Synthesis of 2- and 3-Substituted-1,2,3,4-tetrahydrodibenzo[*f,h*]isoquinolines

Mercedes T. Grande, Gregorio G. Trigo and Mónica M. Söllhuber*

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia,
U. Complutense, Ciudad Universitaria,
28040-Madrid, Spain

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Some 2- and 3-substituted-1,2,3,4-tetrahydrodibenzo[*f,h*]isoquinolines were prepared by a synthetic scheme involving a selective Borch reduction of an amide to the corresponding amine and a Friedel-Crafts cyclization to obtain the dibenzo[*f,h*]isoquinoline system. The title compounds, which have a similarity to the cell growth inhibitory alkaloid cryptopleurine, failed to exhibit significant protein synthesis inhibitory activity.

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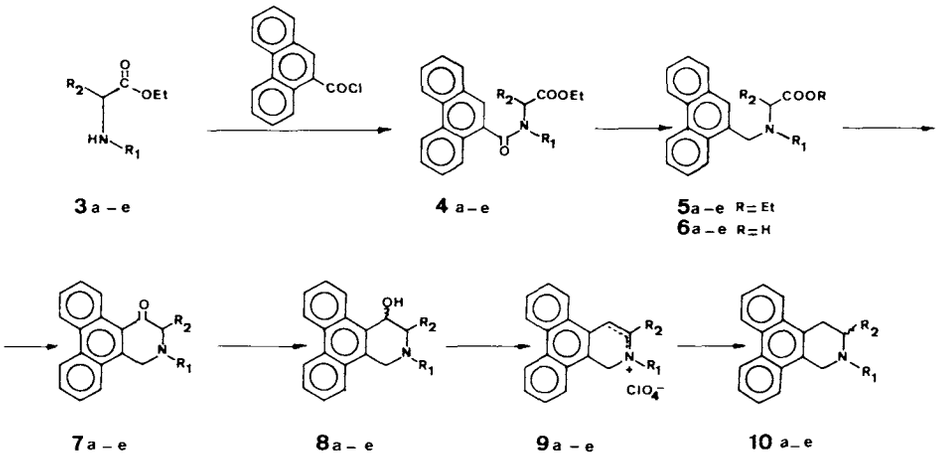
One interesting property of the phenanthroquinolizidine and -indolizidine alkaloids cryptopleurine **1**, tylophorine **2a** and tylocrebrine **2b**, is their antitumor activity [1,2]. These alkaloids inhibit protein synthesis in eukaryotic cells by a common mechanism of action [3,4].

Since the pharmacological profile of these compounds includes some unwanted secondary effects, our studies were directed toward the synthesis of related compounds with a simpler structure in an attempt to detect a pattern of relationship between the chemical structure of these alkaloids and their inhibitory effect on protein biosynthesis. In this context it was of interest to obtain derivatives which contain the basic structure common to both types of phenanthrenic alkaloids, as found in the *N*-alkyl-1,2,3,4-tetrahydrodibenzo[*f,h*]isoquinolines **10a-e**. Mosettig and May [5], in a study of morphine analogs, first described a synthesis of this type of compound, applying a Decker and Becker isoquinoline synthesis.

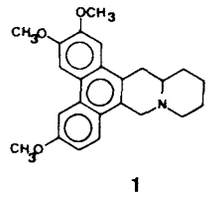
The synthetic route followed in this paper was previously reported by us [6]. The scheme has now been modified allowing for the introduction of different radicals at position 2 and 3 of the 1,2,3,4-tetrahydrodibenzo[*f,h*]isoquinoline system, thereby obtaining new compounds with the common framework of the phenanthrenic alkaloids (Scheme 1).

The *N*-alkylglycinate starting materials **3a-e** were prepared in acceptable yields by allowing primary amines to react with ethyl bromoacetate. Attempts to carry out the condensation with ethyl chloroacetate gave the desired aminoesters in only very modest yields. Condensation of 9-phenanthrenecarbonyl chloride with **3a-e** in the presence of pyridine afforded the corresponding amidoesters **4a-e**. These compounds were converted in quantitative yield to the aminoesters **5a-e** through a Borch reduction [7] consisting of an *O*-alkylation of the tertiary amide with triethyloxonium flouroborate followed by



Scheme 1

	R_1	R_2
a	isopropil	H
b	butyl	H
c	ter-butyl	H
d	cyclohexyl	H
e	H	methyl



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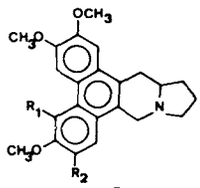


2a R_1=H R_2=OCH_3
2b R_1=OCH_3 R_2=H

FIGURE 1

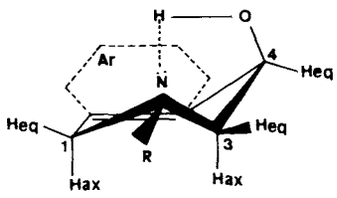
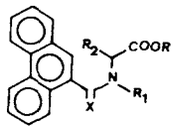


FIGURE 2

a sodium borohydride reduction. The hydrolysis of the ester group was achieved with concentrated hydrochloric acid. A basic hydrolysis in aqueous alcoholic potassium hydroxide gave only modest yields of the desired amino-acids **6a-e**. Intramolecular Friedel-Crafts cyclization of **6a-e** in polyphosphoric acid under nitrogen afforded the unstable aminoketones **7a-e** in approximately 80-90% yield. The aminoketones, which are sensitive to air oxidation, were characterized by spectroscopic means, and were immediately reduced by sodium borohydride to **8a-e**. The aminoalcohols so obtained were easily dehydrated with 70% perchloric acid to give the quaternary perchlorates **9a-e**. These show ir absorption at around 1720 cm^{-1} as described for immonium compounds [8] as well as a shift

Table I

Yields and Physical Data of Compounds **4a-6e**

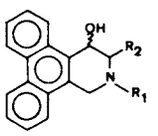


4 X=O R = C_2H_5
5 X=H_2 R = C_2H_5
6 X=H_2 R = H

Compound	Yield %	Mp°C Recrystallization solvent (Bp (mm))	IR max, cm^{-1}	Nmr: ppm (deuteriochloroform) ((:)hexadeuteriodimethylsulfoxide)
4a	50	146 benzene/ether	1730, 1626	1.03 (6H, d), 1.38 (3H, t), 3.82 (1H, m), 4.35 (2H, q), 4.0-4.5 (2H, dd, J = 16 Hz, H-2), 7.7 (6H, m), 8.28 (1H, m), 8.7 (2H, m)
4b	40	74 ether	1757, 1649	0.9-1.7 (7H, m), 1.38 (3H, t), 3.2 (2H, t), 3.88 (2H, s, H-2), 4.34 (2H, q), 7.7 (6H, m), 8.28 (1H, m, H-8'), 8.68 (2H, m)
4c	55	128 ether	1739, 1649	1.08 (3H, t), 1.8 (9H, s), 4.0 (2H, s, H-2), 4.34 (2H, q), 7.7 (6H, m), 8.23 (1H, m, H-8'), 8.68 (2H, m)
4d	40	92 ether	1750, 1642	0.85-2.0 (10H, m), 1.37 (3H, m), 3.43 (1H, m), 4.33 (2H, q), 4.05-4.55 (2H, dd, J = 16 Hz, H-2), 7.7 (6H, m), 8.5 (3H, m)
4e	78	132 benzene	3303, 1742, 1645	1.3 (3H, t), 1.52 (3H, d), 4.23 (2H, q), 4.85 (1H, q), 6.7 (1H, d, N-H), 7.7 (5H, m), 7.85 (1H, m, H-10'), 8.3 (1H, m), 8.6 (2H, m)
5a.HCl	97	136-137 acetone/ether	1742	(:) 0.87 (6H, t), 1.15 (3H, t), 3.55 (1H, m), 3.75 (2H, q), 4.2 (2H. s, H-2), 5.05 (2H, s), 7.9 (5H, m), 8.5 (2H, m), 8.9 (2H, m)
5b.HCl	94	148-149 acetone/ether	1745	(:) 0.9-2 (7H, m), 1.05 (3H, t), 3.37 (2H, m), 3.95 (2H, q), 4.2 (2H, s, H-2), 4.95 (2H, s), 7.8 (5H, m), 8.3 (2H, m), 8.8 (2H, m)
5c	96	54 methanol	1732	1.05 (3H, t), 1.3 (9H, s), 3.41 (2H, s, H-2), 3.9 (2H, q), 4.4 (2H, s), 7.7 (5H, m), 8.1 (1H, s), 8.4 (1H, m), 8.7 (2H, m)
5d	89	61-62 (230-5 (0.6))	1743	0.9-2 (10H, m), 1.15 (3H, t), 2.8 (1H, m), 3.4 (2H, s, H-2), 4.05 (2H,q), 4.4 (2H, s), 7.7 (5H, m), 7.8 (1H, m), 8.6 (3H, m)
5e.HCl	95	199 acetone/ether	1746	1.25 (3H, t), 1.7 (3H, d), 4.1 (2H, q), 4.2 (1H, q, H-2), 5.05 (2H, s), 7.7 (5H, m), 7.9 (1H, s), 8.2 (1H, m, H-8'), 8.7 (2H, m)
6a.HCl	82	113-114 2-propanol/ether	1730	– – – –
6b.HCl	66	192-193 hydrochloric acid	1726	– – – –
6c.HCl	90	177-178 2-propanol/ether	1758	– – – –
6d.HCl	98	124-125 hydrochloric acid	1720	– – – –
6e.HCl	86	250-251 hydrochloric acid	1745	– – – –

Table II

Yields and Physical Data of Dibenzo[*f,h*]isoquinoline derivatives **8a-10e**



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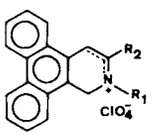

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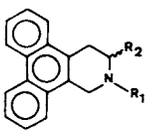

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Compound	Yield %	Mp°C Recrystallization solvent	IR max, cm^{-1} (KBr) (sol 0.003 *M* CCl_4)	MS m/e
8a	77	135 acetone	3330, 1070 (3550)	291 (M^+), 290, 276, 229, 219, 191, 165, 72 (100)
8b	83	125-126 petroleum ether or acetone	3300, 1078 (3555)	
8c	70	141-143 acetone	3505, 1065 (3542)	305 (M^+), 290, 229 (100), 220, 191, 86
8d	81	154-156 acetone	3525, 1051 (3550)	
8e	82	185 2-propanol	3280, 1350, 1050	
9a	78	192 d ethanol	1640, 1110	
9b	79	195 d dimethyl sulfoxide/ water	1643, 1097	
9c	80	280 d ethanol	1642, 1099	
9d	80	200 d ethanol/water	1716, 1648, 1093	
9e	88	290 ethanol	1720, 1651, 1111	
10a	92	84-85 petroleum ether	2964, 2889, 2868, 1605	275 (M^+), 274, 261, 260 (100), 232, 204, 134
10b	93	68 petroleum ether or acetone/ether	2920, 2853, 1619	
10c	89	110 petroleum ether	2978, 2874, 2859, 1605	289 (M^+), 275, 274 (100), 232, 229, 204, 198, 70
10d	99	143-145 petroleum ether	2927, 2846, 2804, 1607	
10e	99	152-153 petroleum ether	3267, 1609, 1497	

to around 1640 cm^{-1} indicative of the more abundant enamine isomer. Reduction with sodium borohydride afforded the recemic 1,2,3,4-tetrahydrodibenzo[*f,h*]isoquinolines **10a-e** in almost quantitative yield.

Spectral details are reported in the experimental section, but there are some features of these compounds of interest. The nmr spectra allowed us to establish clearly whether the attempted ring closure reactions from **6a-e** to the dibenzoisoquinoline ring system **7a-e** were or were not successful. The methylene group situated between the phenanthrene ring and the nitrogen atom appeared as an AB quartet with a coupling constant of *ca* 16 Hz when the aliphatic chain was transformed into the six membered, alicyclic isoquinoline ring **8a-e** (Table III). Similar changes in related situations have been well documented [9,10]. Also, a deshielding effect of the aromatic protons *ortho* to the carbonyl group has been reported to occur in a number of cyclic aromatic ketones. As reported for compound **7c**, if the carbonyl group was attached to position 9 of the phenanthrene ring the affected phenanthrenic proton C-8 appeared at δ 9.45.

Noteworthy is also the rigid conformation observed for the aminoalcohols **8a-d**. The ir band at 3550 cm^{-1} of a highly diluted sample points to an intramolecular hydrogen bond, that forces the hydroxy group to adopt an axial disposition. This was confirmed with nmr data, where the presence of two AB systems, corresponding to C-1 and C-3 protons (Table III), and the small coupling

Table III

^{1}H NMR Spectral Data of the Dibenzo[*f,h*]isoquinoline Derivatives **8** and **10**.

Compound No.	H-1 eq	H-1 ax	$J_{1,1}$ Hz	H-3 eq	H-3 ax	$J_{3,3}$ Hz	H-4	R_1	R_2	OH/NH	Aromatic H
8a	4.2 (d)	3.72 (d)	−16	3.25	2.53	−12.5	5.05 (t)	1.15 (3H, d), 1.20 (3H, d), 3.0 (1H, m)		3.13 (s)	7.6 (5H, m) 8.3 (1H, m) 8.56 (2H, m)
8b	4.25 (d)	3.47 (d)	−16	3.32	2.53	−11.5	5.1 (t)	0.92-1.85 (7H, m) 2.6 (2H, t)		3.35 (s)	7.57 (5H, m) 8.35 (1H, m) 8.62 (2H, m)
8c	4.48 (d)	3.85 (d)	−16.5	3.45	2.52	−12	5.12 (t)	1.3 (9H, s)		3.03 (s)	7.7 (5H, m) 8.32 (1H, m) 8.61 (2H, m)
8d	4.32 (d)	3.9 (d)	−15.5	3.32	2.68	−12	5.12 (t)	1.1-2.1 10H, m) 2.6 (1H, m)		2.7 (s)	7.7 (5H, m) 8.32 (1H, m) 8.62 (2H, m)
8e	4.33 (s)		–	–	3.08	–	4.92 (t)		1.42 (d)		7.6 (5H, m) 8.35 (1H, m) 8.65 (2H, m)
10a	4.12 (t, J = 1.8)			3.2 (t)			2.88 (t)	1.25 (6H, d) 3.03 (1H, m)			7.52 (4H, m) 7.86 (2H, m) 8.6 (2H, m)
10b	3.98 (t, J = 1.8)			3.17 (t)			2.8 (t)	0.9-1.7 (7H, m) 2.62 (2H, m)			7.55 (4H, m) 7.9 (2H, m) 8.62 (2H, m)
10c	4.2 (t, J = 1.8)			3.2 (t)			2.92 (t)	1.3 (9H, s)			7.56 (4H, m) 7.88 (2H, m) 8.6 (2H, m)
10d	4.1 (t, J = 1.8)			3.1 (t)			2.85 (t)	1.15-2.2 (10H, m) 2.5 (1H, m)			7.55 (4H, m) 7.82 (2H, m) 8.65 (2H, m)
10e	4.33 (s)			2.7-3.3 (m)			2.7 (m)		1.35 (d)	2.6 (s)	7.62 (4H, m) 7.95 (2H, m) 8.6 (2H, m)

The ^{1}H nmr spectra were recorded for solutions in deuteriochloroform with TMS as internal standard.

constant (J = 2 Hz) between C-3 and C-4 protons, indicated an equitorial disposition for the C-4 proton with the hydroxy group being axial (Figure 2).

When tested [11], the products **8a-e** and **10a-e** failed to exhibit any significant activity inhibiting protein synthesis. This is probably due to the steric hindrance around the nitrogen atom produced by the substituents at position 2.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer 577 spectrometer. The nmr spectra were measured using tetramethylsilane as the internal standard, with a Perkin-Elmer model R-24B (60 MHz) and a Varian EM 390 spectrometer. Microanalyses were done with a Carlo Erba 1104 analyser. The mass spectra were obtained with a Hitachi Perkin-Elmer, RMU-6M spectrometer.

9-Phenanthrenecarbonyl Chloride.

This compound was prepared as described by Goldberg *et al.*, [12].

Ethyl *N*-Isopropylglycinate **3a**.

A solution of 2 moles of isopropylamine and 1 mole of ethyl bromoacetate in 1 ℓ of toluene was kept in a 95° bath for 5 hours with stirring. The amine hydrobromide was filtered off, the toluene layer was concentrated and the aminoester was distilled under vacuum (30°, 2 mm), yield 56%; ir (potassium bromide): 1749.

Compounds **3b-3d** were prepared in a similar manner, yields for **3b**, 50%; **3c**, 53%; **3d**, 54%; bp for **3b**, 174-176°/20 mm [13]; **3c**, 30-33°/1 mm; **3d**, 90°/0.2 mm; ir (potassium bromide): for **3c**, 1753; **3d**, 1749. Analytical data are given in Table IV.

Ethyl *N*-(9-Phenanthrylcarbonyl)-*N*-isopropylglycinate **4a**.

To a solution of 20 g (0.083 mole) of 9-phenanthrenecarbonyl chloride and 0.083 mole of pyridine in 200 ml of dry benzene was added 0.083 mole of ethyl *N*-isopropylglycinate in 50 ml of dry benzene, dropwise with stirring. The mixture was set aside for 36 hours at room temperature. The pyridine hydrochloride was filtered off and the liquids were washed with diluted hydrochloric acid and water. Evaporation of the dried benzene layer left the product as a syrup, which was recrystallized.

The data on **4a** and on **4b-4e**, which were prepared in a similar manner, are given in Tables I and IV.

Ethyl *N*-(9-Phenanthrylmethyl)-*N*-isopropylglycinate Hydrochloride **5a**.

A solution of 0.020 mole of compound **4a** and triethyloxonium fluoroborate (0.025 mole) [14] in 45 ml of dry methylene chloride was stirred for 24 hours at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in 50 ml of absolute ethanol. Sodium borohydride (1.5 g, 0.04 mole) was added in small portions to the stirred solution at

Table IV

Microanalyses of New Compounds

Compound No.	Molecular Formula	Calcd. C	H	N	Found C	H	N
3a	$C_7H_{15}NO_2$	57.93	10.34	9.66	57.69	10.07	9.48
3c	$C_8H_{17}NO_2$	60.37	10.69	8.81	59.98	10.81	9.03
3d	$C_{10}H_{19}NO_2$	64.86	10.27	7.57	64.91	10.12	7.72
4a	$C_{22}H_{23}NO_3$	75.62	6.63	4.00	75.44	6.74	4.03
4b	$C_{23}H_{25}NO_3$	76.00	6.93	3.85	76.30	7.23	4.14
4c	$C_{23}H_{25}NO_3$	76.00	6.93	3.85	75.87	6.93	3.85
4d	$C_{25}H_{27}NO_3$	77.09	6.98	3.59	77.14	7.19	3.62
4e	$C_{20}H_{19}NO_3$	74.73	5.95	4.36	74.56	6.16	4.15
5a·HCl	$C_{22}H_{26}ClNO_2$	71.05	7.04	3.76	70.86	6.79	3.68
5b·HCl	$C_{23}H_{28}ClNO_2$	71.58	7.31	3.63	71.37	7.01	3.63
5c	$C_{23}H_{27}NO_2$	79.04	7.78	4.00	79.08	7.77	3.86
5d	$C_{25}H_{29}NO_2$	79.96	7.78	3.73	80.20	7.67	3.48
5e·HCl	$C_{20}H_{22}ClNO_2$	69.86	6.45	4.07	70.25	6.45	4.08
6a·HCl	$C_{20}H_{22}ClNO_2$	69.86	6.45	4.07	69.51	6.30	3.94
6b·HCl	$C_{21}H_{24}ClNO_2$	70.48	6.76	3.91	70.33	6.67	3.68
6c·HCl	$C_{21}H_{24}ClNO_2$	70.48	6.76	3.91	70.53	6.56	4.04
6d·HCl	$C_{23}H_{26}ClNO_2$	71.96	6.78	3.65	71.86	6.74	3.71
6e·HCl	$C_{18}H_{18}ClNO_2$	68.46	5.74	4.43	68.38	5.33	4.07
8a	$C_{20}H_{21}NO$	82.43	7.26	4.80	82.30	7.47	4.60
8b	$C_{21}H_{23}NO$	82.62	7.54	4.58	82.41	7.31	4.36
8c	$C_{21}H_{23}NO$	82.62	7.54	4.58	82.54	7.59	4.39
8d	$C_{23}H_{25}NO$	83.38	7.55	4.22	83.25	7.60	3.98
8e	$C_{18}H_{17}NO$	82.12	6.46	5.31	81.97	6.42	5.04
9a	$C_{20}H_{20}ClNO_4$	64.26	5.39	3.74	64.17	5.20	3.51
9b	$C_{21}H_{22}ClNO_4$	65.03	5.71	3.61	64.82	5.58	3.53
9c	$C_{21}H_{22}ClNO_4$	65.03	5.71	3.61	64.89	5.64	3.49
9d	$C_{23}H_{24}ClNO_4$	66.74	5.84	3.38	66.66	5.75	3.35
9e	$C_{18}H_{16}ClNO_4$	63.52	4.66	4.05	63.42	4.43	3.98
10a	$C_{20}H_{21}N$	87.22	7.68	5.08	87.28	7.57	5.00
10b	$C_{21}H_{23}N$	87.14	8.01	4.83	86.92	8.11	4.57
10c	$C_{21}H_{23}N$	87.14	8.01	4.83	86.95	7.89	4.84
10d	$C_{23}H_{25}N$	87.57	7.98	4.44	87.45	7.86	4.39
10e	$C_{18}H_{17}N$	87.40	6.92	5.66	87.25	6.86	5.60

0°; when the addition was complete stirring was continued for 18 hours at room temperature. The solution was poured into 300 ml of water and stirred for 1 hour. The aqueous layer was extracted with ether and the organic layers were dried and evaporated *in vacuo*. The residue obtained was dissolved in dry ether and treated with dry hydrogen chloride under external cooling. The precipitated hydrochloride salt **5a** was collected by filtration.

The data on **5a** and on **5b-5e**, which were prepared in a similar manner, are given in Tables I and IV.

N(9-Phenanthrylmethyl)-*N*-isopropylglycine Hydrochloride **6a**.

A suspension of 6 g (0.0161 mole) of **5a** in 70 ml of concentrated hydrochloric acid was refluxed on a water bath for 12-24 hours. The solution was partially concentrated *in vacuo* and refrigerated overnight. The precipitated crystals were washed with dry acetone.

The data on **6a** and on **6b-6e**, which were prepared in a similar manner, are given in Tables I and IV.

1,2,3,4-Tetrahydro-2-isopropyldibenzo[*f,h*]isoquinolin-4-one **7a**.

The hydrochloride of compound **6a** (0.01 mole) and 25 g of polyphosphoric acid were kept under nitrogen, in a parafin bath, with stirring at 105° for 7 hours. After cooling, the viscous solution was poured onto 150 ml ice water and basified, at 20-30°, with 50% potassium hydrochloride, to *p*H 8.5. The mixture was extracted five times with chloroform, the organic layers washed with water, dried and evaporated *in vacuo* at 30° to give a yellow solid, which was not further purified; ir (potassium bromide): 1677, yield, 82%.

Compounds **7b-7e**, which were prepared in a similar manner, were characterized only by spectroscopic means and were immediately reduced, because of their high sensitivity to air oxidation; ir (potassium bromide): for **7b**, 1674; **7c**, 1684; **7d**, 1674; **7e**, 1672; yields for **7b**, 92%; **7c**, 90%; **7d**, 98%; **7e**, 81%; nmr (deuteriochloroform): for **7c**, δ 9.45 (m, 1H, H-5), 8.61 (m, 2H, H-8, H-9), 8 (m, 1H, H-12), 7.65 (m, 4H, Ar-H), 4.35 (s, 2H, H-1), 3.55 (s, 2H, H-3), 1.28 (s, 9H, 3-CH_3).

1,2,3,4-Tetrahydro-2-isopropyldibenzo[*f,h*]isoquinolin-4-ol **8a**.

To a suspension of ketone **7a** (0.0076 mole) in 80 ml of absolute ethanol was added 0.45 g (0.009 mole) of sodium borohydride in small portions with stirring and external cooling. When the addition was complete, stirring was continued for 12 hours at room temperature. The solution was poured into 125 ml of water and stirred for 2 hours. The solid formed was filtered, or extracted with chloroform and concentrated.

The data on **8a** and on **8b-8e**, which were prepared in a similar manner, are given in Tables II, III and IV.

1,2-Dihydro-2-isopropyldibenzo[*f,h*]isoquinoline Perchlorate **9a**.

A solution of 1 g (0.0034 mole) of aminoalcohol **8a** in 40 ml of glacial acetic acid and 2 ml of 70% perchloric acid was refluxed for 90 minutes. The product was obtained by crystallization on cooling, or by precipitation with addition of water.

The data on **9a** and on **9b-9e**, which were prepared in a similar manner, are given in Tables II and IV.

1,2,3,4-Tetrahydro-2-isopropyldibenzo[*f,h*]isoquinoline **10a**.

To a solution of 0.68 g (0.0018 mole) of compound **9a** in 25 ml of absolute ethanol was added, in small portions, an excess of sodium borohydride (0.5 g, 0.012 mole) with stirring; when the addition was complete, stirring was continued for one hour. The mixture was poured into 100 ml ice water and left for 12 hours at room temperature. The precipitate formed was filtered off and recrystallized.

The data on **10a** and on **10b-10e**, which were prepared in a similar manner, are given in Tables II, III and IV.

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