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REGIOSELECTIVITY IN THE FISCHER INDOLE SYNTHESIS USING 3-SUBSTITUTED CYCLANONES

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Abstract—The Fischer indole synthesis with 3-substituted cyclanones leads to only one of two formally possible isomers. A discussion of the regioselectivity is based on results from "Extended Hückel" calculations on cyclohexene derivatives and on a comparison with various experimental factors. Structures are established by use of the shift reagent $Eu(DPM)_3$.

FROM THE FISCHER condensation[1] of a phenylhydrazine with a 3-substituted ketone two isomeric indoles, **2** and **3**, are expected.

In a recent reexamination of work by Baeyer and Tutein,[2] G. R. Allen has shown that cyclohexanone-3-carboxylic acid reacts with phenylhydrazine to give a single indole **4**; the isomeric compound **5** could not be detected.[3] At the time of Allen's publication we had arrived at the same conclusion by similar methods. Moreover, we have carried out the Fischer indole synthesis with diverse cycloheptanones and cyclopentanones and the products have been identified by their NMR spectra interpreted with the aid of a paramagnetic shift reagent. A discussion of the regioselectivity of the reaction constitutes the object of this communication.

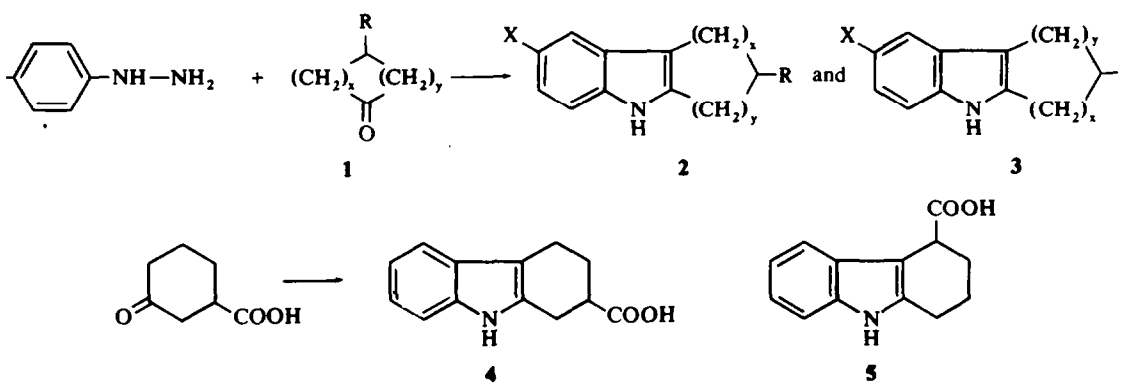


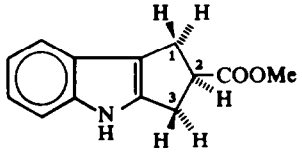
FIG. 1.

Derivatives of cyclopent-(b)*-indole*

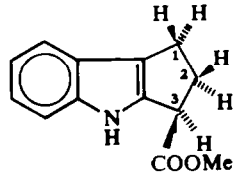
The Fischer condensation of phenylhydrazine with cyclopentanone-3-carboxylic acid leads to the isolation of a single product having structure **6** or **7**. A comparison of the shifts ($\Delta\delta$) induced by trisdipivaloylmethanato-europium $Eu(DPM)_3$[4,5] in the spectrum of the methyl ester **6b** is listed in Table I along with the analogous data obtained for indole **8**, the structure of which is unambiguous since it has been prepared by indolization of 2-carbomethoxycyclopentanone.

The indole skeleton being inert to the shift reagent,[6] the latter is oriented in the neighbourhood of the carbomethoxy group and since the deplacement induced varies with the distance,[6] only structure **6** is compatible with the data from Table I: in the case of **8** there is a single proton *cis*-vicinal to the carbomethoxy function, $H_{2\beta}$, having a high $\Delta\delta$ value while in the case of **6b** there are two protons, $H_{1\beta}$ and $H_{3\beta}$, which behave analogously; **7** would show only one *cis*-vicinal proton.

TABLE I. EFFECT OF THE SHIFT REAGENT $Eu(DPM)_3$ ON THE NMR SPECTRUM OF COMPOUNDS **6b** AND **8**.



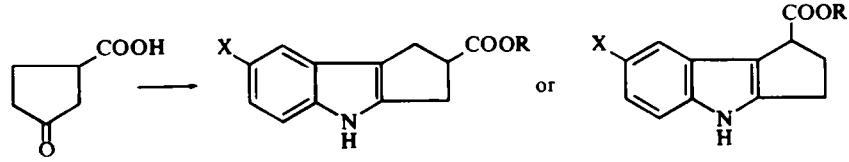
6b



8

	δ $CDCl_3$	δ + 0·3 M $Eu(DPM)_3$	$\Delta\delta$		δ $CDCl_3$	δ + 0·3 M $Eu(DPM)_3$	$\Delta\delta$
Me	3·70	6·25	2·55	Me	3·70	6·50	2·80
H_2 α	3·3–3·8	6·2–6·7	2·9	$H_{3\alpha}$	3·7–4·2	6·3–6·7	2·5
$H_{1\beta}$ or $H_{3\beta}$	2·4–2·7	5·6–6·0	3·2	$H_{2\beta}$	2·7–2·9	4·6–5·1	2·0
$H_{3\beta}$ or $H_{1\beta}$	2·4–2·7	5·2–5·6	2·8	$H_{2\alpha}$	2·7–2·9	3·8–4·3	1·3
$H_{1\alpha}$ or $H_{3\alpha}$	2·4–2·7	4·3–4·7	1·9	$H_{1\alpha}$	2·7–2·9	3·4–3·8	0·8
$H_{3\alpha}$ or $H_{1\alpha}$	2·4–2·7	4·0–4·4	1·6	$H_{1\beta}$	2·7–2·9	3·4–3·8	0·8

The introduction of a substituent (X = OMe) allows the identification of the aromatic protons and their behaviour under the influence of the shift reagent confirms structure **6**. The weak $\Delta\delta$ values for the Me protons of the OMe group indicate that the latter is not the site of a complex with Eu^{3+}. This point has been verified in the



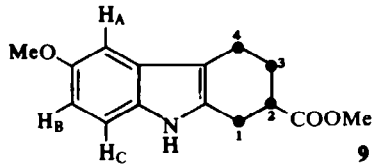
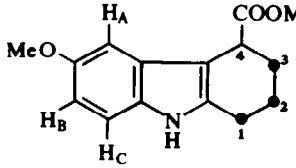
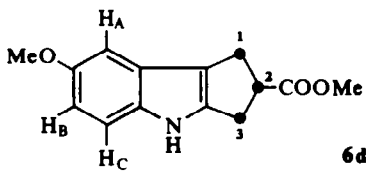
6 **a**: R = H, X = H
b: R = Me, X = H
c: R = H, X = OMe
d: R = Me, X = OMe

7

FIG 2.

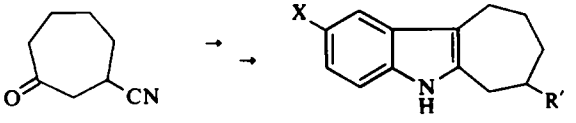
case where the molecule possesses no other group which might act as a complexing centre (*i.e.* **11b**). Data for **6d** (X = OMe, R = Me), **9**[3] and **10**[7] are listed in Table II. In the case of **9**, the centre of the complex is too far from the aromatic protons for $\Delta\delta$ to be seen. With **10**, the Eu^{3+} is closest to H_A which thus has the largest $\Delta\delta$ of the three aromatic protons. Since for **6d** the $\Delta\delta$ is not significant, the carbomethoxy group must be distant from the aromatic ring. This is not consistent with structure **7**.

TABLE II. EFFECTS OF THE SHIFT REAGENT $Eu(DPM)_3$ ON THE AROMATIC PROTONS IN NMR FOR SUBSTANCES 9, 10 AND 7.

60 MHz	 9			 10			 6d		
	δ $CDCl_3$	δ + 0·3 M $Eu(DPM)_3$	$\Delta\delta$	δ $CDCl_3$	δ + 0·3 M $Eu(DPM)_3$	$\Delta\delta$	δ $CDCl_3$	δ + 0·3 M $Eu(DPM)_3$	$\Delta\delta$
ArOMe	3·85	4·05	0·20	3·85	4·20	0·35	3·85	4·05	0·20
H_A	6·95	7·05	0·10	7·05	8·65	1·60	6·95	7·10	0·15
H_B	6·80	6·90	0·10	6·80	7·20	0·40	6·80	6·90	0·10
H_C	7·15	7·15	0·00	7·10	7·40	0·30	7·15	7·15	0·00
COOMe	3·75	5·70	1·95	3·75	6·05	2·30	3·75	5·80	2·05

Derivatives of cyclohept-(b)-indole

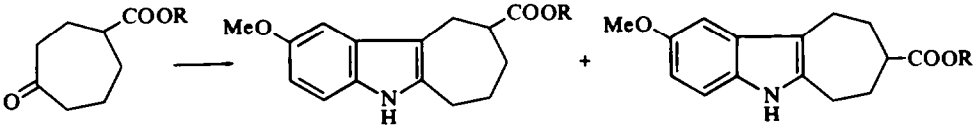
The condensation of phenylhydrazine with 3-cyanocycloheptanone gives **11a** which, on acid hydrolysis followed by esterification with CH_2N_2 furnishes the ester **12b**. The NMR spectrum of **12b** or of **12d** shows four allylic protons (δ = 2·5–3·1). Addition of 0·2 mole of $Eu(DPM)_3$ causes two of these protons to shift downfield by ca. 1·2 ppm. Only structure **12** is compatible with this result.



11, **a**: R′ = CN,X = H
b: R′ = CN,X = OMe
12, **a**: R′ = COOH,X = H
b: R′ = COOMe,X = H
c: R′ = COOH,X = OMe
d: R′ = COOMe,X = OMe

FIG 3.

Condensation of *p*-methoxyphenylhydrazine with cycloheptanone-4-carboxylic acid gives a mixture of two indoles separable by fractional crystallization. They are converted to their methyl esters by CH_2N_2. Examination of the NMR spectra suggest

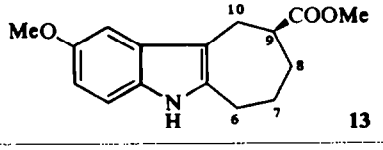


13 **14**

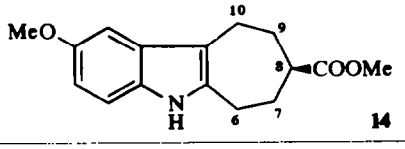
FIG 4.

the structures **13** and **14** and use of $Eu(DPM)_3$ removes any doubt about these assignments. Table III shows that two allylic protons and two alicyclic protons of **13** are very sensitive to the shift reagent whereas in **14** it is the four alicyclic, non-allylic, protons which are most affected. Thus **13** and **14** are easily distinguished.

TABLE III. EFFECT OF THE SHIFT REAGENT $Eu(DPM)_3$ ON THE NMR SPECTRA OF COMPOUNDS **13** AND **14**.



13



14

	δ $CDCl_3$	δ + 0·4 M $Eu(DPM)_3$	$\Delta\delta$ (~)		$\delta CDCl_3$	δ + 0·3 M $Eu(DPM)_3$	$\Delta\delta$ (~)
COOMe	3·7	6·6	2·9	COOMe	3·7	5·7	2·0
H_9	2·7–2·9	5·6–5·8	2·9	H_8	2·6–2·8	4·6–5·0	2·1
2 × H_{10}	2·8–3·2	5·1–5·6	2·3	2 × H_9	1·7–2·4	3·2–3·8	1·4
2 × H_8	1·6–2·5	4·4–5·0	2·4	2 × H_7	1·7–2·4	3·2–3·8	1·4
2 × H_7	1·6–2·0	2·3–3·1	1·0	2 × H_{10}	2·7–3·0	3·2–3·8	0·7
2 × H_6	2·6–2·8	3·1–3·5	0·5	2 × H_6	2·7–3·0	3·2–3·8	0·7

Discussion of the regioselectivity of the Fischer indole synthesis

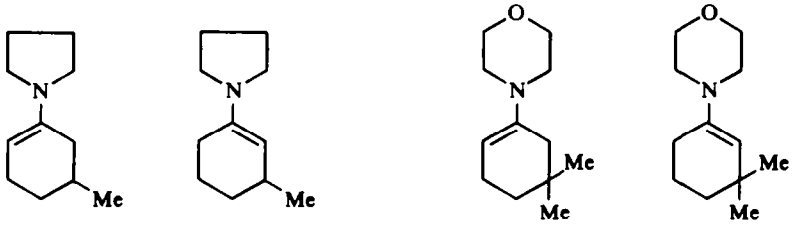
According to the preceding results, it seems that a 3-substituted n-membered-ring ketone leads to indoles which result from cyclization toward the position n. *A priori* this selectivity is unexpected but, in addition, we have noted that bromination of cyclohexanone-3-carboxylic acid gives mainly **15**, the product substituted at position 6, and that the enol acetate obtained from 3-carbomethoxy-cyclohexanone is mainly the $\Delta^{1,6}$ isomer **16**.

15 **16**

FIG 5.

The relative stabilities of equatorial 3-methyl and of 4-methylcyclohexenes have been calculated (Extended Hückel).[8] Using the parameters chosen by Bucourt for cyclohexene,[9] it has been found that equatorial 4-methylcyclohexene is more stable than pseudo equatorial 3-methylcyclohexene by 0·8 kcal/mole. The same calculations applied to the enolates of 3-methylcyclohexanone showed a difference of 0·4 kcal/mole in favour of the 4-methyl form.

Although the method of calculation used lacks precision for this sort of study, it does tend to confirm the preceding observations and is in accord with the energy differences evaluated by Malhotra *et al.*[10] for the case of **17** and **18** (0·6 kcal/mole) and by Descotes *et al.*[11] for the case of **19** and **20** (0·77 kcal/mole) in favour of **17** and **19** respectively.



17 **18** **19** **20**

FIG 6.

According to the recognized mechanism of the Fischer indole synthesis,[1] the intermediate hydrazone A tautomerizes to the enehydrazine form B. This is the product-determining step of the reaction and could formally proceed toward C_2 or C_6. The above results indicate that it proceeds preferentially toward C_6.

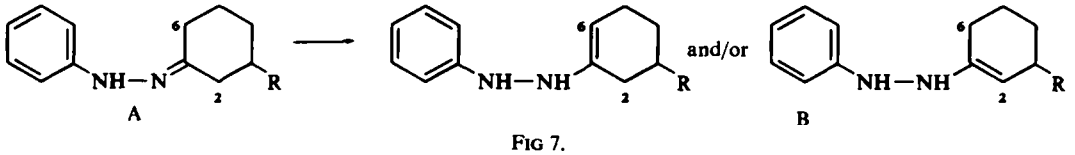
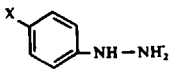
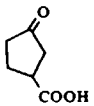
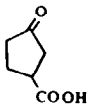
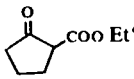
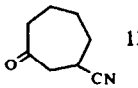
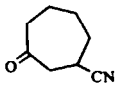
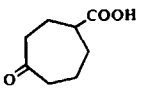


FIG 7.

TABLE IV. PREPARATION OF THE INDOLES.

Preparation of		Starting ketone (ref.)		Method	React. time	Crude reaction product	Yield %	mp of the free carboxylic acid
6a, (X = H)	X = H, (HCl)		12	A	4 h	X = H, R = Et	78	215°
6c, (X = OMe)	X = OMe, base		12	A	2 h	X = OCH_3, R = H	20	208–212°
8	X = H, (HCl)		[c]	A	1 h	R = Et	26	[a]
12a (X = H)	X = H, (HCl)		13	B	½ h	**11a**, X = H, R′ = CN m.p. = 156–166°	67	176–187°
12c (X = OMe)	X = OMe, (base)		13	B	1 h	**11b**, X = OCH_3, R′ = CN m.p. = 155–159°	39	196–200°
13 and **14**	X = OMe, (base)		14	B	1 h	**13** (~50%) + **14** (~50%)[b]	48	**13**: 221–224° **14**: 178–182°

[a] The acid undergoes facile decarboxylation during the hydrolysis, the yield of which is low. Therefore it is not isolated but converted immediately to its methyl ester m.p. 89–91°.

[b] 13 and 14 were separated by fractional crystallization from EtOH. The composition of the crude mixture was estimated by VPC of the methyl esters.

[c] Fluka A.G.

Yields in these reactions are far from excellent and the crude products may contain, as a minor component, the indole which results from tautomerization toward C_2. However we have never been able to detect this second isomer.

From the simultaneous formation of both **13** and **14**, it is clear that this effect does not operate in the case of 4-substituted ketones.

EXPERIMENTAL

Unless otherwise stated, m.ps were taken on a Reichert microscope and were not corrected. NMR spectra were run as 8–10% solutions in $CDCl_3$ at 35° with a 60 MHz Perkin–Elmer R12 A apparatus. Chemical shifts are expressed in units of δ (ppm) with internal TMS as reference. The amount of shift reagent $Eu(DPM)_3$ used was limited by the solubility of the complex. Correct elemental analyses were obtained for the compounds mentioned and IR (Perkin–Elmer 237) and UV (Beckmann DB) spectra were in agreement with proposed structures. Purity of the esters was checked by VPC (SE-30, 4%, 1·80 m). Because of decarboxylation or decarboxyalkylation as primary fragmentation processes, mass spectrometry was of no use in the establishment of structures.

Preparation of the indoles

An outline is given in Table IV. In method A, equimolar amounts of the ketone and of phenylhydrazine hydrochloride were refluxed in EtOH. In the case of *p*-methoxyphenylhydrazine it is preferable to use free base and to add a catalytic amount of gaseous HCl. The EtOH was evaporated and the residue taken up in water and extracted with ether. Usually this procedure led to the ethyl ester; in this case the product was refluxed in EtOH aq containing KOH for two hr. After the usual work up, the product was recrystallized.

In method B, equimolar amounts of the ketone and of the hydrazine or its hydrochloride were refluxed in AcOH. After cooling, the indole was filtered off or extracted with $CHCl_3$ after dilution with water. The nitriles were converted to carboxylic acids in either 50% H_2SO_4 or KOH in EtOH aq at reflux.

All the carboxylic acids were converted to their methyl esters with CH_2N_2 in ether.

4-Bromocyclohexanone-3-carboxylic acid **15**

Br_2 (12 g, 0·075 mole) in $CHCl_3$ (100 ml) was added dropwise with stirring to an ice-cooled solution of cyclohexanone-3-carboxylic acid (10 g, 0·070 mole) in $CHCl_3$ (100 ml). After the addition was complete, the solution was stirred for a further 15 min while warming to room temp., then washed with three portions of brine. Drying and evaporation of solvent gave a viscous yellow-brown oil (15 g). Slow crystallization from ether-petroleum ether gave the bromo derivative **15** (7·2 g, 47%; λ (EtOH) 293 nm (115); ν CH_2Cl_2 3500–2500, 1705 cm^{-1}). In the NMR ($CDCl_3$), the proton geminal to Br appears as a triplet (J = 7 Hz) centred at 4·63 δ.

Enol acetate of 3-carbomethoxy-cyclohexanone **16**

A solution of 3-carbomethoxy-cyclohexanone (2·15 g, 0·014 mole, prepared by treatment of cyclohexanone-3-carboxylic acid with CH_2N_2 in ether)[15] in Ac_2O (20 ml) containing few crystals of *p*-TsOH was refluxed for 3 hr. Ac_2O was removed by evaporation under vacuum, addition of C_6H_6 and distillation at atmospheric pressure. The resulting oil (2·48 g) was not purified and contains *ca.* 10% of starting material (VPC). The NMR spectrum ($CDCl_3$) displayed a vinylic proton as a 16 Hz wide multiplet centred at 5·49 δ.

Acknowledgements—We thank Dr. F. J. Zeelen for the suggestion of, and aid with the calculations and Mr. J. Hoos for adapting the program to the IBM 360–65 system. Our thanks also go to Mr. D. Lebailly for some essential experiments and to Mr. M. Merle and Dr. W. McMeekin for analytical work.

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