtained from compounds III and IV, precipitation again occurred and the resulting products (probably containing XIII and XIV) again gave virtually identical infrared and similar NMR spectra. The latter were particularly revealing. The spectra in DMSO showed no olefinic absorption and two pairs of aromatic quartets were discernible. The aliphatic CH peak was absent but two methylene absorptions at 6.46 τ and 6.57 τ (*cf.* 6.51 τ ($CDCl_3$) for indene-3-carboxylic acid) (of roughly equal intensity from compound III, but with the low-field absorption slightly the larger from compound IV) were introduced. In pyridine solution a methyl peak at 7.47 τ was also observed of relative intensity 3:2 compared with the combined intensity of the methylene peaks. The two products (XI and XII) account for the bulk of the mixture and we have not yet been able to demonstrate the presence or absence of carboxylic acids, substituted in the thiophenic ring. We are pursuing our investigations on the metalation of III and IV.



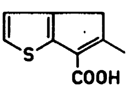
XI



XII



XIII



XIV

EXPERIMENTAL

Reduction of ketones I and II. (a) To a stirred suspension of 1.3 g (0.0343 mole) lithium aluminium hydride in 100 ml of ether at 0° was added dropwise 13.2 g (0.087 mole) of 4,5-dihydro-5-methyl-6H-cyclopenta[b]thiophene-6-one (I; R = CH_3)[1] in 50 ml of ether over 10 min. After a further 10 min stirring at 0°, excess of lithium aluminium hydride was destroyed by dropwise addition of methanol, followed by 20 ml of cold water. The ether layer was decanted off and the thick aqueous emulsion washed with ether several times by decantation. The combined ether phase was washed once with water, dried ($MgSO_4$) and fractionated to give 12.5 g (94 %) of 4,5-dihydro-5-methyl-6H-cyclopenta [b]thiophene-6-ol as a white viscous liquid, b.p. 115–6°/8 mm, n_D^{24} 1.5587. (Sam and Thompson[2] record b.p. 114°/6 mm). (ν_{max} (liq. film) 3300 cm^{-1} (s)).

b) In a similar way from the ketone II (R = CH_3) we obtained 5,6-dihydro-5-methyl-4H-cyclopenta[b]thiophene-4-ol in 93 % yield as a white solid, m.p. 70°. (Found: C 62.16; H 6.35; S 21.18. Calc. for $C_8H_{10}OS$ (154.2): C 62.32; H 6.54; S 20.80).

Preparation of the indene analogues III and IV. To a solution of the above alcohols in pure benzene under nitrogen was added a trace of *p*-toluene sulphonic acid in hot benzene. The solution was heated to 60° and reflux maintained by use of a strong stream of nitrogen. The water of reaction was collected in a Dean and Stark water separator until the theoretical amount was removed (1/2 – 1 h reflux). The pale yellow solution was washed twice with water, dried and evaporated under vacuum. The residue was dissolved in P.A. petroleum ether (b.p. 40–60°) and rapidly eluted through a column of acidic alumina (Fluka – Type 504 e Brockman Activity 1). The eluate, on evaporation yielded the indene analogues III and IV (R = CH_3) as colourless liquids in 50–80 % yields. 5-Methyl-6H-cyclopenta[b]thiophene (IV; R = CH_3) was shown by NMR spectroscopy to contain 13 % of the isomeric compound (III; R = CH_3) and had a m.p. 8–11°, n_D^{22} 1.5819. (Found: C 70.60; H 5.90; S 24.05. Calc. for C_8H_8S (136.2): C 70.57; H 5.92; S 23.56). 5-Methyl-4H-cyclopenta[b]thiophene (III; R = CH_3), m.p. 5–10° was obtained in the same manner. (Found: C 69.89; H 5.85; S 23.21). Calc. for C_8H_8S (136.2): C 70.57; H 5.92; S 23.56).

2-(5-Methyl-5,6-dihydro-4H-cyclopenta[b]thiophene-6-yl)-5-methyl-4H-cyclopenta[b]thiophene. When the crude product from the dehydration of 4,5-dihydro-5-methyl-6-6H-cyclopenta[b]thiophene-6-ol was allowed to stand at 0°C, crystals separated, which recrystallised by cooling a light petroleum (b.p. 40–60°) solution to −30°C to give the pure compound, m.p. 72–73°. (Found: C 69.89; H 5.90; S 24.23; mol. wt. 273 (mass spectrometry). Calc. for $C_{16}H_{16}S_2$ (272.4): C 70.57; H 5.92; S 23.56).

1-Indenecarboxylic acid. To 4.64 g (0.040 mole) of indene in 50 ml of dry ether at −40°, was added over 5 min with stirring and under nitrogen atmosphere 33 ml of ethereal 1.27 N butyllithium. After an additional 10 min of stirring at this temperature the pale yellow reaction mixture was poured rapidly onto 150 g of freshly crushed solid carbon dioxide under 100 ml of ether. The mixture was rapidly warmed to −50° to −40° and then acidified by addition of 150 ml of 10 % hydrochloric acid all in one lot with vigorous stirring. The ether phase of the resulting mixture was separated, washed with water, dried and evaporated to yield 5.9 g (93 %) of crude product. Recrystallisation from petroleum ether (b.p. 40–60°) gave 1-indenecarboxylic acid as white needles, m.p. 73.5–74°. (Found: C 74.97; H 5.04. Calc. for $C_{10}H_8O_2$ (160.2): C 75.00; H 5.04).

Addition of one drop of triethylamine to a saturated chloroform solution immediately caused precipitation of 3-indenecarboxylic acid.

Metalation of the indenes III and IV. To a stirred solution of 4.08 g (0.03 mole) of the indene analogue (III or IV) in 75 ml of dry ether was added dropwise under a nitrogen atmosphere 27.5 ml of 1.2 N butyllithium (0.033 mole) in ether. A pale yellow colour formed immediately. The reaction was performed at −20°, −40°, and −70° and after 15 min extra stirring the reaction mixture was poured onto crushed solid carbon dioxide under ether, the resulting mixture warmed rapidly to −50° and an excess of 10 % hydrochloric acid (100 ml) added all in one lot with rapid hand stirring. The ether phase was washed 5 times with water, dried ($MgSO_4$) and evaporated to give a solid residue. The residue was washed with a small quantity of cold petroleum ether (b.p. 40–60°) to yield 3.0–3.5 g of product in each case (56–65 %). When the metalation was performed at −40° or above in the case of the compound IV, or −10° or above with compound III a white solid precipitated from solution.

The NMR-spectra were obtained with a Varian A-60 high resolution spectrometer belonging to the Instrument Station of the University of Lund. The course of the rearrangement was followed by integrating over the CH_2 peaks of III and IV at 7.02 τ and 6.92 τ. The kinetic runs were made at 32°C in 2 M pyridine solutions. The experimental kinetic data satisfied the following equation for a reversible first-order reaction:

$$\ln (AK - B) - \ln (A_0K - B_0) = -(k_1 + k_2)t$$

in which K is the equilibrium constant and A_0 and B_0 are the concentrations of A and B at zero time.

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REFERENCES

1. Meth-Cohn, O. and Gronowitz, S. *Acta Chem. Scand.* **20** (1966) 1577.
2. Sam, J. and Thompson, A. C. *J. Pharm. Soc.* **52** (1963) 898.
3. Weidler, A.-M. *Acta Chem. Scand.* **17** (1963) 2724.
4. Acheson, R. M., MacPhee, K. E., Philpott, P. G. and Barltrop, J. A. *J. Chem. Soc.* **1956** 698.
5. Elvidge, J. A. and Foster, R. G. *J. Chem. Soc.* **1963** 596.
6. Hoffman, R. A. and Gronowitz, S. *Arkiv Kemi* **16** (1960) 563.
7. Banwell, C. N. and Sheppard, N. *Discussions Faraday Soc.* **34** (1962) 115.
8. Appleby, W. G., Sartoi, A. F., Lee, Jr., S. H. and Kapranos, S. W. *J. Am. Chem. Soc.* **70** (1948) 1552.
9. Bergmann, E. and Taubadel, H. *Ber.* **65** (1932) 463.
10. Dansi, A. and Pasini, C. *Gazz. Chim. Ital.* **81** (1951) 507.
11. Bergson, G. and Weidler, A.-M. *Acta Chem. Scand.* **17** (1963) 1798.
12. Weidler, A.-M. and Bergson, G. *Acta Chem. Scand.* **18** (1964) 1487.
13. Gronowitz, S. *Arkiv Kemi* **13** (1958) 295.
14. Cromwell, N. H., Kuck, J. A. and Elderfield, R. C. *J. Am. Chem. Soc.* **74** (1952) 4448.
15. Meier, R. *Chem. Ber.* **86** (1953) 1483.
16. Meth-Cohn, O. and Gronowitz, S. *Chem. Commun.* **1966** 81.
17. Melera, A., Claesen, M. and Vanderhaeghe, H. *J. Org. Chem.* **29** (1964) 3705.

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