Synthesis of Di- and Tetraalkyl-3-piperazinoisoquinolines and Related Compounds as Potential Antidepressant Agents

Wilhelm Bartmann, Elmar Konz and Wolfgang Rüger*

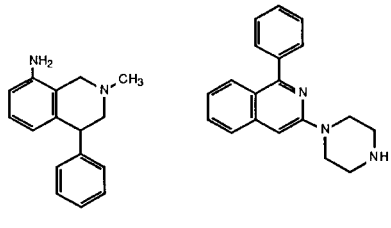
Hoechst AG, Postfach 80 03 20, D-6230 Frankfurt am Main 80, West Germany

Received September 4, 1986

A series of di- and tetraalkyl-3-piperazinoisoquinolines and related compounds was synthesized *via* di- and tetraalkylated 1-indanones as intermediates.

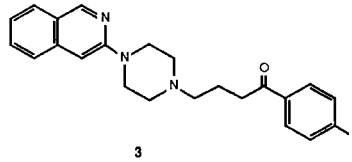
J. Heterocyclic Chem., **24**, 677 (1987).

Isoquinoline alkaloids show a great variety of pharmacological action and therefore have always been of great interest to synthetic as well as pharmaceutical organic chemists [1]. More recently, synthetic isoquinoline derivatives have been introduced as pharmaceutical agents, *e.g.* nomifensine (**1**), a non-tricyclic antidepressant which exhibits its effects mainly through inhibition of the neuronal reuptake of both dopamine and norepinephrine [2]. Perafensine (**2**, HR 459) is a structurally similar compound bearing a piperazine-side chain in position 3 of the isoquinoline nucleus which shows antidepressant properties based upon the selective inhibition of the neuronal reuptake of norepinephrine [3]. HR375 (**3**) lacks the phenyl substituent present in **1** and **2** and is substituted on the piperazine-side chain, which changes its pharmacological activity to a neuroleptic profile [4]. Given these results, it was



1

2

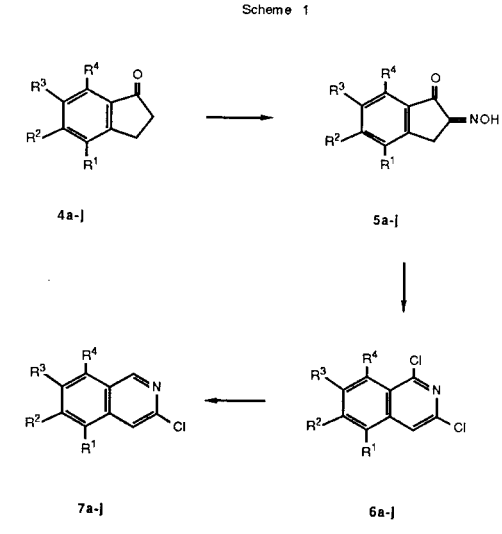


3

thought that isoquinoline derivatives alkylated on the benzene nucleus would show interesting psychotropic properties. We therefore started a project to synthesize di- and tetraalkyl-3-piperazinoisoquinolines, which to our knowledge have not yet been described in the literature, and investigated their pharmacological profile.

As a general method applicable to all patterns of substitution which we envisaged, we chose a reaction sequence starting from the corresponding 1-indanones **4** (Scheme 1). Nitrosation of the 1-indanones **4a-j** by ethyl nitrite or amyl nitrite in ether or ether/ethanol under acid catalysis led to

Scheme 1



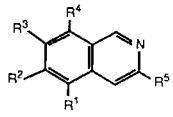
4-8, 10-15	R^1	R^2	R^3	R^4
a	CH_3	CH_3	H	H
b	CH_3	H	CH_3	H
c	CH_3	H	H	CH_3
d	H	CH_3	CH_3	H
e	H	CH_3	H	CH_3
f	H	H	CH_3	CH_3
g	CH_3	CH_3	CH_3	CH_3
h	C_2H_5	H	H	C_2H_5
i	H	$-(CH_2)_3-$		H
j	H	$-(CH_2)_4$		H

the 2-oximino-1-indanone derivatives **5a-j** in good yield. These were submitted to a modified Beckmann rearrangement using excess phosphorus pentachloride in phosphorus oxychloride as solvent saturated with gaseous hydrogen chloride [5] leading to the 1,3-dichloroisoquinoline derivatives **6a-j**. Selective hydrogenolytic removal of the 1-chloro substituent was achieved by treatment with hydriodic aicd and red phosphorus in glacial acetic acid at reflux [6]. Finally, the resulting 3-chloroisoquinoline derivatives **7a-j** were reacted with excess piperazine in refluxing diglyme to yield the final products **8a-j**. The reaction sequence leading from the 1-indanones **4a-j** to the isoquinoline derivatives **8a-j** was accomplished without any puri-

fication of the intermediates. Compounds **5a-j**, **6a-j** and **7a-j** were always used as raw materials. The final products **8a-j** were obtained as analytically pure samples after column chromatography and conversion into their water-soluble hydrochlorides which were submitted to pharmacological testing.

To obtain some information about the importance of the piperazine substituent, we extended our study to some related compounds **9a-m** available by an analogous procedure from the corresponding 3-chloroisoquinolines **7** and the corresponding amines. The following compounds were synthesized (Table 1): The starting compounds **4a-j**

Table 1



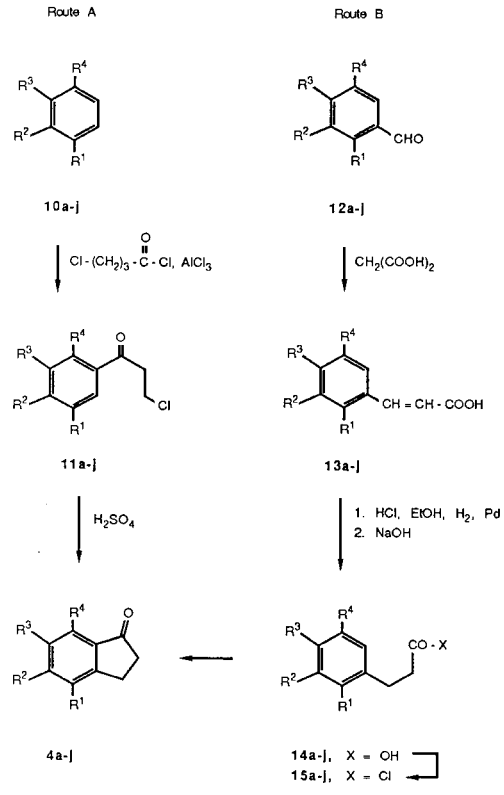
9	R^1	R^2	R^3	R^4	R^5
a	CH_3	H	H	CH_3	3-methylpiperazino
b	CH_3	H	H	CH_3	2-methylpiperazino
c	CH_3	H	H	CH_3	3,5-dimethylpiperazino
d	CH_3	H	H	CH_3	4-methylpiperazino
e	CH_3	H	H	CH_3	2-(diethylamino)ethylamino
f	CH_3	H	H	CH_3	homopiperazino
g	CH_3	H	H	CH_3	4-(2-hydroxyethyl)piperazino
h	H	H	CH_3	CH_3	4-methylpiperazino
i	H	H	CH_3	CH_3	4-(2-hydroxyethyl)piperazino
j	H	H	CH_3	CH_3	4-ethoxycarbonylpiperazino
k	H	H	CH_3	CH_3	piperidino
l	H	H	CH_3	CH_3	2-(dimethylamino)ethylamino
m	H	H	CH_3	CH_3	homopiperazino

have previously been prepared by a great number of different synthetic approaches [7]. We chose to use one of the following generally applicable routes (Scheme 2):

Route A: A substituted benzene derivative **10** was acylated under Friedel-Crafts conditions with 3-chloropropionyl chloride to yield **11** which was then cyclised in concentrated sulfuric acid to indanone **4**. This route was chosen to prepare **4c**, **d**, **e**, **g**, **h**, **i** and **j**.

Route B: A substituted benzaldehyde **12** was condensed with malonic acid under Knoevenagel conditions to yield the cinnamic acid **13**. This was hydrogenated to **14**, transformed into the acid chloride **15** and then cyclised under Friedel-Crafts conditions to the indanone **4**. Alternatively, the acid **14** was cyclised directly by polyphosphoric acid. This route was chosen to prepare **4a**, **b** and **f**.

Scheme 2



Typical procedures for each route are outlined in the experimental. Again, the intemediates were in general used without purification.

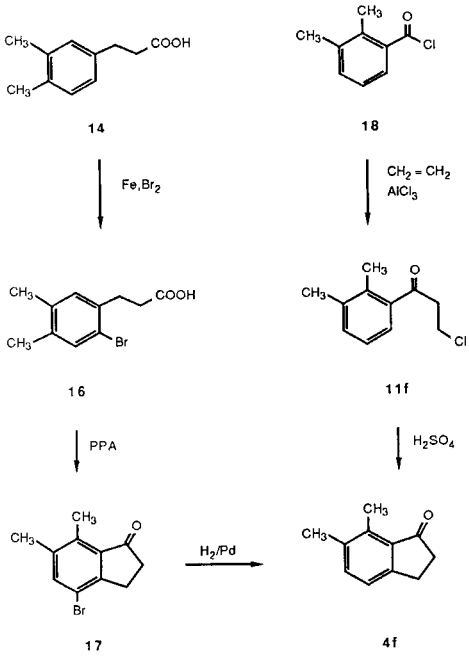
Both routes meet with difficulties when used for the synthesis of 5,6-disubstituted 1-indanones, *e.g.* **4d**, as they lead to isomeric mixtures which are often difficult to separate [15-17]. Our own efforts focused on the synthesis of **4d**. Whereas treatment of **11d** with concentrated sulfuric acid (90°, 4 hours) led to a 85% yield of a 67:33 mixture of **4d** and **4a** in accordance with literature data [15], route B did not lead to higher regioselectivities: Cyclisation of **15d** with aluminum chloride [16] or zinc chloride [17] both led to 65:35 mixtures of **4d** and **4f**, and direct treatment of the precursor acid **14d** with polyphosphoric acid (90°, 3 hours) or anhydrous hydrogen fluoride gave 52:48 and 58:42 mixtures of **4d** and **4f**, respectively. However, **4d** and **4f** could be separated by column chromatography and were gained in sufficient quantities to be used for further reactions.

In principle, the same problems arose during the preparation of **4i** and **j** [16]. In these cases, the isomers were separated by extensive recrystallization.

We were, however, able to develop an unambiguous synthesis of **4f** which so far had only been the minor by-product during the preparation of **4d**. This was achieved by two independent methods (Scheme 3). The first made use

of bromine as an easily removable blocking group on the aromatic nucleus [26]. 3-(2,3-Dimethylphenyl)propionic acid **14d** was regioselectively brominated to **16**, then cyclised to **17** by polyphosphoric acid, and the bromine atom substituted by hydrogen through hydrogenation over palladium at room temperature without reduction of the carbonyl group. The second way was based upon the Friedel-Crafts acylation of ethylene [27]. 2,3-Dimethylbenzoylchloride **18** [28] was added to ethylene under aluminium chloride catalysis, and the resulting **11f** then cyclised to **4f** by the normal procedure. Most of the isoquinoline derivatives **8** and **9** showed interesting psychotropic, especially

Scheme 3



antidepressant activities. The most potent compounds were **8c** and **8f** which both exhibited considerable antidepressant action in different animal models based upon the selective inhibition of the neuronal reuptake of serotonin. They are currently under detailed pharmalogical evaluation. Details of the biological results will be reported elsewhere.

EXPERIMENTAL

All melting points were determined in open capillary tubes on a Büchi melting point apparatus (Dr. Tottoli) and are uncorrected. The ^{1}H-nmr spectra were taken on a ® Varian T 60, ® Bruker WP 60 or ® Hitachi-Perkin-Elmer R-24 B spectrometer at 60 MHz. All ^{1}H shifts are reported in ppm relative to tetramethylsilane as an internal standard. Mass spectra (electron impact ionisation at 70 eV) were recorded on a ® Kratos MS 30 or ® Kratos MS 902 S spectrometer. Gas-chromatographic analyses were carried out on a OV 101-2 capillary column at temperatures between 120 and 190°.

Route A, Typical Procedure: Synthesis of 5,6-Dimethyl-1-indanone (**4d**).

a) ω-Chloro-3,4-dimethylpropiophenone (**11d**).

A mixture of 58.0 g (0.546 mole) o-xylene and 69.6 g (0.548 mole) 3-chloropropionylchloride was added dropwise to 164 g (1.23 moles) of anhydrous aluminium chloride in 550 ml of nitromethane over a period of one hour. The reaction was stirred five hours at room temperature and poured into a mixture of 100 ml of concentrated hydrochloric acid and 500 g of ice. The organic phase was separated, the aqeuous phase extracted twice with ether and the combined organic phases washed twice with 2*N* hydrochloric acid, once with a saturated aqueous solution of sodium chloride, cleared by treating with activated carbon, dried over magnesium sulfate and evaporated, leaving 102 g (95%) of raw **11d**. Recrystallisation of a sample from petroleum ether led to pure product, mp 69-70° (lit [15] mp 72-72.5°).

b)5,6-Dimethyl-1-indanone (**4d**).

To 900 ml of concentrated sulfuric acid 213 g (1.08 moles) of raw ω-chloro-3,4-dimethylpropiophenone (**11d**) were added in portions and heated at 90° for 4 hours. The cooled reaction mixture was poured onto an excess of ice and extracted twice with toluene. The combined organic phases were washed twice with saturated aqueous sodium bicarbonate and once with saturated aqueous sodium chloride, cleared by treating with activated carbon, dried over magnesium sulfate and evaporated. The raw material (148,2 g, 85%) contained about 33% of the undesired isomer **4a** (gc) and was recrystallized from 2000 ml of petroleum ether (40-60°) at room temperature giving 54 g of a first crop, 92% pure (gc). A second recrystallisation under identical conditions left 19.0 g of 5,6-dimethyl-1-indanone (**4d**), mp 85-86°, 99.5% pure (gc) (lit [15] mp 87-88°).

The same procedure was applied to the synthesis of the following 1-indanones:

4,7-Dimethyl-1-indanone (**4c**).

This compound was obtained as colorless crystals, mp 74-75° (lit [13] mp 78-79°).

5,7-Dimethyl-1-indanone (**4e**).

This compound was obtained as colorless needles, mp 74-76° (lit [18] mp 76-77°).

4,5,6,7-Tetramethyl-1-indanone (**4g**).

This compound was obtained as colorless crystals, mp 152-154° (lit [14] mp 152-153°).

4,7-Diethyl-1-indanone (**4h**).

This compound was obtained as a colorless oil, (lit [22] bp 96-98°/0.1 mm).

3,5,6,7-Tetrahydro-s-indacen-1(2*H*)-one (**4i**).

This compound was obtained as white crystals, mp 78-80° (lit [24] mp 80-81°).

2,3,5,6,7,8-Hexahydro-1*H*-benz[*f*]inden-1-one (**4j**).

This compound was obtained as colorless crystals, mp 50-52° (lit [25] mp 47°).

Route B, Typical Procedure: Synthesis of 5,6-Dimethyl-1-indanone (**4d**).

a) 3,4-Dimethylcinnamic Acid (**13d**).

To a solution of 85.3 g (0.643 mole) of 3,4-dimethylbenzaldehyde (**12d**) in 250 ml pyridine, 92.9 g (0.893 mole) of malonic acid and 5.4 ml of piperidine were added subsequently and the reaction mixture heated to reflux for 6 hours. After cooling, the *p*H was adjusted to 1 by addition of concentrated hydrochloric acid, the precipitate collected by filtration, washed extensively with water and dried *in vacuo* at 80°, yield, 92.3 g (82.4%) of white crystalline **13d**, mp 171°, (lit [17] mp 155-157°).

b) 3-(3,4-Dimethylphenyl)propionic Acid (**14d**).

3,4-Dimethylcinnamic acid (**13d**) (92.3 g, 0.524 mole) was dissolved in 1500 ml of ethanol, 75 ml of ethanolic hydrochloric acid and 3.0 g of palladium on charcoal (10%) were added and hydrogenated in an autoclave

at 120° and 100 bars for 20 hours. After cooling, the catalyst was filtered off and the solution evaporated. The oily residue was dissolved in 250 ml of ethanol, a solution of 65.6 g of sodium hydroxide in 250 ml of water was added and the reaction mixture refluxed for one hour. After evaporation of the ethanol, more water was added and the solution acidified to *p*H 1 by addition of concentrated hydrochloric acid. The precipitated product was collected, washed with water and dried *in vacuo* at 60° over phosphorus pentoxide, yield, 92.2 g (99%) of white crystalline **14d**, mp 81° (lit [17] mp 80-82°).

c) 5,6-Dimethyl-1-indanone (**4d**) and 6,7-Dimethyl-1-indanone (**4f**).

Phosphoric acid (85%, 500 ml) was warmed up to 60°. 800 g of phosphorus pentoxide were added in portions leading to a temperature rise up to 150°. After cooling to 90°, 87.5 g (0.491 mole) of 3-(3,4-dimethylphenyl)propionic acid (**14d**) was added and the mixture held at that temperature for three hours. The reaction mixture was then hydrolysed by pouring onto excess ice and extracted twice with methylene chloride. The organic extracts were washed with water, dried over magnesium sulfate and evaporated leaving 81.1 g of raw material containing a 52:48-mixture of **4d** and **4f**.

These were separated by column chromatography on 1500 g of silicagel eluting with cyclohexane/ethyl acetate 9:1 yielding 31.9 g (41%) of 6,7-dimethyl-1-indanone (**4f**), mp 47-50° (lit [16] mp 45.5°) as the first fraction, and 39.2 g (50%) of 5,6-dimethyl-1-indanone (**4d**), mp 85-86° (lit [15] mp 87-88°), identical in every respect to the above described product, as the second fraction.

The same procedure was applied to the synthesis of the following 1-indanones:

4,5-Dimethyl-1-indanone (**4a**).

This compound was obtained as colorless needles, mp 96-98° (lit [8] mp 99°).

4,6-Dimethyl-1-indanone (**4b**).

This compound was obtained as white crystals, mp 119-121° (lit [10] mp 121°).

Synthesis of 6,7-Dimethyl-1-indanone (**4f**) According to Scheme 3.

a) 3-(2-Bromo-4,5-dimethylphenyl)propionic Acid (**16**).

To a solution of 121.3 g (0.681 mole) of 3-(3,4-dimethylphenyl)propionic acid (**14d**) in 360 ml of methylene chloride, 2.4 g of iron powder was added and a solution of 108.9 g (1.36 moles) of bromine in 120 ml of methylene chloride added dropwise. After addition of the first drops the reaction was started by some crystals of iodine and heating to 40°. The reaction mixture was then refluxed overnight, cooled, extracted with 1000 ml of saturated aqueous sodium hydrogensulfite, washed with water, dried over magnesium sulfate and evaporated leaving 169.6 g (97%) of raw grey **16**, mp 83°.

Recrystallisation from petroleum ether yielded analytically pure product; nmr (deuteriochloroform): 2.16 (s, 6H), 2.2-3.2 (m, 4H), 6.92 (s, 1H), 7.20 (s, 1H), 10.8 (br s, 1H); ms: (m/e) 258, 256, 199, 197, 177, 150, 135, 105.

Anal. Calcd. for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.09; Br, 31.07. Found: C, 51.12; H, 5.24; Br, 30.75.

b) 4-Bromo-6,7-dimethyl-1-indanone (**17**).

To 300 ml phosphoric acid (85%), warmed up to 60°, 500 g of phosphorus pentoxide were added in portions. After cooling, 50.0 g (0.195 mole) of 3-(2-bromo-4,5-dimethylphenyl)propionic acid (**16**) was added at 90° and the mixture held at that temperature for 2 hours. Hydrolysis was accomplished by pouring on 1000 g of ice and stirring up for one hour. The solution was extracted with methylene chloride, the extracts were washed with water, dried over magnesium sulfate and evaporated, yield 46.2 g (99%) of yellowish **17**, mp 144°. A sample was recrystallised to analytical purity from *n*-hexane; nmr (deuteriochloroform): 2.29 (s, 3H), 2.54 (s, 3H), 2.5-3.1 (m, 4H), 7.40 (s, 1H).

Anal. Calcd. for $C_{11}H_{11}BrO$: C, 55.25; H, 4.64; Br, 33.42. Found: C, 55.52; H, 4.85; Br, 33.10.

c) 6,7-Dimethyl-1-indanone (**4f**).

To a solution of 8.81 g (36.8 mmoles) of 4-bromo-6,7-dimethyl-1-indanone in 360 ml of absolute ethanol, 6.3 ml (36.8 mmoles) of ethyldiisopropylamine and subsequently 1.7 g of palladium on charcoal (10%) were added and the mixture hydrogenated at room temperature and normal pressure during 10 minutes. After filtration of the catalyst the solution was evaporated, the residue dissolved in methylene chloride, washed with diluted hydrochloric acid and water, dried over magnesium sulfate and evaporated, yield, 5.70 g (96%) of raw **4f** showing some minor impurities on tlc. Recrystallisation from *n*-pentane led to colorless crystals, mp 43-45° (lit [16] mp 45.5°).

Independent Synthesis of 6,7-Dimethyl-1-indanone (**4f**).

To 40.0 g (0.30 mole) of anhydrous aluminium chloride in 1000 ml of 1,2-dichloroethane, 50.4 g (0.30 mole) of 2,3-dimethylbenzoylchloride (**18**) [28] was added all at once. During 5 hours, gaseous ethylene was bubbled through this solution at 10-20° and the reaction mixture left overnight. It was then poured on 1000 ml of 4 *N* hydrochloric acid and stirred vigorously for five minutes. The organic phase was separated, the aqueous phase extracted with 300 ml of ether and the combined organic phases washed with saturated aqueous sodium hydrogencarbonate and with water, dried over magnesium sulfate and evaporated. The raw 2-(2,3-dimethylbenzoyl)ethyl chloride (**11f**) (60.7 g) contained some dichloroethane and some **4f** (tlc) and was used without further purification.

This was added to 250 ml of concentrated sulfuric acid and stirred at 80-90° during 30 minutes. After cooling to room temperature the solution was poured into 1000 ml of ice and extracted several times with ether. The organic phases were washed with saturated aqueous sodium hydrogencarbonate and water, dried over magnesium sulfate and evaporated. The oily product (39.6 g) crystallized on standing yielding 29.9 g (69%) of **4f**, identical in all respects to the above described product.

Typical Procedure for the Preparation of Isoquinoline Derivatives **8** and **9**.

a) 5,6-Dimethyl-2-oximino-1-indanone (**5d**).

To a solution of 18.0 g (0.112 mole) of 5,6-dimethyl-1-indanone (**4d**) in 270 ml ether, first 4.5 ml of saturated ethanolic hydrogen chloride and then 100 ml of a 15% ethanolic solution of ethyl nitrite were added dropwise at 0°. After 30 minutes at 0° the precipitated product was collected by filtration, washed with ether and dried yielding 19,5 g (92%) of raw **5d**, mp 240-242°; nmr (dimethylsulfoxide-d_6): 2.29 (s, 6H), 3.61 (s, 2H), 7.28 (s, 1H), 7.41 (s, 1H).

b) 1,3-Dichloro-6,7-dimethylisoquinoline (**6d**).

To a suspension of 19.0 g (0.100 mole) of 5,6-dimethyl-2-oximino-1-indanone (**5d**) in 600 ml of phosphorus oxychloride, 23.6 g (0.113 mole) of phosphorus pentachloride was added at 0-5°. Then gaseous hydrogen chloride was introduced until the solution was saturated and the reaction stirred at 60° during four hours. Then again 8.0 g (0.038 mole) of phosphorus pentachloride was added and stirring was continued for two hours at 80°. After evaporating the solvent the residue was slowly hydrolysed by addition of water, the precipitate collected by filtration, washed extensively with water and dried, yield 22.0 g (97%) of crude **6d**, mp 135-136°; nmr (deuteriochloroform): 2.33 (s, 6H), 7.17 (s, 2H), 7.64 (s, 1H).

c) 3-Chloro-6,7-dimethylisoquinoline (**7d**).

A mixture of 21.0 g (92.9 mmoles) of 1,3-dichloro-6,7-dimethylisoquinoline (**6d**), 6.9 g of red phosphorus, 100 ml of glacial acetic acid and 42 ml of hydriodic acid (57%) was refluxed for eight horus. The hot reaction mixture was filtered, evaporated, the residue dissolved in water and basified by addition of concentrated aqueous sodium hydroxide. The precipitate was collected by filtration, dissolved in methylene chloride, washed once with saturated aqueous sodium chloride, cleared by treating with activated carbon, dried over magnesium sulfate and evaporated. The residue (12.4 g) was purified by column chromatography (250 g of silicagel, elution with methylene chloride/ethyl acetate 9:1), yield 11.6 g (65%) of

crude **7d**, mp 114-117°; nmr (deuteriochloroform): 2.35 (s, 6H), 7.2-7.5 (m, 3H), 8.79 (s, 1H).

d) 6,7-Dimethyl-3-piperazinoisoquinoline (**8d**).

To a solution of 5.74 g (30.0 mmoles) 3-chloro-6,7-dimethylisoquinoline (**7d**) in 50 ml diglyme, 39 g (450 mmoles) of piperazine were added and stirred at 150° for 72 hours. After cooling the reaction mixture was distributed between toluene and water, the organic phase was separated, washed several times with water and extracted with 2 *N* hydrochloric acid three times. The acidic extracts were basified by addition of potassium carbonate, extracted with methylene chloride, the organic extracts dried over magnesium sulfate, evaporated and chromatographed on 250 g of silicagel, eluting with methylene chloride/methanol 9:1, yield, 5.0 g (69%) of **8d**, nmr (deuteriochloroform): 1.78 (s, 1H), 2.40 (s, 6H), 2.9-3.2 (m, 4H), 3.4-3.7 (m, 4H), 6.70 (s, 1H), 7.37 (s, 1H), 7.54 (s, 1H), 8.85 (s, 1H); ms: (m/e) 241 (M^+), 226, 211, 199, 185, 172, 156, 56.

Compound **8d** was dissolved in acetone and the hydrochloride precipitated by addition of one equivalent of saturated ethanolic hydrogen chloride, yield, 4.1 g of **8d**-hydrochloride, mp 272-276°.

Anal. Calcd. for $C_{15}H_{20}ClN_3$: C, 64.86; H, 7.26; N, 15.13; Cl, 12.76. Found: C, 64.59; H, 7.50; N, 14.92; Cl, 12.80.

According to the typical procedure and by applying the appropriate 1-indanone derivatives and amines the following compounds have been prepared:

5,6-Dimethyl-3-piperazinoisoquinoline (**8a**).

This compound was obtained in 69% yield; nmr (deuteriochloroform): 2.45 (s, 6H), 2.9-3.7 (m, 3H), 6.80 (s, 1H), 7.08 (d, J = 7 Hz, 1H), 7.56 (d, J = 7 Hz, 1H), 8.85 (s, 1H); ms: (m/e) 241 (M^+), 199, 191, 185, 172, 59; **8a**-hydrochloride, mp >260°.

Anal. Calcd. for $C_{15}H_{20}ClN_3$: C, 64.86; H, 7.26; N, 15.13; Cl, 12.76. Found: C, 65.05; H, 7.55; N, 14.97; Cl, 12.48.

5,7-Dimethyl-3-piperazinoisoquinoline (**8b**).

This compound was obtained in 83% yield; nmr (deuteriochloroform): 2.42 (s, 3H), 2.55 (s, 3H), 3.0-3.3 (m, 4H), 3.4-3.8 (m, 5H), 6.76 (s, 1H), 7.22 (s, 1H), 7.42 (s, 1H), 8.86 (s, 1H); ms: (m/e) 241 (M^+) 211, 199, 191, 185, 172, 156; **8b**-dihydrochloride, mp >260°.

Anal. Calcd. for $C_{15}H_{21}Cl_2N_3$: C, 57.33; H, 6.74; N, 13.37; Cl, 22.56. Found: C, 57.25; H, 7.00; N, 13.10; Cl, 22.20.

5,8-Dimethyl-3-piperazinoisoquinoline (**8c**).

This compound was obtained in 86% yield, mp 91-92° (from *n*-heptane); nmr (deuteriochloroform): 2.46 (s, 1H), 2.53 (s, 3H), 2.66 (s, 3H), 3.0-3.3 (m, 4H), 3.4-3.8 (m, 4H), 6.80 (s, 1H), 6.8-7.3 (AB, J = 7 Hz, 2H), 9.14 (s, 1H); ms: (m/e) 241 (M^+), 226, 211, 199, 185, 172, 157, 128, 56; **8c**-hydrochloride; mp >260°.

Anal. Calcd. for $C_{15}H_{20}ClN_3$: C, 64.83; H, 7.26; N, 15.13; Cl, 12.76. Found: C, 64.71; H, 7.44; N, 14.88; Cl, 12.99.

6,8-Dimethyl-3-piperazinoisoquinoline (**8e**).

This compound was obtained in 89% yield, **8e**-hydrochloride, mp 214-217°; nmr (deuteriochloroform): 2.43 (s, 3H), 2.65 (s, 3H), 3.2-4.1 (m, 8H), 6.78 (s, 1H), 6.96 (s, 1H), 7.25 (s, 1H), 9.05 (s, 1H), 10.0 (br s, 1H); ms: (m/e) 241 (M^+), 211, 199, 185, 172, 157.

Anal. Calcd. for $C_{15}H_{20}ClN_3$: C, 64.83; H, 7.26; N, 15.13; Cl, 12.76. Found: C, 65.10; H, 7.31; N, 14.79; Cl, 12.60.

7,8-Dimethyl-3-piperazinoisoquinoline (**8f**).

This compound was obtained in 60% yield; nmr (deuteriochloroform): 1.76 (s, 1H), 2.40 (s, 3H), 2.60 (s, 3H), 2.9-3.7 (m, 8H), 6.72 (s, 1H), 7.31 (s, 2H), 9.55 (s, 1H); ms: (m/e) 241 (M^+), 226, 211, 199, 185, 173, 157, 128, 56; **8f**-hydrochloride, mp 250° dec.

Anal. Calcd. for $C_{15}H_{20}ClN_3$: C, 64.83; H, 7.26; N, 15.13; Cl, 12.76. Found: C, 64.45; H, 6.98; N, 14.85; Cl, 12.85.

5,6,7,8-Tetramethyl-3-piperazinoisoquinoline (**8g**).

This compound was obtained in 46% yield, **8g**-hydrochloride, mp >260°; nmr (deuteriochloroform): 2.36 (s, 3H), 2.41 (s, 3H), 2.50 (s, 3H), 2.63 (s, 3H), 3.0-4.0 (m, 8H), 6.92 (s, 1H), 9.14 (s, 1H), 9.9 (br s, 1H); ms: (m/e) 269 (M^+), 239, 227, 213, 200, 138.

Anal. Calcd. for $C_{17}H_{24}ClN_3$: C, 66.76; H, 7.91; N, 13.74; Cl, 11.59. Found: C, 66.52; H, 8.11; N, 13.52; Cl, 11.54.

5,8-Diethyl-3-piperazinoisoquinoline (**8h**).

This compound was obtained in 89% yield, **8h**-hydrochloride, mp 160-163°; nmr (dimethylsulfoxide-d_6): 1.55 (t, J = 7 Hz, 6H), 2.7-4.0 (m, 12H), 7.06 (d, J = 7 Hz, 1H), 7.35 (d, J = 7 Hz, 1H), 9.18 (s, 1H), 9.3 (br s, 2H); ms: (m/e): 269 (M^+), 239, 227, 213, 200.

Anal. Calcd. for $C_{17}H_{24}ClN_3$: C, 66.76; H, 7.91; N, 13.74; Cl, 11.59. Found: C, 66.77; H, 8.10; N, 14.01; Cl, 11.63.

7,8-Dihydro-3-piperazino-6*H*-cyclopenta[*e*]isoquinoline (**8i**).

This compound was obtained in 67% yield, mp 114-120°; nmr (deuteriochloroform): 2.10 (quint, J = 7 Hz, 2H), 2.7-3.2 (m, 8H), 3.3-3.7 (m, 4H), 6.71 (s, 1H), 7.40 (s, 1H), 7.57 (s, 1H), 8.85 (s, 1H); ms: (m/e): 253 (M^+), 223, 211, 197, 184, 168, 140, 112, 56; **8i**-hydrochloride, mp >260°.

Anal. Calcd. for $C_{16}H_{20}ClN_3$: C, 66.31; H, 6.96; N, 14.50; Cl, 12.23. Found: C, 65.95; H, 7.30; N, 14.24; Cl, 12.60.

6,7,8,9-Tetrahydro-3-piperazinocyclohexa[*e*]isoquinoline (**8j**).

This compound was obtained in 53% yield; nmr (deuteriochloroform): 1.6-2.0 (m, 4H), 2.7-3.4 (m, 9H), 3.5-3.9 (m, 4H), 6.76 (s, 1H), 7.27 (s, 1H), 7.47 (s, 1H), 8.85 (s, 1H); ms: (m/e): 267 (M^+), 252, 237, 225, 211, 198, 183, 168, 155, 45; **8j**-hydrochloride, mp 236-239°.

Anal. Calcd. for $C_{17}H_{22}ClN_3$: C, 67.20; H, 7.30; N, 13.83; Cl, 11.67. Found: C, 66.88; H, 7.40; N, 13.52; Cl, 11.50.

5,8-Dimethyl-3-(3-methylpiperazino)isoquinoline (**9a**).

This compound was obtained in 49% yield; nmr (deuteriochloroform): 1.23 (d, J = 6 Hz, 3H), 2.55 (s, 3H), 2.67 (s, 3H), 2.3-4.4 (m, 8H), 6.80 (s, 1H), 6.95 (d, J = 7 Hz, 1H), 7.23 (d, J = 7 Hz, 1H), 9.15 (s, 1H); ms: (m/e) 255 (M^+), 240, 225, 211, 199, 185, 172, 157, 128, 56; **9a**-hydrochloride, mp 246-248°.

Anal. Calcd. for $C_{16}H_{22}ClN_3$: C, 65.85; H, 7.60; N, 14.40; Cl, 12.15. Found: C, 65.48; H, 7.50; N, 14.28; Cl, 11.83.

5,8-Dimethyl-3-(2-methylpiperazino)isoquinoline (**9b**).

This compound was obtained in 31% yield as a byproduct during the preparation of **9a**. The two isomers could be separated by column chromatography (silica gel; methylene chloride/methanol 95:5); nmr (deuteriochloroform): 1.62 (d, J = 6 Hz, 3H), 2.53 (s, 3H), 2.67 (s, 3H), 2.9-4.6 (m, 8H), 6.85 (s, 1H), 7.00 (d, J = 7 Hz, 1H), 7.30 (d, J = 7 Hz, 1H), 9.11 (s, 1H); ms: (m/e) 255 (M^+), 240, 225, 211, 199, 185, 172, 157, 128, 115, 56; **9b**-hydrochloride, mp 246-247°.

Anal. Calcd. for $C_{16}H_{22}ClN_3$: C, 65.85; H, 7.60; N, 14.40; Cl, 12.15. Found: C, 65.70; H, 7.41; N, 14.57; Cl, 11.78.

3-(3,5-Dimethylpiperazino)-5,8-dimethylisoquinoline (**9c**).

This compound was obtained in 41% yield; nmr (deuteriochloroform): 1.25 (d, J = 6 Hz, 6H), 2.55 (s, 3H), 2.66 (s, 3H), 2.3-4.5 (m, 7H), 6.79 (s, 1H), 6.95 (d, J = 7 Hz, 1H), 7.22 (d, J = 7 Hz, 1H), 9.13 (s, 1H); ms: (m/e) 269 (M^+), 248, 211, 199, 185; **9c**-hydrochloride; mp >260°.

Anal. Calcd. for $C_{17}H_{24}ClN_3$: C, 66.76; H, 7.91; N, 13.74; Cl, 11.59. Found: C, 66.38; H, 8.05; N, 13.39; Cl, 11.85.

5,8-Dimethyl-3-(4-methylpiperazino)isoquinoline (**9d**).

This compound was obtained in 86% yield; nmr (deuteriochloroform): 2.40 (s, 3H), 2.51 (s, 3H), 2.64 (s, 3H), 2.5-2.8 (m, 5H), 3.5-3.8 (m, 4H), 6.78 (s, 1H), 6.91 (d, J = 7 Hz, 1H), 7.20 (d, J = 7 Hz, 1H), 9.10 (s, 1H); ms: (m/e) 255 (M^+), 240, 211, 185, 172, 157, 128, 71; **9d**-hydrochloride; mp >260°.

Anal. Calcd. for $C_{16}H_{22}ClN_3$: C, 65.85; H, 7.60; N, 14.40; Cl, 12.15. Found: C, 65.60; H, 7.40; N, 14.44; Cl, 11.92.

3-[2-(Diethylamino)ethylamino]-5,8-dimethylisoquinoline (**9e**).

This compound was obtained in 41% yield; nmr (deuteriochloroform):

1.08 (t, J = 7 Hz, 6H), 2.49 (s, 3H), 2.61 (s, 3H), 2.5-3.0 (m, 7H), 3.41 (q, 2H), 5.25 (br s, 1H), 6.56 (s, 1H), 6.83 (d, J = 7 Hz, 1H), 7.15 (d, J = 7 Hz, 1H), 9.00 (s, 1H); ms: (m/e) 271 (M^+), 254, 191, 176, 172, 156, 100, 99, 86; **9e**-dihydrochloride, mp 208-210°.

Anal. Calcd. for $C_{17}H_{27}ClN_3$: C, 59.30, H, 7.90; N, 12.20; Cl, 20.59. Found: C, 58.96; H, 7.75; N, 11.95; Cl, 20.30.

3-Homopiperazine-5,8-dimethylisoquinoline (**9f**).

This compound was obtained in 86% yield, **9f**-hydrochloride, mp 201-202°; nmr (deuteriochloroform): 2.50 (s, 3H), 2.65 (s, 3H), ~2.5 (m, 2H), 3.1-3.6 (m, 4H), 3.85 (t, J = 7 Hz, 2H), 4.1-4.3 (m, 2H), 6.66 (s, 1H), 6.91 (d, J = 7 Hz, 1H), 7.12 (d, J = 7 Hz, 1H), 9.08 (s, 1H), 9.8 (br s, 2H); ms: (m/e) 255 (M^+), 240, 225, 213, 199, 186, 173, 157.

Anal. Calcd. for $C_{16}H_{22}ClN_3$: C, 65.85; H, 7.60; N, 14.40; Cl, 12.15. Found: C, 65.45; H, 7.52; N, 14.31; Cl, 12.00.

3-[4-(2-Hydroxyethyl)piperazino]-5,8-dimethylisoquinoline (**9g**).

This compound was obtained in 80% yield, **9g**-hydrochloride, mp 255-258°; nmr (deuteriochloroform): 2.50 (s, 3H), 2.66 (s, 3H), 3.0-3.7 (m, 6H), 3.9-4.3 (m, 6H), 4.9 (br s, 1H), 6.86 (s, 1H), 6.96 (d, J = 7 Hz, 1H), 7.08 (d, J = 7 Hz, 1H), 9.10 (s, 1H); ms: (m/e): 285 (M^+), 270, 254, 225, 211, 199, 185, 172, 157, 101.

Anal. Calcd. for $C_{17}H_{24}ClN_3O$: C, 63.44; H, 7.52; N, 13.06; Cl, 11.01. Found: C, 63.33; H, 7.30; N, 12.92; Cl, 10.76.

7,8-Dimethyl-3-(4-methylpiperazino)isoquinoline (**9h**).

This compound was obtained in 42% yield as yellow crystals, mp 86-88°; nmr (deuteriochloroform): 2.37 (s, 3H), 2.40 (s, 3H), 2.60 (s, 3H), 2.60 (t, J = 6 Hz, 4H), 3.60 (t, J = 6 Hz, 4H), 6.73 (s, 1H), 7.32 (s, 2H), 9.18 (s, 1H); ms: (m/e) 255 (M^+), 240, 211, 197, 185, 172, 157, 71; **9h**-hydrochloride; mp 254-256° dec.

Anal. Calcd. for $C_{16}H_{22}ClN_3$: C, 65.85; H, 7.60; N, 14.40; Cl, 12.15. Found: C, 65.55; H, 7.70; N, 14.25; Cl, 12.50.

3-[4-(2-Hydroxyethyl)piperazino]-7,8-dimethylisoquinoline (**9i**).

This compound was obtained in 52% yield as yellow crystals, mp 108-110°; nmr (deuteriochloroform): 2.40 (s, 3H), 2.58 (s, 3H), 2.5-2.9 (m, 7H), 3.5-3.8 (m, 6H), 6.73 (s, 1H), 7.32 (s, 2H), 9.18 (s, 1H); ms: (m/e) 285 (M^+), 270, 254, 225, 211, 185, 172, 157, 101; **9i**-malenate, mp 126-128°.

Anal. Calcd. for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6.78; N, 10.47. Found: C, 62.55; H, 6.80; N, 10.30.

3-(4-Ethoxycarbonylpiperazino)-7,8-dimethylisoquinoline (**9j**).

This compound was obtained in 39% yield, mp 77-80°; nmr (deuteriochloroform): 1.25 (t, J = 7 Hz, 3H), 2.40 (s, 3H), 2.59 (s, 3H), 2.5-2.7 (m, 8H), 4.14 (q, J = 7 Hz, 2H), 6.73 (s, 1H), 7.33 (s, 2H), 9.17 (s, 1H); ms: (m/e) 313 (M^+), 298, 268, 240, 211, 197, 185, 172, 157; **9j**-oxalate (salt with 1.5 equivalents of oxalic acid), mp 154-155°.

Anal. Calcd. for $C_{21}H_{26}N_3O_8$: C, 56.24; H, 5.84; N, 9.37. Found: C, 56.15; H, 5.90; N, 9.20.

7,8-Dimethyl-3-piperidinoisoquinoline (**9k**).

This compound was obtained in 48% yield, mp 72-75°; nmr (deuteriochloroform): 1.6-1.9 (m, 6H), 2.40 (s, 3H), 2.58 (s, 3H), 3.4-3.7 (m, 4H), 6.71 (s, 1H), 7.28 (s, 2H), 9.17 (s, 1H); ms: (m/e) 240 (M^+), 225, 211, 197, 172, 157, 84; **9k**-hydrochloride, mp 196-205°.

Anal. Calcd. for $C_{16}H_{21}ClN_2$: C, 69.42; H, 7.65; N, 10.12; Cl, 12.81. Found: C, 69.12; H, 7.65; N, 9.75; Cl, 13.04.

3-[2-(Dimethylamino)ethylamino]-7,8-dimethylisoquinoline (**9l**).

This compound was obtained in 37% yield; nmr (deuteriochloroform): 2.33 (s, 6H), 2.38 (s, 3H), 2.57 (s, 3H), 2.3-4.0 (m, 5H), 6.50 (s, 1H), 7.28 (s, 2H), 9.05 (s, 1H); ms: (m/e) 243 (M^+), 199, 185, 172, 157, 156, 145, 58; **9l**-dioxalate, mp 182-184°.

Anal. Calcd. for $C_{15}H_{25}N_3O_8$: C, 53.90; H, 5.95; N, 9.92. Found: C, 53.52; H, 6.01; N, 9.78.

3-Homopiperazino-7,8-dimethylisoquinoline (**9m**).

This compound was obtained in 47% yield; nmr (deuteriochloroform): 2.03 (m, 2H), 2.39 (s, 3H), 2.58 (s, 3H), 2.7-4.0 (m, 9H), 6.55 (s, 1H), 7.27 (s, 2H), 9.11 (s, 1H); ms: (m/e) 255 (M^+), 240, 225, 213, 211, 199, 186, 173, 157; **9m**-hydrochloride, mp 184°.

Anal. Calcd. for $C_{16}H_{22}ClN_3$: C, 65.85; H, 7.60; N, 14.40; Cl, 12.15. Found; C, 65.66; H, 7.52; N, 14.21; Cl, 12.50.

Acknowledgements.

Acknowledgement is made to S. Granata, M. Metz and P. Seufert for conducting most of the experiments, to Dr. H.-W. Fehlhaber for supplying the spectra and to Dr. F. Hein for performing the gc analysis. Fa. Riedel-de Haen supported us by performing one reaction in anhydrous hydrogen fluoride.

REFERENCES AND NOTES

[1] M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, 1972.

[2a] "Drugs of the Future", **1**, 72 (1976); [b] I. Hoffmann, *Int. Pharmacopsychiatry,* **17**, Supplement 1, 4 (1982); [c] S. Fielding and M. R. Szewczak, *J. Clin. Psychiatry,* **45**/4 II, 12 (1984).

[3a] H. J. Kruse, E. Konz, H. Geyer, U. Schacht and M. Leven, 8th IUPHAR Congress, Tokyo, July 19-24, 1981, *Abstr.,* 527, p 383; [b] H. J. Kruse, F. J. Hock, U. Schacht and E. Konz, 3rd World Congress of Biological Psychiatry, Stockholm, 28 June-3 July 1981, Abstr. **2**, Abstr. No. F 1034.

[4] F. J. Hock, H. J. Kruse, H. Gerhards and E. Konz, *Drug. Develop. Res.,* **6**, 301 (1985).

[5] G. Simchen and W. Krämer, *Chem. Ber.,* **102**, 3666 (1969).

[6a] S. Gabriel, *Ber.,* **19**, 1653, 2354 (1886); [b] R. D. Hawarth and S. Robinson, *J. Chem. Soc.,* 777 (1948).

[7] **4a**, [8] [9]; **4b**, [10] [11]; **4c**, [12] [13] [14]; **4d**, [14] [15] [16] [17]; **4e**, [14] [18] [19]; **4f**, [16] [17]; **4g**, [14] [20] [21]; **4h**, [22]; **4i**, [16] [23] [24]; **4j**, [16] [25].

[8] W. Herz and J. L. Rogers, *J. Am. Chem. Soc.,* **75**, 4498 (1953).

[9] Y. Nakada, Y. Yura and K. Murayama, *Bull. Chem. Soc. Japan,* **45**, 2243 (1972).

[10] T. Wagner-Jauregg, H. Arnold and F. Hüter, *Ber.,* **75**, 1293 (1942).

[11] S. Muravalli, *Bull. Soc. Chim. France,* 785 (1965).

[12] F. Mayer and P. Müller, *Ber.,* **60**, 2278 (1927).

[13] P. A. Plattner and J. Wyss, *Helv. Chim. Acta,* **24**, 483 (1941).

[14] G. Baddeley, G. Holt and S. M. Makar, *J. Chem. Soc.,* 3289 (1952).

[15] R. T. Arnold and P. N. Craig, *J. Am. Chem. Soc.,* **70**, 2791 (1948).

[16] R. Granger, H. Orzalesi and A. Muratelle, *Compt. Rend. Acad. Sci.,* Ser. C, **252**, 1971 (1961).

[17] L. Fisnerova, B. Kakac, O. Nemecek, A. Simek and Z. J. Vejdelek, *Collect. Czech. Chem. Commun.,* **32**, 4082 (1967).

[18] R. G. Kadesch, *J. Am. Chem. Soc.,* **66**, 1207 (1944).

[19] W. von Bebenburg, G. Steinmetz and K. Thiele, *Chem. Z.,* **103**, 387 (1979).

[20] R. Criegee, F. Förg, H.-A. Brune and D. Schönleber, *Chem. Ber.,* **97**, 3461 (1964).

[21] E. Marechal, P. Evrard and P. Sigwalt, *Bull. Soc. Chim. France,* 2049 (1968).

[22] P. T. Lansbury and N. R. Mancuso, *J. Am. Chem. Soc.,* **88**, 1205 (1966).

[23] R. T. Arnold and R. A. Barnes, *J. Am. Chem. Soc.,* **66**, 960 (1944).

[24] R. T. Arnold and E. Rondestvest, *J. Am. Chem. Soc.,* **67**, 1265 (1945).

[25] G. Darzens and A. Lévy, *Compt. Rend. Acad. Sci.,* **201**, 902 (1935).

[26] N. J. Mc Corkindale, A. W. Mc Culloch, D. S. Magrill, B. Caddy, M. Martin-Smith, S. J. Smith and J. B. Stenlake, *Tetrahedron,* **25**, 5475 (1969).

[27] T. Matsumoto and K. Hata, *J. Am. Chem. Soc.,* **79**, 5506 (1957).

[28] O. Brunner, H. Hofer and R. Stein, *Monatsh. Chem.,* **63**, 79 (1933).