ACTA CHEMICA SCANDINAVICA 25 (1971) 3625–3633

Enamines from 1-Methyl-2-indanone*

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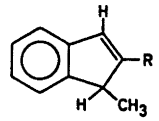
The reaction between 1-methyl-2-indanone and secondary amines has been investigated. The amines used were pyrrolidine, piperidine, hexamethylenimine, and morpholine. Mixtures of two isomeric (tautomeric) enamines are formed, and the kinetic and thermodynamic control of the reactions were studied. One of the isomeric enamines formed from 1-methyl-2-indanone and piperidine could be obtained in a state almost free from the other isomer. Isomerization of the enamines is strongly catalyzed by acids. The enamine formed from 2-indanone-d_4 and pyrrolidine catalyzes the rearrangement of 1-methylindene to 3-methylindene without hydrogen exchange. Convenient syntheses of 1-methyl-2-indanone and 2-indanone-d_4 are described.

Alkyl-substituted indenes have been found to undergo facile base-catalyzed prototropic rearrangements.[1,2] Substituted indenes having an amine nitrogen bound to the 2-carbon atom would be expected to undergo acid-catalyzed prototropic reactions due to their enamine structure. In this paper, we will report some studies of the enamines (I and II, a-d) derived from 1-methyl-2-indanone (III), and also some experiments using the deuterated enamine (IV) as a base-catalyst in the rearrangement of 1-methylindene to 3-methylindene.

In the alkyl-substituted indenes (R = alkyl or hydrogen) the equilibrium between the tautomers I and II is strongly shifted in favour of II (over 98 %).[3,4] The enamines I and II (R = a – d), however, are both present at equilibrium in approximately equal amounts (*vide infra*). This difference between amine-substituted indenes and other indene derivatives was also noted by Ham and Leeming [5] in their recent study of enamines derived from 1-phenyl-2-indanone and 1-benzyl-2-indanone. Earlier reports on phenyl-substituted indene-enamines by Blomquist and Moriconi [6] are critizised by Ham and Leeming.

Previous studies of tautomeric enamines formed from ketones and amines have apparently described only the formation of thermodynamic equilibrium

Part XVI in the series "Proton-mobility in the Indene Ring-System". Part XV, *Acta Chem. Scand.* **23** (1969) 2175.



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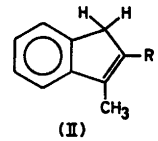

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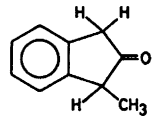

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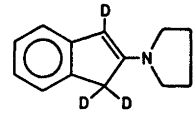

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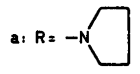
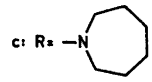
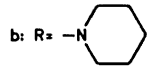
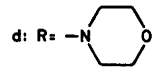


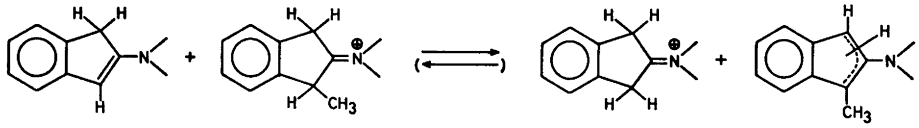






mixtures of the isomers.[5,7] In this paper, however, we will report the successful preparation of non-equilibrium mixtures formed by kinetic control of the reaction between 1-methyl-2-indanone and secondary amines. From an equilibrium mixture, Mazarguil and Lattes[14] obtained one isomer of the enamines formed from 2-methylcyclohexanone and *N*-phenylpiperazine in a pure form by recrystallization.

Syntheses and physical properties. Our enamines have been prepared from 1-methyl-2-indanone in a way similar to that used by Schroth and Fischer [8] for the syntheses of enamines derived from the unsubstituted 2-indanone. The starting material, 1-methyl-2-indanone (III), was first obtained by Wallach [9] through reduction of methyl-2-nitroindene. Curiously enough, Blomquist and Moriconi [6] describe III as a light yellow oil (b.p. 140–143°/3.5–3.7 mmHg) which turned black overnight even under nitrogen at −28°C. Their product was obtained by methylation of enamines of 2-indanone. The iminium salt which precipitates from the reaction mixture (in dioxane-tetrahydrofuran) was claimed to be V. By repeating their experiment and analyzing the product by NMR, we found that the iminium salt mainly consisted of VI, formed by simple proton exchange. This explains the low yield of III obtained, and also the formation of unsubstituted 2-indanone (after hydrolysis), the appearance of which is ascribed by Blomquist and Moriconi as a result of *N*-alkylation.



(V)

(VI)

1-Methyl-2-indanone (III) is most conveniently prepared by oxidation of 1-methylindene in a way analogous to the synthesis of 2-indanone from indene.[10]

The reaction between 1-methyl-2-indanone (III) and the appropriate amine gave a mixture of the isomeric enamines I and II. The proportion of the isomers at equilibrium was determined from the NMR-spectrum by comparing the intensity of the vinylic proton signal with that of the aromatic protons. As can be seen from Table 1, there is no significant solvent effect on the equilibrium constant. That the values given in Table 1 really represent the equilibrium was proved by the fact that no changes were observed upon the addition of perchloric acid or *p*-toluenesulphonic acid. As mentioned later on in this paper, strong acids rapidly catalyze the equilibration of the isomers. The reactions between (III) and the amines were either carried out analytically in NMR tubes using the solvents given in Table 1, or preparatively using methanol as a solvent as described in detail in the Experimental part. Examples of NMR-spectra are given in the Experimental part (Figs. 2 and 3).

Table 1. Percentage (±2 %) of the isomeric enamines I, a-d and II, a-d in different solvents at 39°C.

Amine part	Isomer I in			Isomer II in		
	DMSO	CH_3CN	CH_3OH	DMSO	CH_3CN	CH_3OH
a. Pyrrolidine	47	47	49	53	53	51
b. Piperidine	61	61	65	39	36	35
c. Hexamethylenimine	60	59	63	40	41	37
d. Morpholine	59	59	56	41	41	44

Interestingly, in all cases except for the pyrrolidine enamines, the 1-methyl-substituted isomer (I) is slightly more stable than the 3-methyl-substituted one (II). As mentioned above, for alkyl-substituted indenes, *e.g.* methylindene and dimethylindene, the isomer with an alkyl group in the 3-position is much more stable than the 1-substituted isomer. A contributing cause of this difference is that the amine part in the enamines tends to be coplanar with the indene ring in order to facilitate π-conjugation. This possibly implies a greater steric hindrance with a 3-methyl group than with a methyl group in 1-position. The π-conjugation is clearly manifested in the vinylic proton shifts in the enamines (Table 2) as compared to the corresponding shift in 1-methylindene (6.71 ppm), and also in the difference in the UV-spectra (Table 3).

All the enamine isomer mixtures (I a-d, II a-d) are crystalline at room temperature and can be stored for long periods in a refrigerator, but they are fairly hygroscopic.

Non-equilibrium mixtures. In order to investigate the possibility of obtaining non-equilibrium mixtures of the enamines, we studied the reaction between 1-methyl-2-indanone and piperidine in chloroform, an aprotic solvent. The

Table 2. The NMR chemical shift (δ, ppm rel. TMS) of the vinylic proton in the enamines I,a-d and some related enamines. Solvent: chloroform-*d*. Temp.: 32°C.

Ketone / Amine	1-Methyl-2--indanone [a]	2-Indanone [a]	1-Indanone [b]	1-Phenyl-2-indanone [b]
Pyrrolidine	5.42	5.36	5.34	5.35
Hexamethylenimine	5.47	5.41	–	5.42
Piperidine	5.72	5.66	–	5.61
Morpholine	5.76	5.71	–	–

[a] The shifts are extrapolated to zero concentration. [b] From Ref. 5.

Table 3. Ultraviolet absorption for some enamines. Solvent: cyclohexane.

Enamine	λ_{max} [nm] (ε_{max})		
2-(*N*-Pyrrolidyl)-indene [a]		227 (10.800)	298 (24.900)
1-Phenyl-2-(*N*-pyrrolidyl)indene and 3-phenyl-2-(*N*-pyrrolidyl)indene [b,c]	214 (17.770)	228 (11.100)	305 (20.150)
1-Methyl-2-(*N*-pyrrolidyl)indene and 3-methyl-2-(*N*-pyrrolidyl)indene [c]	212 (13.300)	230 (10.300)	304 (18.800)

[a] From Ref. 6. [b] From Ref. 5. [c] Equilibrium mixture.

course of the reaction was followed directly by NMR-spectroscopy as described under section C.a. in the Experimental part. The result of a typical experiment is given in Fig. 1 where the relative concentrations of 1-methyl-2-indanone (III), 1-methyl-2-(*N*-piperidyl)indene (Ib) and 3-methyl-2-(*N*-piperidyl)indene (IIb) are given as a function of time.

It is evident from Fig. 1 that the isomer I is formed much more rapidly than the isomer II, and that, therefore, the concentration ratio [I]/[II] in the beginning of the reaction is much higher than at equilibrium. As the reaction proceeds, equilibrium is slowly approached, probably *via* the protonated forms

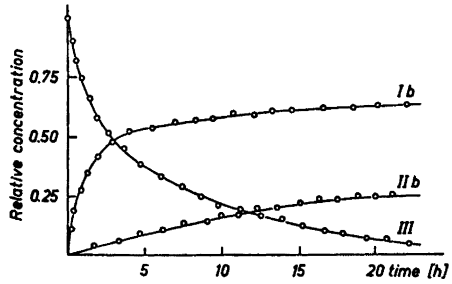
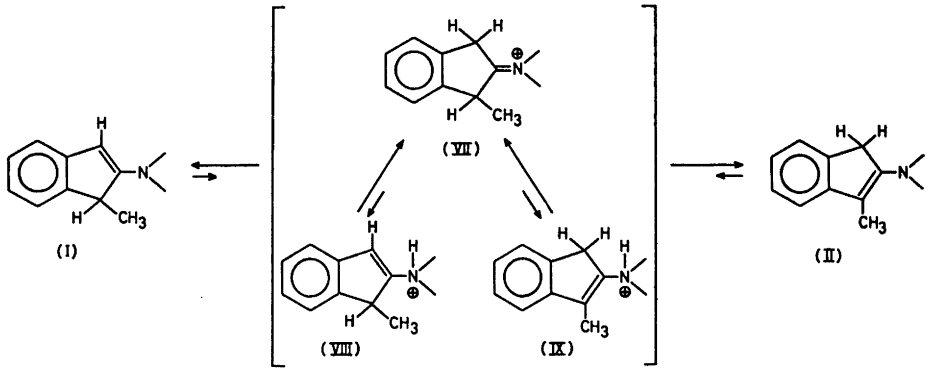


Fig. 1. Relative concentration *vs.* time for 1-methyl-2-indanone (III), 1-methyl-2-(*N*-piperidyl)indene (Ib) and 3-methyl-2-(*N*-piperidyl)indene (IIb). Solvent: chloroform-*d*. Temperature: 39°C. Concentration of III and piperidine at zero time: 1.00 mol/l.

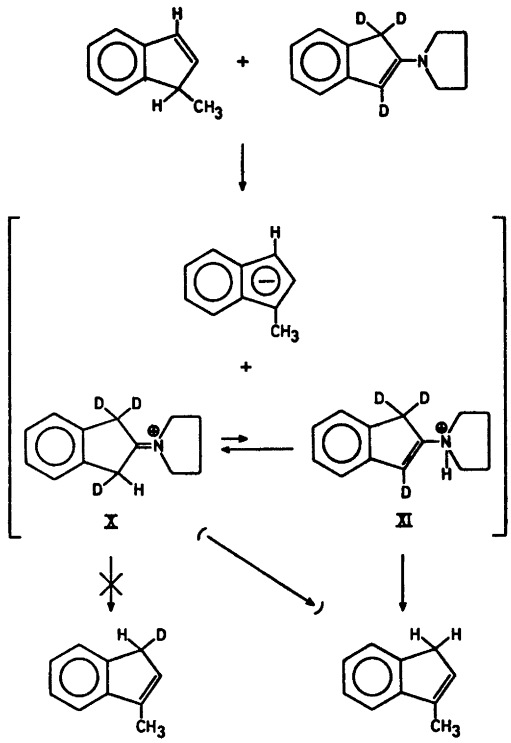
(VII – IX). Addition of a small amount of *p*-toluenesulphonic acid to the reaction mixture strongly accelerates the equilibration of the isomers I and II. Similar results were obtained when morpholine was used instead of piperidine. These two amines were used in this study because of the favourable NMR-spectra obtained. As described in section C.b. in the Experimental part, we succeeded in preparing a non-equilibrium mixture of Ib and IIb by interrupting a reaction between III and piperidine after 3 h. Later we discovered that Ib had a greater tendency than IIb to crystallize from methanolic solutions. Thus, at 0°C in methanol where the isomerization between Ib and IIb is rather rapid, it is possible to obtain a good yield of a crystalline product which contained not less than 96 % of Ib. The NMR-spectrum of this product is given in Fig. 4, and the experimental procedure is described in section C.c.



A more detailed investigation of the kinetics of the formation of the enamines Ib and IIb and their acid-catalyzed isomerization is in progress.

Some additional observations. As mentioned in the introduction, alkyl-substituted indenes undergo facile base-catalyzed isomerization. Thus, 1-methylindene is rearranged to 3-methylindene [11] using diaza-bicyclo[2.2.2]-octane (DABCO), in pyridine as solvent, with a rate constant of 1.43 l mol^{-1} min^{-1} at 30°C. The enamines Ib and Id, however, are very slowly rearranged by aliphatic amines at this temperature, and preliminary estimates based on MO-LCAO calculations indicate that they are weaker acids than indenes by more than two powers of ten.

The activity of 2-(*N*-pyrrolidyl)indene (IV) as a basic catalyst has been studied using 1-methylindene as a substrate. We found that IV rearranged this indene to 3-methylindene with a rate constant of 7×10^{-3} l mol^{-1} min^{-1} at 43°C in DMSO, which, as expected, is lower than the rate constant found for triethylamine [11] (290×10^{-3} at 30°C). During this rearrangement, no incorporation of deuterium into the indene system was observed. A *necessary* condition for such a hydrogen exchange is the formation of the imonium ion (X) in the ion-pair, which is an intermediate in this type of rearrangement.[1,2] From NMR-studies we have found that salts of the indene-enamines exist exclusively in the imonium form, but the ammonium ion (XI) is presumably kinetically favoured.



EXPERIMENTAL

The NMR-spectra were recorded on a Varian A-60A instrument with TMS as internal standard, and the UV-spectra on a Perkin-Elmer 137 UV-VIS spectrophotometer. Melting points are uncorrected. The microanalyses were performed at the Department of Analytical Chemistry, University of Uppsala.

A. Synthesis of 1-methyl-2-indanone (III)

To a mixture of 80 ml of 90 % formic acid (*puriss.*) and 17 ml of 30 % hydrogen peroxide were added dropwise with stirring 12.6 g (0.097 mol) of 1-methylindene during 90 min. During this addition, and for another 2 h, the temperature should be kept at 35°C. After standing overnight at room temperature, a solution of 2.1 g of ferrous sulphate in 10 ml of water was added dropwise to the reaction mixture, which was then evaporated to 1/3 of its volume. A mixture of 200 ml of water and 30 ml of conc. sulphuric acid was added and the resulting reaction mixture was steam distilled until about 2000 ml of distillate had been collected. Upon cooling the colourless crystalline product separated. The mother liquor was extracted with methylene chloride which gave additional product. The combined yield of 1-methyl-2-indanone was 8.8 g (0.060 mol, 62 %), m.p. 61 – 61.5°C (lit.[9] 62 – 63°C).

B. Synthesis of equilibrium mixtures of enamines

1-Methyl-2-(N-pyrrolidyl)indene (Ia) *and 3-methyl-2-(N-pyrrolidyl)indene* (IIa). To 4.01 g (0.0275 mol) of 1-methyl-2-indanone in 15 ml of abs. methanol (*p.a.*) were added 1.95 g (0.0275 mol) of pyrrolidine (*p.a.*). The mixture was heated at 50°C for 15 min

under nitrogen with stirring. The crystalline product which separated on cooling in ice-water was recrystallized from 40 ml of methanol. Yield 3.50 g (0.0176 mol, 64 %), m.p. 53.5–54°C. Found: C. 83.6; H. 8.5; N 6.9. Calc. for $C_{14}H_{17}N$ (199): C 84.4; H 8.5; N 7.1. The product is a mixture of Ia and IIa roughly in the proportions given in Table 1.

1-Methyl-2-(N-hexamethyleneimino)indene (Ic) *and 3-methyl-2-(N-hexamethyleneimino) indene* (IIc). The synthesis was performed quite analogously to that of Ia, IIa above, Yield 44 %, m.p. 50.5–51°C. (Found: C 84.4; H 9.3; N 6.1. Calc. for $C_{16}H_{21}N$ (227): C 84.5; H 9.3; N 6.2.) The product is a mixture of (Ic) and (IIc) in roughly the proportions given in Table 1.

1-Methyl-2-(N-piperidyl)indene (Ib) *and 3-methyl-2-(N-piperidyl)indene* (IIb). To 4.01 g (0.0275 mol) of 1-methyl-2-indanone in 15 ml of abs. methanol (*p.a.*) were added 2.34 g (0.0275 mol) of piperidine (*p.a.*). The mixture was refluxed under nitrogen and with stirring for 1 h. Upon cooling in ice-water, a yellow oil separated. The mother liquor, together with 20 ml of abs. methanol, was transferred under nitrogen to a 100 ml flask. This flask was now cooled, with rapid stirring, in a dry-ice acetone bath. Colourless crystals of enamine separated and the above mentioned oil was added dropwise. Cooling

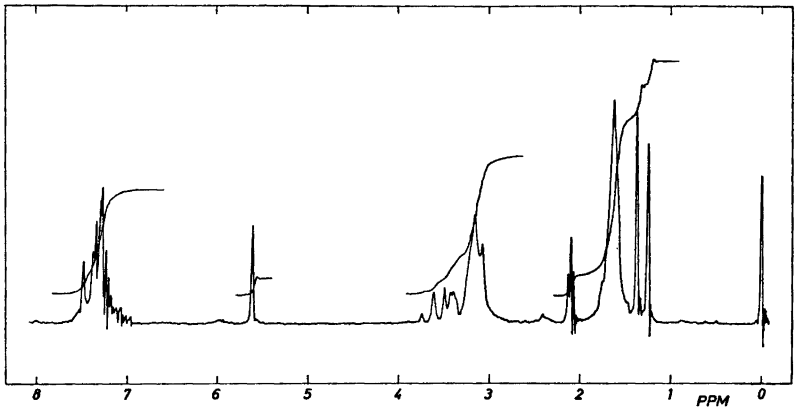


Fig. 2. NMR-spectrum of a mixture of Ib and IIb in chloroform-*d*. Concentration: 1.4 mol/l.

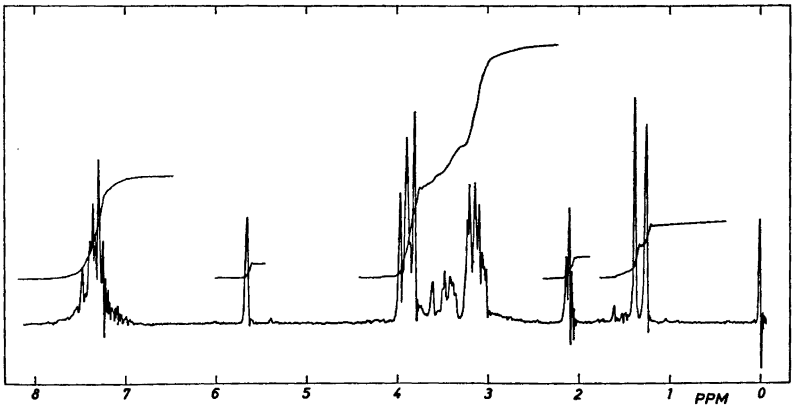


Fig. 3. NMR-spectrum of a mixture of Id and IId in chloroform-*d*. Concentration: 0.86 mol/l.

and stirring was continued for about 15 min when the entire product had crystallized. The crystalline product was filtered in the cold, and redissolved in 20 ml of abs. methanol. Repeated cooling in dry-ice acetone gave a product with m.p. 25–27°C. Yield 2.47 g (0.0116 mol, 42 %). (Found: C 84.3; H 8.9; N. 6.4. Calc. for $C_{15}H_{19}N$ (213): C 84.5; H 8.9; N 6.6.) The product is a mixture of Ib and IIb roughly in the proportions given in Table 1. An NMR-spectrum of the product is given in Fig. 2. The isomer Ib is characterized by the methyl doublet at about 1.3 ppm (δ, rel. TMS) and the vinyl singlet at about 5.6 ppm. The methyl triplet from isomer IIb appears at about 2.1 ppm (*cf.* the spectrum in Fig. 4 of a mixture containing 96 % of Ib and 4 % of IIb).

1-Methyl-2-(N-morpholinyl)indene (Id) *and 3-methyl-2-(N-morpholinyl)indene* (IId). The synthesis was performed quite analogously to that of Ib, IIb, above. Yield 26 %, m.p. 32–40°C. (Found: C 77.7; H 7.7; N 6.1. Calc. for $C_{14}H_{17}ON$ (215): C 78.1; H 7.9; N 6.5.) An NMR-spectrum of the product is given in Fig. 3. The isomer Id is characterized by the methyl doublet at about 1.3 ppm (δ, rel. TMS) and the vinyl singlet at about 5.7 ppm. The methyl triplet from isomer IId appears at about 2.1 ppm.

C. Non-equilibrium mixtures of 1-methyl-2-(*N*-piperidyl)indene (Ib) and 3-methyl-2-(*N*-piperidyl)indene (IIb)

a. *Preliminary kinetic studies.* A solution of 1-methyl-2-indanone and piperidine or morpholine in deuterated chloroform was placed in an NMR-tube held at 39°C (probe temperature). The concentration of both reactants was 1.00 mol/l. The concentration of 1-methyl-2-indanone and of the enamines Ib and IIb or Id and IId as a function of time could be determined by repeated integration of the peaks characteristic of the enamines (see the description given above and Figs. 2 and 3) and the methyl doublet from the methyl-indanone. A typical result is given in Fig. 1.

b. *Quenching of a kinetically controlled mixture.* A solution of 1-methyl-2-indanone (1 M) and piperidine (2 M) in tetrachloroethylene (*p.a.*) was kept at 40°C for 3 h. The solution was then rapidly evaporated in vacuum and unreacted starting material removed by washing with a little methanol. The remaining enamine mixture consisted of 85 % of Ib and 15 % of IIb as determined by NMR-measurements in deuterated chloroform.

c. *Fractional crystallization at 0°C.* To 4.38 g (0.030 mol) of 1-methyl-2-indanone in 28 ml of abs. methanol (*p.a.*) were added 4.25 g (0.050 mol) of piperidine (*p.a.*). The mixture was refluxed under nitrogen and with stirring for 30 min. The reaction mixture was cooled in ice-water, a small crystal of the enamine mixture obtained according to C.b. was added. The flask was placed in a refrigerator at 0°C for 24 h, and the crystalline

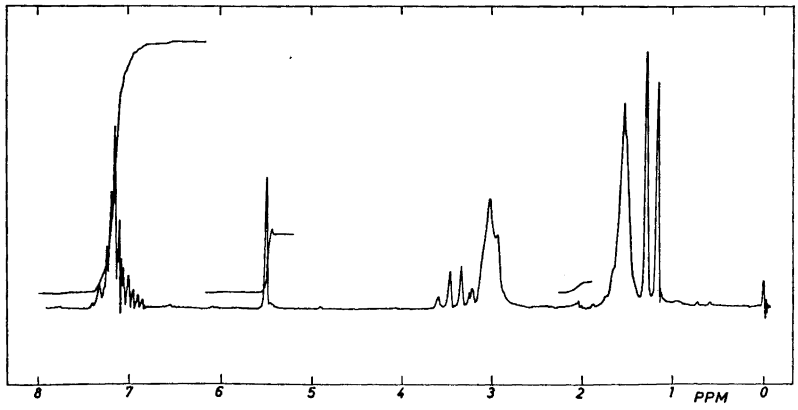


Fig. 4. NMR-spectrum of Ib contaminated with 4 % of IIb in tetrachloroethylene. Concentration: 1.0 mol/l.

product was filtered and washed with cold methanol. Yield 3.99 g (0.0187 mol, 62 %), m.p. 29 – 30.5°C. Integration of the NMR-spectrum (Fig. 4) showed that the product was a mixture of 96 % of Ib and 4 % of IIb. No changes of the spectrum (in tetrachloroethylene) could be detected after 30 min at 30°C. After addition of a small amount of *p*-toluenesulphonic acid, however, rapid equilibration of the isomers took place and the spectrum changed to one analogous to the spectrum given in Fig. 2.

D. 2-Indanone-d_4

A mixture of 7.0 g of freshly distilled 2-indanone[13] and 10 ml of D_2O (99.7 % D) was refluxed under a nitrogen atmosphere with rapid stirring for 4 h. After cooling, the liquid was decanted off and the product dried in vacuum at room temperature. The whole procedure was repeated 7 times. The product, m.p. 56.5 – 58°C, which is obtained in almost quantitative yield, was deuterated to 98 % as determined from NMR.

E. 2-(*N*-Pyrrolidyl)indene-d_3 (IV)

The synthesis was done (using pyrrolidine-*d* and ethanol-*d*) according to the method used by Schroth and Fischer [8] for the synthesis of the undeuterated compound. The product was deuterated to 94 %, m.p. 117 – 119°C.

Acknowledgement. This work is part of a research project, financially supported by the *Swedish Natural Science Research Council.*

REFERENCES

1. Bergson, G. and Ohlsson, L. *Acta Chem. Scand.* **23** (1969) 2175, and earlier papers in this series.
2. Almy, J., Garwood, D. C. and Cram, D. J. *J. Am. Chem. Soc.* **92** (1970) 4321, and earlier papers.
3. Bergson, G. and Weidler, A.-M. *Acta Chem. Scan.* **17** (1963) 862.
4. Plénat, F. and Bergson, G. *Arkiv Kemi* **25** (1965) 109.
5. Ham, A. L. and Leeming, P. R. *J. Chem. Soc.* **C 1969** 2017.
6. Blomquist, A. T. and Moriconi, E. J. *J. Org. Chem.* **26** (1961) 3761.
7. Cook, A. G. *Enamines: Synthesis, Structure and Reactions*, Dekker, New York 1969.
8. Schroth, W. and Fischer, G. W. *Chem. Ber.* **102** (1969) 575.
9. Wallach, O. *Ann.* **336** (1904) 6.
10. *Org. Syn.* **41** (1961) 53.
11. Weidler, A.-M. and Bergson, G. *Acta Chem. Scand.* **18** (1964) 1487.
12. Bergson, G. and Ohlsson, L. *Acta Chem. Scand.* **21** (1967) 1393.
13. Horar, J. E. and Schliesser, R. W. *Org. Syn.* **41** (1961) 53.
14. Mazarguil, H. and Lattes, A. *Bull. Soc. Chim. France* **1969** 319.

Received March 16, 1971.