Fischer Indole Synthesis from *cis*- and *trans*-Hexahydro-7-methyl-6-isoquinolones. ^{1}H NMR Determination of the Configuration and Conformation of Products

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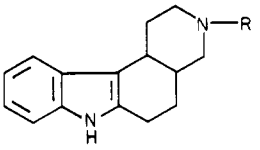
The indole and indolenine derivatives obtained from hexahydro-7-methyl-6-isoquinolones are investigated by ^{1}H NMR spectroscopy. Acid-catalyzed ring closure of the cis-fused heterocycle **9a** gives either the indolenine **10a** or the indole **12a** depending on the acidity of the reaction medium. The trans isomer **9b** forms only indolenine derivative (**10b**). Analysis of vicinal ^{1}H–^{1}H coupling constants in terms of dihedral angles yields the conformation and relative configuration of key intermediates and products. The factors influencing the stereochemical course of these reactions are discussed.

Introduction

We were interested in the synthesis of octahydropyrido[3,4-*c*]carbazole **1**, because the bioisosteric pyrido[3,4-*b*]pyrano[3,4-*b*]indoles (**2**) showed some pharmacological activity.[1] The fully aromatic heterocycle of **1** had



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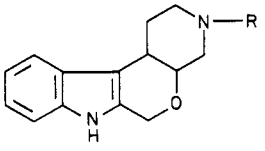

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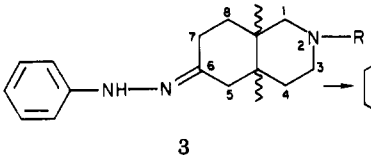

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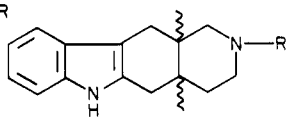

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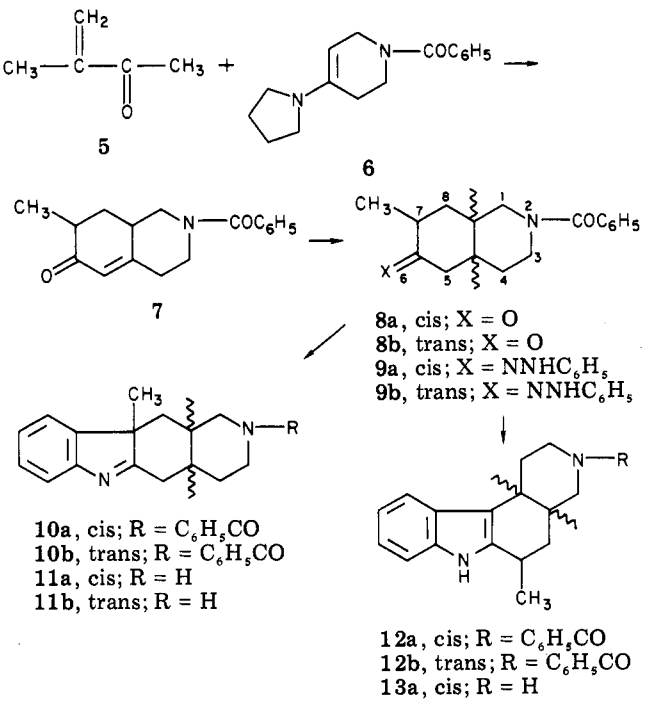
been prepared in a manner unsuitable for synthesis of the octahydro derivative.[2]

The cis and trans linear isomers of octahydropyrido[4,3-*b*]carbazole **4** (the ring system of the ellipticine class of alkaloids) had been synthesized[3] by Fischer cyclization of the phenylhydrazones of the *cis*- and *trans*-isoquinolones **3**. There was a slight chance that under suitable conditions the cis isomer of **3** might close to form the angular system, a regioselectivity observed in the indolosteroid group,[4] but on repetition of the cyclization of **3** under the published[3] or stronger acidic conditions by us, only the linear system **4** could be detected.

To enhance the probability of the desired ring closure, the methylisoquinolones **8** (Scheme I) were selected as key intermediates, with the hope, that a methyl group attached at C(7) might direct the reaction sterically to form the angular product with 6,5-annelation.

In this paper we present the synthesis of the desired indole (**12**) and of the linear indolenines (**10**), as well as a detailed ^{1}H NMR analysis of their configuration and conformation. Introduction of the methyl group complicates the stereochemistry considerably. Instead of the two enantiomeric pairs possible for **1**, **3**, and **4**, (cis and trans ring fusion), there are potentially four enantiomeric pairs possible (3-chiral centers) for the methyl derivatives **8**-**13**. This stereochemistry is investigated by measuring the

Scheme I



5 **6** **7**

8a, cis; X = O
8b, trans; X = O
9a, cis; X = $NNHC_6H_5$
9b, trans; X = $NNHC_6H_5$

10a, cis; R = C_6H_5CO
10b, trans; R = C_6H_5CO
11a, cis; R = H
11b, trans; R = H

12a, cis; R = C_6H_5CO
12b, trans; R = C_6H_5CO
13a, cis; R = H

vicinal ^{1}H coupling constants for key compounds within the synthetic pathway with the aid of two-dimensional NMR (2DNMR) and high-temperature decoupling. Dihedral angles estimated from these coupling constants and NOE (nuclear Overhauser effect)[5] measurements are combined to yield definitive molecular structures.

Results

The methylhexahydroisoquinolone **7** was obtained without difficulty by the Stork method[6] from the enamine of benzoylpiperidone (**6**) and methyl isopropenyl ketone (**5**); catalytic hydrogenation gave the octahydroiso-

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Table I. Coupling Constants (Hz) and Torsional Angles

J	7 (I)	χ (SD)[a]	8a (V)	χ (SD)	8b (III)	χ (SD)
3ax, 3eq	−12.6[b]		−13.5		−13.0	
3ax, 4ax	12.6		12.2		11.6	
3ax, 4eq	3.9	+56 (1)	4.4	−52 (3)	2.6	+53 (10)
3eq, 4ax	c		4.4		4.4	
3eq, 4eq	c		c		c	
4ax, 4eq	c		−12.2		−12.8	
4ax, 4a	d		12.2	+49	12.8	−60
4eq, 4a	d		c		c	
4a, 5ax	d		5.9	+51 (5)	12.5	+53
4a, 5eq	d		2.3		c	
5ax, 5eq	d		−13.5		−12.5	
7, 8ax	12.7	−56 (1)	12.7	+56 (6)	12.2	−48 (1)
7, 8eq	4.7		5.0		5.8	
8ax, 8eq	−12.7		−12.7		−12.2	
8ax, 8a	10.0	+42 (16)	12.7	+60	12.2	+53
8eq, 8a	4.7		c		3.5	
8a, 1ax	11.9	−45	3.1	+60	11.0	−38
8a, 1eq	c		c		c	
1ax, 1eq	−12.0		−13.2		−12.4	
4a, 8a	d		c		c	

[a] Standard deviation (SD). [b] Measured in Me_2SO-d_6 at elevated temperature. [c] Obscured by overlap or broadness. [d] Not applicable.

Table II. ^1H Chemical Shifts[a]

	compd		
^1H	7	8a	8b
1ax	2.67	3.11	2.53
1eq	4.16	3.98	4.12
3ax	3.03	2.88	2.84
3eq	4.10	3.98	4.05
4ax	2.4-2.5[c]	1.30	1.31
4eq	2.4-2.5[c]	1.35	1.52
4a		2.34	1.60
5ax	5.79[b]	2.71	2.22
5eq		2.02	2.22
7	2.35	2.54	2.48
8ax	1.28	1.59	1.05
8eq	1.97	1.73	1.86
8a	2.74	2.34	1.78
CH_3	1.03	0.92	0.92
phenyl	7.41[d]	7.35[d]	7.39[d]

[a] Ppm relative to internal Me_4Si in Me_2SO-d_6. [b] Alkene proton. [c] Obscured by solvent. [d] Av of broad multiplet.

Table III. Coupling Constants (Hz) and Torsional Angles

J	11a (VII)	χ (SD)[a]	13a	χ (SD)
3ax, 3eq	−13.0[b]		−12.5[c]	
3ax, 4ax	13.0		12.0	
3ax, 4eq	4.3	+60 (7)	3.5	−52 (6)
3eq, 4ax	d		4.8	
3eq, 4eq	4.8		d	
4ax, 4eq	−12.4		−14.0	
4ax, 4a	d	−64	12.0	+48 (2)
4eq, 4a	2.3		5.2	
4a, 5ax	12.9	−56 (6)	e	
4a, 5eq	4.8		e	
5ax, 5eq	−12.5		e	
7, 8ax	e		12.5	−53
7, 8eq	e		d	
8ax, 8eq	−13.8		−12.5	
8ax, 8a	6.1	−54 (11)	12.5	+67
8eq, 8a	3.8		d	
8a, 1ax	12.8	−55 (7)	d	
8a, 1eq	5.2		d	
1ax, 1eq	−12.8		d	
4a, 8a	d		d	

[a] Standard deviation. [b] Measured in $CDCl_3$ at ambient probe temperature. [c] Measured in pyridine-d_5 at ambient probe temperature. [d] Obscured by overlap. [e] Not applicable.

quinolones 8 (Scheme I). Although it is conceivable that the Stork method might result in a product with the double bond between C(4a) and C(8a), we observe an olefinic ^1H resonance at 6.79 ppm consistent with a double bond between C(4a) and C(5). By conducting the hydrogenation of **7** in acidic medium,[7] we obtained two isomers in the ratio **8a**:**8b** = 2:1. These two ketones were then separated by preparative HPLC.

The phenylhydrazones **9a** and **9b** ring closed to the indolenines **10a** and **10b**, when the dichloromethane solution was treated with ethereal hydrogen chloride at room temperature. When **9a** was dissolved in 85% sulfuric acid, Fischer cyclization to the angular system **12a** occurred. This is in agreement with earlier observations, that higher acidity directs the cyclization towards the less substituted position.[8] No cyclization of the hydrazone **9b** was observed; either the starting material remained unchanged, or—with increasing sulfuric acid concentrations—decomposition to tars occurred.

Distinction between the indolenines and indole can be accomplished readily: The CH_3 resonance of the indole **12a** is split by the vicinal proton and the spectrum shows an indole NH resonance, whereas the indolenines display a CH_3 singlet and no indole NH peak. This was corroborated by the characteristic shift[9] of the UV maxima from 255 to 279 nm on protonation of **11a** and **11b**, whereas no shift occurs in the UV spectrum of **13a** (λ_{max} 284 nm) under the same conditions.

The protecting benzoyl groups were removed by alkaline saponification (from **12a** in poor yield) to give the bases **11a**, **11b**, and **13a**. In contrast to **2**, none of these compounds had interesting biological activities.

^1H NMR coupling constant analysis was conducted on the three ring intermediates, **7**, **8a**, and **8b**. Slow rotation about the exocyclic amide bond causes severe broadening of the ^1H resonances at ambient probe temperature (ca. 293 °K). Consequently all measurements on these three compounds were made at temperatures 373–403 °K depending on the degree of resonance sharpening desired. When the compounds were kept at these extreme tem-

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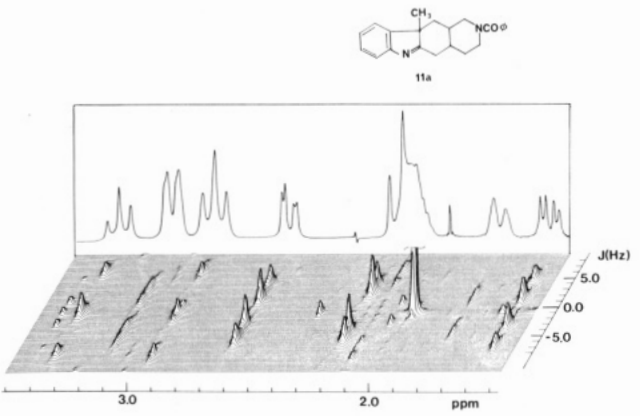

Figure 1. Two-dimensional ^1H–^1H *J*-resolved NMR spectrum of the aliphatic protons of **11a**.

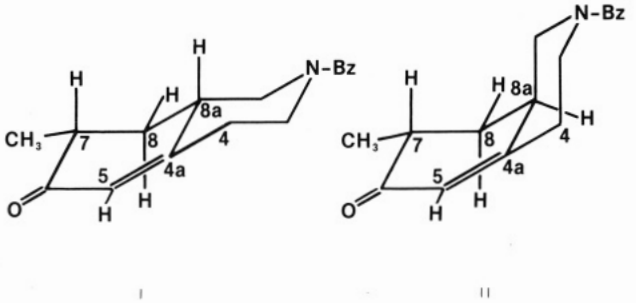

Figure 2. Discussion in the text indicates I to be the correct structure of **7**. Bz = benzoyl.

peratures for extended periods of time (ca. 5 h), some decomposition could be observed.

The critical vicinal coupling constants, which can be analyzed to describe completely the relative configuration and conformation of **7**, **8a**, **8b**, **11a**, and **13a**, are shown in Tables I and III. These data were obtained in $CDCl_3$, Me_2SO-d_6, and/or pyridine-d_5 solution; the solvent(s) was chosen to minimize overlap among the resonances of interest. The choice of solvent had no noticeable effect on solution conformation. For some closely overlapping peaks, 2D *J*-resolved spectroscopy[10] yielded the desired coupling constants and 2D ^1H shift correlated spectroscopy[11] provided assignments. An example of the 2D *J*-resolved technique applied to **11a** is shown in Figure 1.

Discussion

Conformation and Relative Configuration. The conformation of these fused ring systems can be described with dihedral angles (ϕ) estimated from the Karplus[12] equation $J = 12.7 \cos^2 \phi$.[13] Average torsional angles (χ) calculated from these dihedral angles are shown in Table I (chemical shifts in Table II); χ is defined viewing the carbon–carbon bond end on with the lowest numbered carbon nearest the viewer; clockwise rotation of the carbon farthest away produces a positive χ; χ is zero for a fully eclipsed conformation. The multiplicative constant 12.7 was chosen to provide maximum internal consistency.

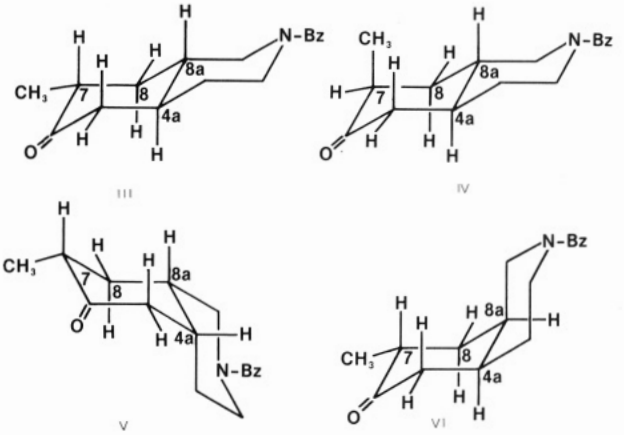

Figure 3. Discussion in the text indicates **8b** as III, and **8a** as V.

Table IV. ^1H Chemical Shifts[a]

^1H	11a[b]	13a[c]
1ax	3.43	3.04[d]
1eq	3.17	3.04[d]
3ax	3.02	2.73
3eq	3.17	3.04[d]
4ax	2.17	1.70
4eq	1.77	2.13
4a	2.15	3.04[d]
5ax	3.02	*e*
5eq	2.67	*e*
7	*e*	3.09
8ax	1.56	2.20
3eq	2.23	1.89
8a	2.15	1.65
CH_3	1.36	1.39

[a] Ppm relative to Me_4Si. [b] In $CDCl_3$. [c] In pyridine-d_5. [d] Overlapping resonances. [e] Not applicable.

Consider first the configuration of **7** (Figure 2). The key coupling constants for distinguishing between I and II are those involving protons 7, 8ax, 8eq, and 8a. H(8ax) displays three large coupling (Table I), one geminal and two axial–axial couplings. This is possible only with structure I, since in structure II, *J* (8ax, 8a) would be an axial–equatorial coupling (ca. 4–6 Hz). The remaining coupling constants are also consistent with this assignment. The C(8)–C(8a) bond is twisted from the staggered conformation due to steric strain produced by the C(4a)–C(5) double bond (J (8ax, 8a) = 10.0 Hz instead of ca. 12.7 Hz). An additional compound was present in this sample at a level less than 10%. This other compound might be isomer II; however, structure elucidation was precluded by spectral overlap. Other less likely conformers of II were considered, such as the one with an axial methyl group, but these were ruled out because of disagreement with the coupling constants.

Possible isomers of **8** are shown in Figure 3. It is assumed that the configuration at C(7) and C(8a) of **7** will be retained in both **8a** and **8b**, which thus differ at C(4a). To identify **8a** and **8b** unambiguously, we also analyzed their coupling constants in terms of the Karplus equation.

As with **7**, three large coupling constants were observed for H(8ax) of **8a**, one germinal and two axial–axial. This rules out structure IV and VI, for which only two large H(8ax) couplings would be observed. Only one large coupling constant (geminal) is observed for H(5ax), eliminating III, for which two large couplings would be predicted. Hence, **8a** corresponds to the *cis* fused system V.

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(12) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870. Karplus, M., *J. Chem. Phys.* **1959**, *30*, 11.

(13) For reviews for the conformational dependence of ^1H–^1H vicinal coupling constants in ring systems see: Thomas, W. A. *Ann. Rep. NMR Spectrosc.* **1970**, *3*, 91. Booth, H. In "Progress in Nuclear Magnetic Resonance Spectroscopy"; Emsley, J. W., Feeney, J., Sutcliffe, L. H., Eds.; Pergamon Press: New York, 1969, Vol. 5, p 149. Thomas, W. A. *Annu. Rev. NMR Spectrosc.* **1968**, *1*, 43.

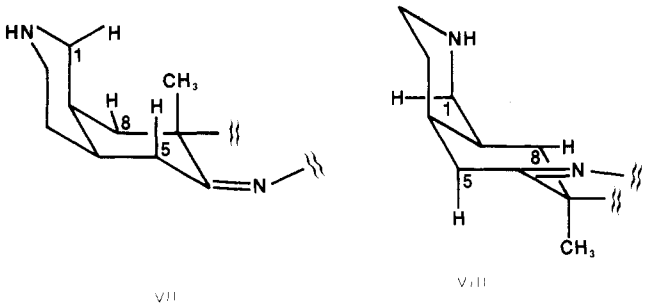

Figure 4. NOE measurements support VII as the structure for **11a**.

For **8b**, three large H(8ax) couplings are again observed, removing IV and VI from consideration. The two large H(5ax) coupling constants rule out V, leaving III, the trans-fused ring system, as the structure for **8b**. Coupling constant considerations also eliminate conformations of V and VI in which the methyl group is axial; these would correspond to higher energy conformations of the enantiomers of VI and V, respectively.

The above rationale also defines the configuration and conformation of **9a** and **9b**, and since formation of the angular system **12a** does not affect any of the chiral centers, the configuration of **12a** is determined by the configuration of **8a**. This is borne out by analysis of the coupling constants (Table III; chemical shifts in Table IV) of the 3 and 4, and of the 8 and 8a protons of **13a**.[14] The line of reasoning for determining the configuration of **13a** follows closely that given previously for **8a**; the key coupling constants of **8a** and **13a** are nearly identical, indicating the same configurational features in both of these molecules. Since **13a** and **12a** differ only by nitrogen substitution, they must have the same configuration.

The indolenines **11a** and **11b** were obtained from the pure *cis*- and *trans*-phenylhydrazones **9a** and **9b**, respectively via the benzoyl compounds **10**. They appeared to be uniform by TLC; however, for **11b** two superimposed ^{1}H spectra were obtained. Extensive overlap prevents detailed analysis of the spectra; there is no doubt, however, about the indolenine structure. Since **11b** originated from **9b**, the trans configuration must be retained at C(4a) and C(8a), so that these two isomers very likely correspond to opposite relative configuration at C(7).

In contrast, only a single *cis*-indolenine (**11a**) is formed. Since the relative configuration at C(4a) and C(8a) is not affected by ring closure, it is necessary only to determine the configuration at C(7)[14] (Figure 4). Analysis of the structure of **11a** is made more difficult than in the previous compounds by one factor. In these compounds, C(7) bears a hydrogen, so the first ring hydrogen H(7) could be assigned by decoupling of the CH_3 resonance. H(7) could then be linked to adjacent ring protons either by decoupling or by 2D chemical shift correlation maps. However, in **11a** there is no hydrogen on C(7), so that additional methods had to be employed to arrive at a consistent pairing between ring proton spectral parameters and structure. The NOE provides key assignments which point to VII rather than VIII (Figure 4) as the structure of **11a**. Irradiation of the methyl resonance produces nuclear Overhauser enhancements of 6%, 3%, and 4% for the protons assigned as H(1ax), H(5ax) and H(8eq), respectively. In VIII H(1ax) would be located at a much greater distance from the CH_3 group, so that no NOE would be possible. In addition, the coupling constants in Table III rule out structure VIII: the H(1ax–H(8a) coupling constant would not be 12.8 Hz for VIII, but rather have a value near 5.0 Hz.

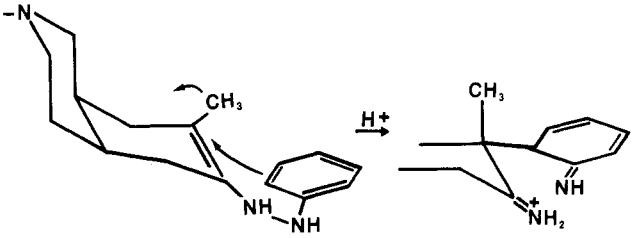

Figure 5. Suggested mechanism for the formation of **11a**.

Mechanistic Factors Influencing Stereochemistry. For ring closure of the phenyl hydrazones to occur, the intermediate formation of either of the two possible ene–hydrazines is necessary with the double bond in the 5,6-position as precursor for the indole or with Δ^6 for the indolenine. It appears from the results of this study, that the intermediate formation of the 5,6-ene–hydrazine is not as likely in the trans as in the cis series.

We suggest the following explanation for the fact that in the *cis*-indolenine series only one isomer (with respect to C(7))[14] is formed: The critical step, which determines this configuration is shown in Figure 5. At the beginning of this step, the methyl group is attached to a planar sp^2 carbon, so that the phenyl ring could attack from below or above. Steric repulsion, however, from the cis-fused piperidine ring forces the phenyl moiety to attack from the bottom, directing the methyl group upward and leading ultimately to the indolenine **11a** (VII in Figure 4). A similar steric restriction is not present in **9b**, which accounts for the two isomers in **11b**.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were obtained with a Bruker WM250 or with an IBM Instruments WP200, both operating in the pulse-Fourier transform mode. 2DNMR spectra were obtained with standard literature pulse sequences, as described in the manuals supplied by Bruker and IBM Instruments. Samples were dissolved in either pyridine-d_5, $CDCl_3$ (Merck Isotopes), or Me_2SO-d_6 (Merck Isotopes or Aldrich). NOE's were measured by presaturation of the resonance of interest for 2 s prior to application of the observing pulse.

2-Benzoyl-1,2,3,4,8,8a-hexahydro-7-methyl-6-isoquinolone (7). A soluiton of 28.8 g (0.405 mol) of pyrrolidine, 74.2 g (0.365 mol) of 1-benzoyl-4-piperidone in 360 mL of toluene was refluxed under nitrogen for 12 h, the water formed was collected in a Dean-Stark water separator. After removal of the toluene under vacuum, the oily residue was dissolved in dioxane (360 mL), and methyl isopropenyl ketone (**5**)[15] (31 g, 0.36 mol) was added. The solution was stirred at room temperature for 1 h followed by refluxing for 3.5 h. The mixture was then hydrolyzed by refluxing for 1 h with 36 g (0.44 mol) of sodium acetate in water (75 mL) and acetic acid (75 mL). The cold mixture was poured over 2 L ice/water and extracted with dichloromethane, which was washed with 10% NaOH, dried, and evaporated to yield a brownish semisolid, which was crystallized from ethyl acetate to give 36.5 g (37%) of **7**: mp 167–170 °C. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.02. Found: C, 75.64; H, 7.23; N, 5.08.

***cis*- and *trans*-2-Benzoyl-1,2,3,4,4a,7,8,8a-octahydro-7-methyl-6-isoquinolone (8a and 8b).** A mixture of **7** (25 g, 0.93 mol), ethanol (450 mL), 3 N hydrochloric acid (45 mL), and 10% palladium-on-charcoal (2.3 g) was hydrogenated for 2.5 h at room temperature and atmospheric pressure. After filtration from the

(14) To avoid confusion, the ^{1}H NMR discussion of all compounds uses the isoquinoline numbering shown in Scheme I for **8** and **9**; the correct numbering for **10**, **11**, **12**, and **13** is used in the experimental part.

(15) Morgan G.; Megson, N. J. L.; Pepper, K. W. *Chem. Ind. (London)* **1938**, 885.

catalyst and evaporation a white solid remained, which was recrystallized from ethyl acetate: yield, 16.6 g (66%); mp 116–120 °C.

The mixture was chromatographed on a silica gel column (Waters Prep LC-500 apparatus) with ethyl acetate. Two fractions with slightly different R_f values on TLC (ethyl acetate) were obtained. **8a**: eluting last; 10.5 g (46%); mp 143–145 °C. **8b**: eluting first; 4.8 g (19%); mp 162–165 °C. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H 7.80; N, 5.16. Found **8a**: C, 75.39; H, 7.87; N, 5.08. Found **8b**: C, 74.90; H, 7.68; N, 4.92.

***cis*-2-Benzoyl-1,2,3,4,4a,7,8,8a-octahydro-7-methyl-6-isoquinolone Phenylhydrazone (9a).** A mixture of **8a** (25 g, 92 mmol) and phenylhydrazine (10 g, 92 mmol) in ethanol (600 mL) was refluxed for 16 h. The solution was then concentrated to half the volume and chilled. The crystalline phenylhydrazone **9a** was recrystallized from ethanol to give 28.5 g (86%): mp 203–209 °C. Anal. Calcd for $C_{23}H_{27}H_3O$: C, 76.42; H, 7.53; N, 11.63. Found: C, 76.36; H, 7.60; N, 11.35.

***trans*-2-Benzoyl-1,2,3,4,4a,7,8,8a-octahydro-7-methyl-6-isoquinolone Phenylhydrazone (9b).** **9b** was prepared analogously to the cis isomer: 72% yield; mp 176–182 °C. Anal. Calcd for $C_{23}H_{27}H_3O$: C, 76.42; H, 7.53; N, 11.63. Found: C, 76.15; H, 7.49; N, 11.43.

***trans*-2-Benzoyl-10b-methyl-1,2,3,4,4a,5,11,11a-octahydro-10b*H*-pyrido[4,3-*b*]carbazole (10b).** The trans-phenylhydrazone **9b** (3.6 g, 10 mmol) was dissolved in dichloromethane (70 mL); ether saturated with HCl (5 mL) was added to the solution and the mixture was stirred for 2 h at room temperature. The residue from evaporation of the solvents was dissolved in acetic acid (5 mL) and poured on ice/ammonia. The precipitate was filtered and crystallized from ethanol–ether: yield 1.3 g (38%); mp 204–206 °C. Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02, N, 8.13. Found: C, 79.76; H, 7.03; N, 7.95.

***cis*-2-Benzoyl-10b-methyl-1,2,3,4,4a,5,11,11a-octahydro-10b*H*-pyrido[4,3-*b*]carbazole (10a).** This compound was prepared from **9a** analogously to **10b**: yield, 61%; mp 196–198 °C. Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 79.80; H, 7.09; N, 8.00.

***cis*-10b-Methyl-1,2,3,4,4a,5,11,11a-octahydro-10b*H*-pyrido[4,3-*b*]carbazole (11a).** A mixture of **10a** (2.8 g, 8 mmol), ethanol (60 mL), and 50% KOH (6 mL) was refluxed for 3 h. After evaporation of the ethanol, the remaining oil was treated with water and ethyl acetate, and the organic extracts were washed, dried, and evaporated. From the residue a small amount of the free base **11a** could be crystallized from ether–ethanol: yield, 0.2 g (10%); mp 238–240 °C. Anal. Calcd for $C_{16}H_{20}N_2 \cdot H_2O$: C, 74.20; H, 8.39; N, 11.66. Found: C, 74.38; H, 8.15; N, 11.84.

The ether–ethanol filtrate was treated with ethereal HCl, which precipitated the dihydrochloride of **11a**, 1.2 g (48%), mp 248–251 °C, from ethanol. Anal. Calcd for $C_{16}H_{20}N_2 \cdot 2HCl$: C, 61.34; H, 7.07; N, 8.94; Cl, 22.63. Found: C, 61.15; H, 7.08; N, 8.53; Cl, 22.15.

***trans*-10b-Methyl-1,2,3,4,4a,5,11,11a-octahydro-10b*H*-pyrido[4,3-*b*]carbazole (11b).** A mixture of **10b** (2.3 g, 6.7 mmol) butanol (25 mL), and 50% KOH (12 mL) was refluxed for 3.5 h. After evaporation of the solvent the residue was treated with water and ethyl acetate and the oily base was converted to the hydrochloride with ethereal HCl. NMR analysis as discussed in the result section indicates the presence of two isomers: yield, 1.8 g (91%); mp 172–180 °C. Anal. Calcd for $C_{16}H_{20}N_2 \cdot H_2O \cdot HCl$: C, 65.18; H, 7.86; N, 9.50; Cl, 12.03. Found: C, 65.38; H, 7.75; N, 8.97; Cl, 12.04.

***cis*-3-Benzoyl-6-methyl-1,2,3,4,4a,5,6,11c-octahydropyrido[3,4-*c*]carbazole (12a).** The *cis*-hydrazone **9a** (1.0 g, 2.8 mmol) was added at ice bath temperature to 85% sulfuric acid (20 mL) and the mixture was stirred without further cooling until all hydrazone was dissolved. The solution was poured on ice/ammonia, and the solid was collected and purified on a silica gel column with dichloromethane/methanol (97/3) as eluant: yield, 0.4 g (42%); mp 218–226 °C. Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.17; H, 7.37; N, 7.90.

***cis*-6-Methyl-1,2,3,4,4a,5,6,11c-octahydropyrido[3,4-*c*]-carbazole (13a).** A mixture of the *cis*-benzoylindole derivative **12a** (0.45 g, 1.3 mmol), *n*-butanol (8 mL), and 50% KOH (1.5 mL) was refluxed for 18 h. The butanol was removed in vacuo and the remaining oil was treated with water and extracted with dichloromethane. The residue of the organic extract was purified by silica gel chromatography with dichloromethane/methanol (97/3) followed by dichloromethane/methanol (70/30) as eluant. The main fraction crystallized on evaporation: yield, 40 mg (12%); mp 225–227 °C. Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 79.52; H, 8.13; N, 11.78.

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Synthesis of 3-Methyl-5,6-dihydro-3*H*-benzofuro[3,2-*e*]isoquinolin-7(7a*H*)-ones

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The coupling of 2-(alkoxymethoxy)phenylcopper derivatives with the salt of ethyl chloroformate and ethyl 3-(pyridin-3-yl)propenoate was found to be an efficient method for the preparation of 4-(2-hydroxyphenyl)pyridines **13** substituted at C-3 with a propanoate side chain. N-Methylation and O-alkylation with ethyl bromoacetate gave salts **3** which when treated with base underwent an intramolecular enolate addition to the pyridinium nucleus to produce spiro[benzofuran-3(2*H*),4′(1′*H*)-pyridines] **4**. Prolonged base treatment of **4** yielded ethyl 3-methyl-7-hydroxy-5,7a-dihydro-3*H*-benzofuro[3,2-*e*]isoquinoline-6-carboxylates **5** by a Dieckmann reaction. Reduction of **5** led to predominately *trans*-3-methylhexahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7(7a*H*)-ones, while reduction of **4** and then Dieckmann cyclization yielded mainly the cis isomers.

Recently derivatives of octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline have been found to be potent analgesics.[1] These tetracyclic compounds, of general structure **1**, are fragments of morphine **2** which possess the ACNO ring skeleton. Of particular interest are those compounds having the trans CN ring junction as in morphine. Importantly, compounds possessing the *N*-cyclopropylmethyl substituent exhibit both strong agonistic and antagonistic properties and are thus likely to have a low potential for

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