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ALKYLATION OF THE ISOQUINOLINE SKELETON IN THE 1-POSITION

LITHIATED 2-PIVALOYL- AND 2-BIS(DIMETHYLAMINO)-PHOSPHINOYL-1,2,3,4-TETRAHYDROISOQUINOLINES[1,2]

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Abstract—Nucleophilic reactivity in the 1-position of 1,2,3,4-tetrahydroisoquinoline is generated by lithiation of the N-pivaloyl- (**16a**) and N-phosphinoyl-derivatives (**17a**). The organolithium compounds (**16b**, **17b**) thus obtained are highly nucleophilic and can be alkylated even with poor alkylating reagents such as secondary halides, neopentyl bromide and cyclopentanone. Hydrolysis of the phosphorylamide products with hydrochloric acid leads to 1-substituted tetrahydroisoquinolines in excellent yields (Table 2).

A. INTRODUCTION

The isoquinoline skeleton is part of a large group of alkaloids.[6] There are many classical methods by which this heterocycle can be constructed.[7] Especially attractive are those methods which introduce substituents R in the 1-position, because they enable the synthetic chemist to carry out convergent syntheses of the isoquinoline target molecules. The intrinsic acceptor or a^1-reactivity in the 1-position of isoquinolines which is enhanced by leaving groups such as Cl or CH_3SO_2[8] in the 1-position, or by quaternization of the nitrogen in the 2-position[9] has so far been exploited most often, see **1**.

Also, the attack of radicals is preferred in the 1-position and can be used for alkylations,[10] see **2**, while donor or d^1-reactivity as indicated in **3** can be called an umpolung[11] of the intrinsic reactivity **1** and must be generated by special tricks. The classical preparation of the isoquinoline nucleus for attack by electrophiles in the 1-position is the conversion to Reissert-compounds[12] which are deprotonated to anions **4**; a recent modification is provided by the introduction of a phosphonate group and generation of Li derivatives of **5** which undergo Horner-olefination with aldehydes.[13] The Stevens-rearrangement **6** was used for 1-benzylation of tetrahydroisoquinolines.[14] The least disguised form of a tetrahydroisoquinoline d^1-reagent **8** is thus far produced by Zn or electrochemical cathodic reduction of dihydroisoquinolinium salts **7** in the presence of benzylic bromides.[15]

In the course of our own work on the acidification of α-N–CH-groups[16] we became interested in applications of the newly developed methods to the syntheses of isoquinoline derivatives.[1,2,16,17] As with other secondary amines, the lithiation of the 1-position of tetrahydroisoquinolines is possible, and in this present case additionally favored by the benzylic activation, if groups A=B with a non-bonding lone pair on B are attached to the N atom, see **9**. In the absence of structural information about organolithium compounds of this general type—conclusions drawn from product configurations[18,19] are often misleading—we are not as sure as others[20,21] that a "dipole stabilization", see **10**, is responsible for the kinetics of their formation and/or for their thermodynamic stability.[22] In fact, the formula **9** with a Li,C-bond in the 1-position of the isoquinoline nucleus is justified only by the results of reactions, i.e. attack of electrophiles at

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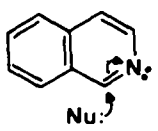

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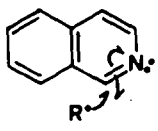

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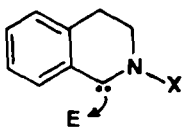

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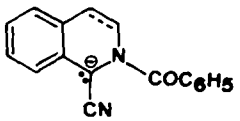

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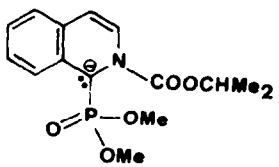

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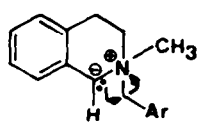

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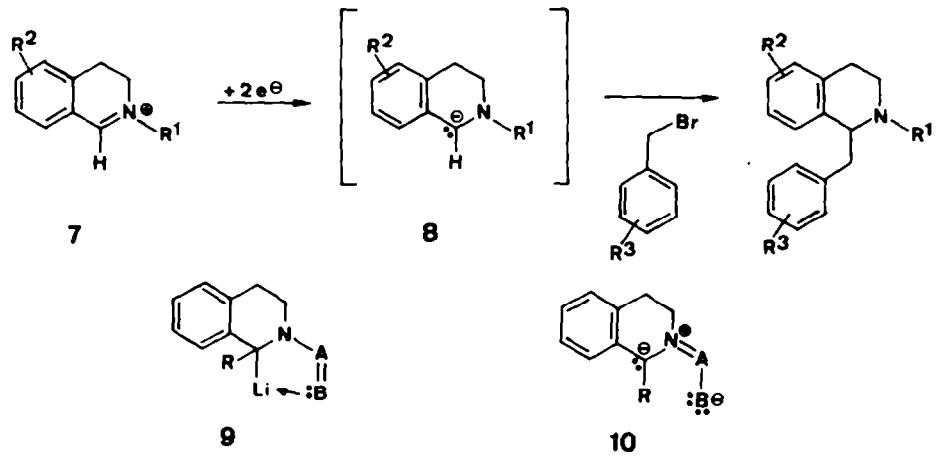
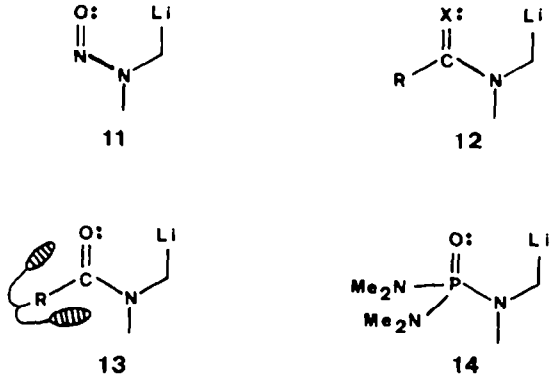


this position. Before discussing alkylations of isoquinolines, a brief evaluation and comparison of the different "activating" groups A=B is appropriate.

B. THE α-N-CH-ACTIVATORS

The A=B-group in **9**/**10** must have low enough electrophilicity and acidity, i.e. Lewis- and Broensted-acidity, so that it does not interfere with the metallation step. In Scheme 1 a list of suitable groups is assembled together with some leading references. The first one used in synthesis[31] was the nitroso group (see **11**) which withstands the lithium diisopropylamide (LDA) used for lithiation. For safety reasons, it was desirable to switch to amides, the carbonyl acceptor reactivity of which is reduced enough to prevent addition of the nucleophilic base. One way of achieving this reduction is to replace O by S or N (see **12**), another one is to sterically protect the C=O-group from attack (see **13**). Thiopivalamides and—most recently—formamidines are readily lithiated even by s-BuLi, the preferred metallating reagent for most of these reactions. The choice of the bulky substituents in **13** is dictated by the necessity that they be cleaved under mild conditions. Some examples are described in the equations (a)–(d) of Scheme 2. Thus, triphenylacetamides are metallated by s-BuLi to give **13**, R = $(H_5C_6)_3C$, their CO group is not attacked by this nucleophile; on the other hand, LAH and lithium triethylborohydride (superhydride ®) transfer a hydride to the carbonylcarbon which eventually leads to C–C bond cleavage with formation of triphenylmethane [see Eq (a) and (b) in Scheme 2]. In the tris-(t-butyl)phenyl-urethane of Eq (c), the CO group is protected from BuLi attack, the t-Bu groups are later stripped off by Friedel–Crafts-transalkylation, so that a mild hydrolysis becomes possible. The urea in Eq (d) of Scheme 2 fragments with formation of acetone in a retro-Mannich-reaction under the acidic conditions of the ethylene glycol acetal hydrolysis. Finally, hexamethylphosphoramide (HMPT) can be lithiated to give **14**, the products of which with electrophiles can be hydrolyzed.

Inspection of the list of "activating" groups in Scheme 1 reveals, that they all possess a heteroatom with lone-pair(s) in a position to form an internal, 5-membered chelate with the Li-atom, see **9**, which is reminiscent of the "chelation controlled orthometallation" or aromatic systems.[32]

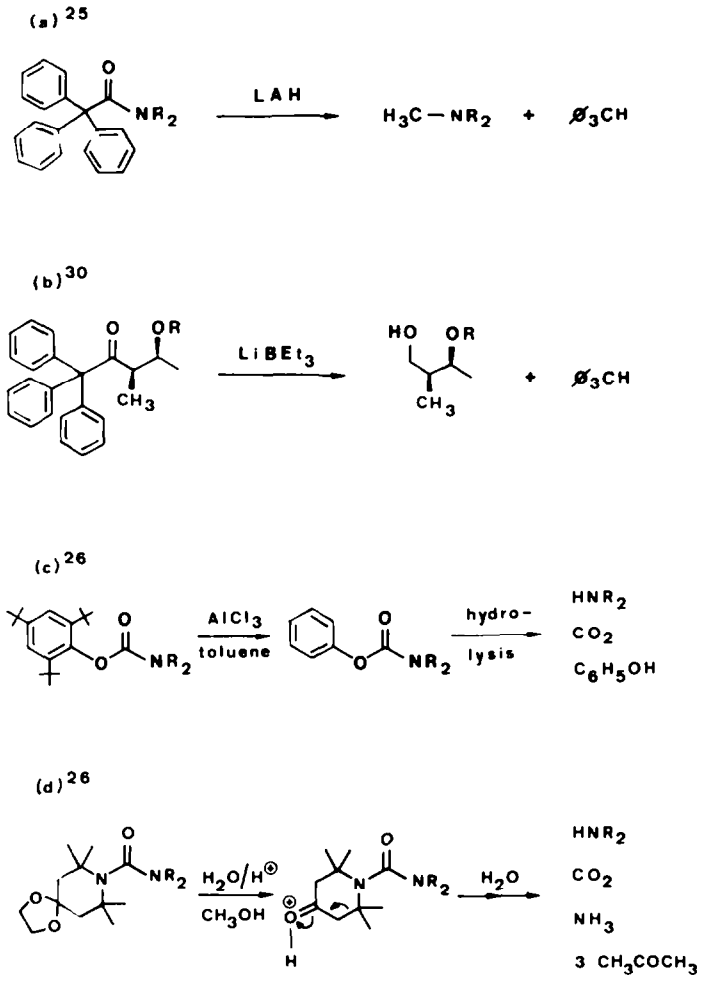


11: Ref. 16, 17*a–c*, 18
12, R = t-C_4H_9/X = S: Ref. 23
12, R = H/X = N(t-C_4H_9): Ref. 24
12, R = H/X = N(C_6H_{11}): Ref. 24
13, R = $(H_3C)_3C$: Ref. 23
13, R = $(H_3C_2)_3C$: Ref. 21
13, R = $(H_3C)_2(LiO)C$: Ref. 1
13, R = $(H_5C_6)_3C$: Ref. 25
13, R = 2.4.6-$[(H_3C)_2CH]_3C_6H_2$: Ref. 20, 25
13, R = 2.4.6-$[(H_3C)_3C]_3C_6H_2O$: Ref. 26
13, R = 2,2,6,6-$(H_3C)_4$-4-(OCH_2CH_2O)-piperidyl: Ref. 26
14: Ref. 27–29

Scheme 1.

C. LITHIATION AND ALKYLATIONS OF 2-PIVALOYL- AND 2-BIS(DIMETHYLAMINO)-PHOSPHINOYL-1,2,3,4-TETRAHYDROISOQUINOLINE

Earlier attempts with the carcinogenic nitrosamine,[16,17a-c] with the triphenylacetamide,[17d,25] and with a urea[26] derived from tetrahydroisoquinoline **15a** revealed that lithiation is facile due to benzylic activation, but also that the resulting reagents of type **13** with the bulky acyl groups were not nucleophilic enough for preparative purposes. During screenings of less hindered amides[33] we found that the pivalamide **16a** gave a highly nucleophilic reagent **16b**. As usual, the optimum conditions for metallation were found by deuterolysis to **16c**. The Li-derivative **16b** is generated with t-BuLi/tetramethylethylenediamine (TMEDA) in tetrahydrofuran (THF) at −78°, it forms an orange-red solution, the color of which can be used as an indicator in reactions with

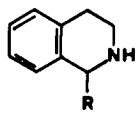


Scheme 2.

electrophiles. The nucleophilicity of **16b** is evident from the following observations: iodo-, bromo- and chloro-octane all react (→**16f**) at −78° with decolorization within two, two, and 24 hr, respectively; 2-iodopropane and iodocyclohexane alkylate **16b** in yields of 90% within 2 hr at −78° (→**16k,l**); addition to cyclopentanone, a most readily deprotonated ketone occurs with 75% yield (→**16n**). In view of this unusual nucleophilicity, the methylation (→**16d**), benzylation (→**16j**), silylation (→**16p**), stannylation (→**16q**), and addition to benzophenone (→**16o**) are not surprizing. Reactions, in which more than one diastereomer can be formed, will be described in a subsequent paper. A second alkylation leading for instance to the 1,1-dimethyl-derivative **18**, is also possible.

It will become obvious from the discussion in the following chapter that the cleavage of the pivalamides **16** to the parent tetrahydroisoquinolines **15** is difficult. We therefore also tested the phosphorylamides **17** (*cf.* **14** above).[34]

The parent P-amide **17a** is readily available from the amine **15a** and the corresponding acid chloride, both of which are commercially available. Metallation to **17b** was found to be essentially quantitative (>95% **17c** by ^{1}H-NMR) at −78° with n-BuLi in THF. The deep-red solutions of **17b** are stable even at room temperature for prolonged periods of time. All electrophiles tested so far caused decolorization within a few hours at −78°, only neopentyl bromide took several days at +25°. Of the methylating reagents iodomethane, dimethylsulfate and methyl tosylate, the last one produced **17d** (66, 69 and 87%, respectively) in the best yield. From the yields of reactions with 2-iodopropane (→**17k**), with iodocyclohexane (→**17l**), with neopentylbromide (→**17g**), and with cyclopentanone (→**17n**) a somewhat larger basicity of the phosphorus derivative **17b** as compared with the lithiated pivalamide **16b** can be deduced. The high yields of butylation (→**17e**), allylation (→**17h**), benzylation (→**17i**), and addition to benzophenone (→**17o**) are again not surprizing. Phenylation with benzene chromium tricarbonyl furnishes **17m** in 45% yield. The 1,1-dialkylated derivatives **19d** and **19e** could be prepared in only moderate yields of 20 and 40%, respectively. According to deuterolyses (→**19c**), an only 65% metallation of the monomethylated phosphorylamide **19a** to the Li derivative **19b** was achieved.[35] Again, all reactions of the Li-compounds **17b** and **19b** which can lead to



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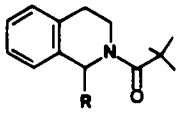

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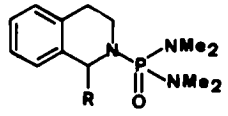
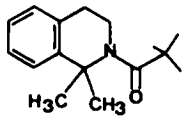


17

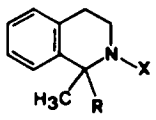
15/16/17	
a	H
b	Li
c	D
d	CH_3
e	C_4H_9
f	C_8H_{17}
g	CH_2-$C(CH_3)_3$
h	CH_2-$CH{=}CH_2$
i	CH_2-C_6H_5
j	CH_2-C_6H_3(3,4-OCH_2O) (3,4-methylenedioxybenzyl)

15/16/17	
k	$CH(CH_3)_2$
l	C_6H_{11}(cyclohexyl)
m	C_6H_5
n	$(CH_2)_4C(OH)$(hydroxy-cyclopentyl)
o	$(H_5C_6)_2C(OH)$(hydroxy--benzhydryl)
p	$Si(CH_3)_3$
q	$Sn(C_4H_9)_3$



18

19



19 a: X = $PO(NMe_2)_2$, R = H
b: X = $PO(NMe_2)_2$, R = Li
c: X = $PO(NMe_2)_2$, R = D
d: X = $PO(NMe_2)_2$, R = CH_3
e: X = $PO(NMe_2)_2$, R = $CH_2C_6H_5$
f: X = H, R = CH_3
g: X = H, R = $CH_2C_6H_5$

diastereomeric mixtures of products, such as the addition to aldehydes and the dimerization, will be described separately.

D. CLEAVAGES OF PIVALAMIDES 16 AND OF PHOSPHORYLAMIDES 17, 19 TO TETRAHYDROISOQUINOLINES 15

A comparison of the two d^1-reagents **16b** and **17b** derived from tetrahydroisoquinoline so far favors the pivaloyl derivative: pivaloyl chloride is less expensive than the phosphoric acid chloride, the pivaloyl group has a lower molecular weight (85 vs 135), and the lithiated carboxamide **16b** is more nucleophilic than the phosphoric amide **17b**; the latter one has the only definite advantage of being generated by the most common and most readily available lithiating reagent n-BuLi. The situation is however reversed, at least at the present stage of our investigations, if the cleavage step is included into the consideration and comparison: We have not been able to find a general and reliable method of cleaving the pivalamides **16**. Neither alkaline nor acidic aqueous hydrolysis, nor aminolysis with primary amines were successful. Reductive cleavages furnish mixtures of the N–H and N-neopentyl tetrahydroisoquinolines. A set of experiments demonstrating the subtle dependence of the ratio of these two amines from the particular conditions in the case of reduction with sodium bis-(methoxyethoxy)aluminum dihydride (vitride ®) is shown in the accompanying Table 1. In contrast, both the mono- and disubstituted phosphorus derivatives **17** and **19** are hydrolyzed quite readily and in high yields by aqueous, methanolic, or ethanolic hydrochloric acid, see Table 2.

Table 1. Reduction of the pivalamide **16a** with $NaAlH_2(OCH_2CH_2OCH_3)_2$ to a mixture of the 1,2,3,4-tetrahydroisoquinoline **15a** (A) and of the *N*-neopentyl derivative (B) [2-(2,2-dimethylpropyl)-1.2.3.4-tetrahydroisoquinoline] under various conditions. The reactions were run on a 2–5 mmolar scale (rt ≡ room temperature)

Equivalents $NaAlH_2(OCH_2CH_2OCH_3)_2$	Conditions: temp. [°C] / reaction time [hr]	Conditions: solvent; conc. of 16a [M/l]	Yield crude [%]	Ratio A : B
0.92	10 / 1.5 rflx. / 1	C_6H_6; 0.05	80	70:30
0.90	10 / 0.5 rflx. / 1	C_6H_6; 0.05	90	54:46
1.00	5 / 20	C_6H_6; 0.09	98	80:20
1.00	5 - rt / 20	C_6H_6; 0.03	83	87:13
1.00	5 - rt / 20	C_6H_6; 0.03	94	80:20
0.98	0-5 / 7	THF; 0.08	84	96:4
0.96	0-5 / 7	THF; 0.08	89	96:4
0.98	-48 - rt/ 22	THF; 0.10	86	88:12
0.97	-30 - rt/ 24	THF; 0.10	100	85:15
0.90	-20 - rt/ 20	THF; 0.10	95	90:10

Table 2. Acidic hydrolysis of phosphorylamides **17**, **19d** and **19e** to the corresponding amines **15**, **19f** and **19g** by refluxing in aqueous or alcoholic hydrochloric acid

Amide	Conditions: amount of amide [g]	Conditions: vol. 2 N HCl/MeOH [ml]	Conditions: reflux time [hr]	Amine	Yield [%]
17a	0.55	10/0	0.5	15a	90
17d	0.79	15/0	4	15d	93
17e	1.03	15/0	16	15e	84
17g	0.92	50/10	31	15g	75
17h	0.97	20/0	20	15h	75
17i	3.28	30/0	23	15i	76
17k	1.08	15/0	8	15k	83
17ℓ	0.88	40/25	49	15ℓ	66
17m	0.72	50/10	27	15m	79
17o	1.00	50/60 (EtOH)	5	15o	52
19d	0.32	35/10	40	19f	74
19e	0.79	55/25	41	19g	89

Our continuing investigations about the stereoselectivities of reactions of the two reagents **16b** and **17b** and of related compounds may uncover new facts which might eventually allow the full synthetic exploitation of the "supernucleophile"[36] **16b**.

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer 297 or 283 IR spectrometer. ^{1}H-NMR spectra were measured with Varian Associates EM-390 (90 MHz), AH-100 and XL-100 spectrometers and are reported in ppm from the internal standard TMS (on the δ scale). Data are listed in the following order: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad) and coupling constant (Hz). ^{13}C-NMR spectra were determined on a Varian CFT 20 spectrometer. Mass spectra were taken with a Hitachi Perkin–Elmer RMU-6 M spectrometer. M.p. were determined with a Büchi 510 m.p. apparatus and are uncorrected. B.ps correspond to the air bath temps for bulb-to-bulb distillations (Büchi GKR-50 or Custilator (Chemophor) for samples > 6 g).

The silica gel used for chromatography was silica gel 60 (E. Merck, 63-200 μm). Flash chromatography was carried out following the procedure of Still, Kahn and Mitra.[37]

THF was distilled from LAH under argon gas prior to use. TMEDA was distilled from LAH and stored over molecular sieves. n-BuLi, s-BuLi and t-BuLi were purchased from Metallgesellschaft AG and titrated before use. All metallation reactions were carried out under an atmosphere of argon.[38]

A. PREPARATION OF STARTING MATERIALS

2-Pivaloyl-1,2,3,4-tetrahydroisoquinoline **16a**. A soln of pivaloyl chloride (3.62 g; 30 mmol) in 40 ml ether was added dropwise at room temp to a mixture of **15a** (4.05 g; 30.4 mmol) and Et_3N (4.25 ml; 30.5 mmol) in 20 ml ether. After stirring for 24 hr at room temp, the white mixture was poured into water and extracted (3 ×) with CH_2Cl_2. The combined extracts were washed with 0.5 M HCl aq, water, 7% KOH aq, and water. Drying over $MgSO_4$ and concentration under reduced pressure gave a yellow solid. Recrystallization from hexane afforded **16a** (6.53 g; 91%), m.p. 65°. IR (CCl_4): 3060, 3020, 2970, 2930, 2910, 2870, 2840, 1635, 1585, 1500, 1480, 1450, 1415, 1390, 1365, 1335, 1295, 1285, 1255, 1195, 1110, 1055, 1040, 1030, 980, 935, 900, 835, 715, 695, 625 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.33 (s, 9 H, t-butyl); 2.80 (t, J = 6 Hz, 2 H, Ar–CH_2); 3.77 (t, J = 6 Hz, 2 H, –CH_2–N); 4.67 (s, 2 H, Ar–CH_2–N), 7.07 (s, 4 H, aromatic protons). MS *m/e*(%): 218 (M^+ + 1, 16); 217 (95); 202 (25); 174 (20); 161 (16); 160 (100); 142 (19); 132 (36); 117 (47); 116 (14); 104 (28); 103 (10); 79 (10); 41 (14); 29 (11). (Found: C, 77.23; H, 8.80; N, 6.44. $C_{14}H_{19}NO$ requires: C, 77.38; H, 8.81; N, 6.45%.)

2-Bis(dimethylamino)phosphinoyl-1, 2, 3, 4-tetrahydroisoquinoline (**17a**). A soln of bis(dimethylamino)phosphorochloridate (42.4 g; 0.24 mol) in 50 ml ether was added during 30 min to a mixture of **15a** (32.4 g; 0.24 mol) and Et_3N (34 ml; 0.24 mol) in 50 ml ether at room temp. After heating under reflux for 6 hr, the cooled suspension was filtered and concentrated under reduced pressure. The residue was dissolved in 500 ml ether, washed with brine (3 × 200 ml), and dried over $MgSO_4$. Distillation of the crude product[39] (72.5 g yellow oil) at 130°/0.005 torr from barium oxide afforded **17a** (59.4 g; 91%), as a colorless oil, which crystallized on standing (m.p. 40–42°). IR ($CHCl_3$): 3060, 2990, 2920, 2840, 2800, 1490, 1480, 1450, 1425, 1370, 1350, 1320, 1295, 1270, 1150, 1120, 1080, 1065, 1025, 980, 960 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.5–2.92 (m, 14 H, Ar–CH_2 + 2 × N(CH_3)$_2$); 3.27–3.52 (m, 2 H, –CH_2–N); 4.27 (d, J = 6 Hz, Ar–CH_2–N), 7.08 (s, 4 H, aromatic protons). MS *m/e*(%): 267 (M^+, 30), 223 (10), 222 (18), 178 (20), 149 (12), 135 (19), 133 (12), 132 (100), 131 (19), 130 (13), 104 (10), 92 (9), 45 (13), 44 (18). (Found: C, 58.39; H, 8.45; N, 15.49. $C_{13}H_{22}N_3OP$ requires: C, 58.41; H, 8.30; N, 15.72%).

B. METALLATION PROCEDURES

Procedure for the metallation of **16a**. To a cooled (–78°) soln of **16a** (1.74 g; 8 mmol) and TMEDA (1.2 ml; 8 mmol) in 50 ml THF was added 1.40 M t-BuLi in isopentane (6.0 ml; 8.4 mmol). The resulting deep-red soln was stirred for 20 min at –78° before addition of the electrophile (solids dissolved in a small amount of THF). After stirring (as described later), the solution was hydrolysed with water (or a soln of AcOH in THF) and warmed to room temp. The mixture was poured into water and extracted with CH_2Cl_2 (3 × 25 ml). The combined organic phases were washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude products, which were purified by one or a combination of chromatography, recrystallization, and distillation.

Procedure for the metallation of **17a**. To a cooled (–78°) soln of **17a** (2.76 g; 10 mmol) in 30 ml THF was added 1.49 M n-BuLi (7.5 ml; 11.2 mmol). The wine-red soln was stirred for 1 hr before addition of the electrophile. The soln was hydrolyzed with water (1–2 ml). Three work-up procedures were used:

Method A. The solvent was removed and the residue was partitioned between 300 ml ether and 75 ml brine. The organic phase was separated, washed with 75 ml brine, and dried over $MgSO_4$. Evaporation of the solvent afforded the crude products.

Method B. The solvent was removed and the residue partitioned between 400 ml dichloromethane and 100 ml brine. The organic layer was separated, washed with 100 ml brine, and dried over $MgSO_4$. Concentration under reduced pressure gave the crude products.

Method C. The mixture was diluted with 400 ml ether, washed with brine (3 × 10 ml), dried over $MgSO_4$, and concentrated under reduced pressure to give the crude products.

C. REACTIONS OF 1-LITHIO-2-PIVALOYLTETRAHYDROISOQUINOLINE (16b)

1-Methyl-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**16d**). A soln of **16a** (8.0 mmol) was metallated (as described before) and MeI (0.62 ml; 10 mmol) was added. After stirring for 15 min at –78° the mixture was worked up. Distillation of the crude product (1.92 g) at 115°/0.02 torr afforded **16d** (1.74 g; 94%), as an oil, which crystallized on standing (m.p. 66°). IR (CCl_4): 3065, 3025, 2980, 2930, 2905, 2875, 2840, 1630, 1585, 1495, 1480, 1445, 1430, 1415, 1395, 1370, 1365, 1325, 1300, 1295, 1280, 1225, 1210, 1195, 1180, 1165, 1115, 1080, 1065, 1050, 1040, 1035, 1025, 980, 945, 930, 895, 875, 690, 625 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.33 (s, 9 H, t-butyl); 1.47 (d, J = 7 Hz, 3 H, CH_3); 2.56–3.55 (m, 3 H) and 4.37 (br d, J = 4 Hz, 1 H) (–CH_2–CH_2–); 5.60 (q, J = 7 Hz, 1 H, HC–N); 7.14 (s, 4 H, aromatic protons). MS *m/e* (%): 231 (M^+, 14); 216 (100), 132 (6), 131 (7), 130 (6), 57 (12), 41 (8). (Found: C, 77.78; H, 9.21; N, 6.02. $C_{15}H_{21}NO$ requires: C, 77.88; H, 9.15; N, 6.05%).

1-Octyl-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**16f**)

(a) A soln of **16a** (8.0 mmol) was metallated and n-octyl iodide (1.52 ml; 8.42 mmol) was added. After stirring for 2 hr at –78° the reaction was worked up by the usual method. Bulb-to-bulb distillation of the crude oil (2.8 g) at 180°/0.02 torr gave **16f** (2.27 g; 86%), as a solid (m.p. 40°). IR (CCl_4): 3065, 3015, 2960, 2930, 2875, 2860, 1635, 1585, 1495, 1480, 1470, 1455, 1415, 1395, 1370, 1345, 1325, 1295, 1280, 1205, 1195, 1175, 1165, 1115, 1040, 1025, 945, 935, 845, 690, 650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.33 (s, 9 H, t-butyl); 1.20–1.97 (br m, 17 H, n-C_8H_{17}); 2.56–3.70 (m, 3 H) and 4.30 (m, 1 H), (–CH_2–CH_2–N); 5.67 (t, J = 7 Hz, 1 H, CH–N); 7.16 (br s, 4 H, aromatic protons). MS *m/e* (%): 329 (M^+, 3), 217 (16), 216 (100), 132 (27), 85 (11), 57 (46).

(Found: C, 80.06; H, 10.75; N, 4.16. $C_{22}H_{35}NO$ requires: C, 80.19; H, 10.70; N, 4.25%).

(b) A soln of **16a** (8.0 mmol) was metallated and n-octyl bromide (1.46 ml; 8.41 mmol) was added. The mixture was stirred for 2 hr at −78° and left overnight to warm to room temp. Usual work-up and recrystallization from pentane afforded **16f** (2.25 g; 85%).

(c) A soln of **16a** (8.0 mmol) was metallated and n-octyl chloride (1.43 ml; 8.41 mmol) was added. After stirring at −78° for 2 hr, the soln was warmed to room temp. overnight and stirred for 24 hr. The crude product was purified by distillation and subsequent recrystallization to give **16f** (2.25 g; 85%).

1-*Piperonyl*-2-*pivaloyl*-1,2,3,4-*tetrahydroisoquinoline* (**16j**)

A soln of **16a** (8.0 mmol) was metallated and piperonyl bromide (1.78 g; 8.27 mmol) was added. The soln was stirred for 12 hr at −78°, warmed and kept for 60 hr at 3°. Usual work-up gave a yellow oil which was triturated with ether–pentane (1:1). The residue was collected (1.45 g) and the soln was concentrated. Chromatography of the resulting oil on 40 g silica gel with ether–pentane (1:1) afforded 1.05 g crystals, which were combined with the residue of trituration. Recrystallization from MeOH–hexane (1:1) gave **16j** (2.17 g; 77%), as colorless crystals (m.p. 101°). IR (CCl_4): 3065, 3020, 2970, 2930, 2900, 2880, 2840, 2770, 1630, 1580, 1505, 1490, 1445, 1415, 1395, 1365, 1335, 1320, 1280, 1245, 1190, 1175, 1165, 1120, 1110, 1095, 1045, 970, 945, 935, 925, 875, 855, 670 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.26 (s, 9 H, t-butyl); 2.50–3.58 (m, 3 H) and 4.00–4.33 (m, 1 H) ($-CH_2-CH_2-N$); 3.03 (d, J = 7 Hz, 2 H, CH_2–Ar), 5.78 (t, J = 7 Hz, 1 H, CH–N); 5.91 (s, 2 H, $-O-CH_2-O$); 6.40–7.28 (m, 7 H, aromatic protons). MS *m/e* (%): 352 ($M^+ + 1$, 2), 350 (3), 217 (50), 216 (100), 135 (33), 133 (15), 132 (63), 131 (11), 130 (17), 117 (11), 105 (12), 77 (20), 58 (11), 57 (70), 41 (14). (Found: C, 75.07; H, 7.24; N, 3.90. $C_{22}H_{25}NO_3$ requires: C, 75.19; H, 7.17; N, 3.99%).

1-*Isopropyl*-2-*pivaloyl*-1,2,3,4-*tetrahydroisoquinoline* (**16k**)

A soln of **16a** (8.0 mmol) was metallated and isopropyl iodide (0.84 ml; 8.40 mmol) was added. After stirring for 2 hr at −78°, the mixture was worked up as described. Distillation of the crude oil (2.12 g) at 130°/0.01 torr afforded a solid which was purified by sublimation to give **16k** (1.87 g; 90%), as colorless crystals (m.p. 71°). IR (CCl_4): 3060, 3020, 2965, 2930, 2910, 2875, 2840, 1630, 1580, 1490, 1475, 1450, 1415, 1385, 1365, 1310, 1295, 1255, 1205, 1190, 1180, 1165, 1120, 1115, 945, 935, 905, 855, 640 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 0.98 (d, J = 7 Hz, 6 H, $C(CH_3)_2$); 1.31 (s, 9 H, t-butyl); 1.73–2.27 (m, 1 H, $HC(CH_3)_2$; 2.60–3.80 (m, 3 H) and 4.31 (br d, 1 H) ($-CH_2-CH_2-N$); 5.29 (d, J = 9 Hz, 1 H, HC–N); 7.13 (s, 4 H, aromatic protons). MS *m/e* (%): 217 (17), 216 (100), 132 (53), 131 (8), 130 (11), 117 (8), 85 (17), 57 (77), 41 (10). (Found: C, 78.73, H, 9.67; N, 5.37. $C_{17}H_{25}NO$ requires: C, 78.72; H, 9.71; N, 5.40%).

1-*Cyclohexyl*-2-*pivaloyl*-1,2,3,4-*tetrahydroisoquinoline* (**16l**)

A soln of **16a** (8.0 mmol) was metallated and cyclohexyl iodide (1.08 ml; 8.35 mmol) was added. After stirring for 2 hr at −78° the reaction was worked up by the normal method. The crude solid (2.52 g) was sublimed (oil bath temp. 115°/0.02 torr) to yield **16l** (2.14 g; 89%), as colorless crystals (m.p. 125°). IR (CCl_4): 3065, 3025, 2975, 2935, 2895, 1630, 1580, 1475, 1450, 1415, 1370, 1350, 1325, 1305, 1295, 1270, 1205, 1195, 1180, 1165, 1130, 1110, 1080, 1045, 1025, 965, 945, 930, 895, 850, 705, 640 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 0.77–2.00 (m, 11 H, H-cyclohexyl); 1.30 (s, 9 H, t-butyl); 2.60–3.86 (m, 3 H) and 4.10–4.51 (m, 1 H) ($-CH_2-CH_2-N$); 5.30 (d, J = 8 Hz, 1 H, CH–N); 7.10 (s, 4 H, aromatic protons). MS *m/e* (%): 298 ($M^+ - 1$,3), 217 (30), 216 (100), 132 (52), 131 (11), 130 (12), 117 (9), 85 (18), 57 (55), 41 (12). (Found: C, 80.11; H, 9.72; N, 4.61. $C_{20}H_{29}NO$ requires: C, 80.22; H, 9.76; N, 4.68%).

1-(α-*Hydroxycyclopentyl*)-2-*pivaloyl*-1,2,3,4-*tetrahydroisoquinoline* (**16n**)

A soln of **16a** (8.0 mmol) was metallated and cyclopentanone (0.80 ml; 9.04 mmol) was added during 5 min. After stirring for 1.5 hr at −78° the mixture was warmed to room temp. (during 30 min), cooled to −78° and worked up. The crude product (2.42 g) contained a small amount of **16a** (4%) and was purified by recrystallization from hexane to give **16n** (1.82 g; 75%), as colorless crystals (m.p. 131.5°). IR (CCl_4): 3590, 3530, 3430, 3065, 3025, 2970, 2875, 2840, 1625, 1580, 1495, 1475, 1450, 1415, 1375, 1365, 1350, 1325, 1310, 1295, 1265, 1205, 1195, 1180, 1165, 1115, 1085, 1050, 1025, 1000, 925, 910, 875, 850, 690, 670 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.16 (s, 1 H, OH), 1.40 (s, 9 H, t-butyl), 1.56–2.19 (br, s, 8 H, $-(CH_2)_4-$), 2.67–3.31 (m, 3 H) and 4.16–4.37 (m, 1 H) ($-CH_2-CH_2-N$), 5.87 (s, 1 H, –HC–N), 7.16–7.46 (m, 4 H, aromatic protons). MS *m/e* (%): 283 (4), 218 (16), 217 (100), 216 (53), 202 (11), 162 (25), 133 (11), 132 (82), 131 (11), 130 (17), 117 (25), 85 (12), 57 (91), 41 (24), 29 (13). (Found: C, 75.71; H, 9.06; N, 4.64. $C_{19}H_{28}NO_2$ requires: C, 75.46; H, 9.33; N, 4.63%).

1-(α-*Hydroxybenzhydryl*)-2-*pivaloyl*-1,2,3,4-*tetrahydroisoquinoline* (**16o**)

A soln of **16a** (8.0 mmol) was metallated and benzophenone (1.51 g; 8.29 mmol) in 5 ml THF was added. The mixture was stirred for 3 hr at −78° and worked up. Recrystallization of the crude product (3.2 g) from hexane afforded **16o** (2.65 g; 83%), as a solid (m.p. 181.5°). IR (CCl_4): 3570, 3060, 3020, 2980, 2930, 1625, 1600, 1495, 1480, 1450, 1415, 1375, 1365, 1335, 1320, 1205, 1180, 1160, 1115, 1055, 1045, 1035, 1000, 975, 955, 895, 875, 845, 695, 660, 645, 630 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 0.98 (s, 9 H, t-butyl), 2.10 (s, 1 H, OH), 2.68–3.24 (m, 2 H) and 3.70–4.30 (m, 2 H) (CH_2-CH_2-N), 6.51–8.00 (m, 15 H, –CH–N and aromatic protons). MS *m/e* (%): 400 ($M^+ + 1$, 3), 382 (11), 296 (14), 218 (26), 217 (87), 216 (100), 183 (17), 133 (16), 132 (69), 131 (21), 130 (25), 117 (22), 105 (54), 103 (10), 85 (41), 77 (43), 58 (11), 57 (77), 41 (18), 29 (11). (Found: C, 81.00; H, 7.30; N, 3.51. $C_{27}H_{29}NO_2$ requires: C, 81.17; H, 7.32; N, 3.51%).

1-*Trimethylsilyl*-2-*pivaloyl*-1,2,3,4-*tetrahydroisoquinoline* (**16p**)

A soln of **16a** (8.0 mmol) was metallated and trimethylsilylchloride (1.15 ml; 9.06 mmol) was added. The mixture was stirred for 3 hr at −78°, warmed to room temp. and hydrolyzed. Recrystallization of the crude product (2.34 g) from hexane afforded **16p** (2.06 g; 88%), as colorless crystals (m.p. 111°). IR (CCl_4): 3060, 3020, 2970, 2960, 2930, 2900, 2880, 2840, 1620, 1580, 1495, 1480, 1450, 1415, 1380, 1355, 1345, 1305, 1295, 1280, 1260, 1250, 1205, 1180, 1110, 1045, 1025, 995, 955, 935, 860, 840, 695, 625, 610 cm^{-1}. ^1H-NMR (CCl_4 without TMS): δ0 [s, 9 H, $-Si(CH_3)_3$], 1.25 (s, 9 H, t-butyl), 2.40–3.63 (m, 3 H) and 4.10–4.45 (m, 1 H) ($-CH_2-CH_2-N$), 5.29 (s, 1 H, –HC–N), 6.79–7.20 (m, 4 H, aromatic protons). MS *m/e* (%): 289 (M^+, 45), 274 (31), 246 (10), 216 (10), 204 (35), 132 (36), 130 (14), 117 (42), 116 (12), 101 (13), 77 (100), 57 (56), 45 (11), 41 (13), 29 (10). (Found: C, 70.56; H, 9.36; N, 4.81. $C_{17}H_{27}NOSi$ requires: C, 70.53; H, 9.40; N, 4.84%).

1-(*Tri-n-butylstannio*)-2-*pivaloyl*-1,2,3,4-*tetrahydroisoquinoline* (**16q**)

A soln of **16a** (8.0 mmol) was metallated and tri-n-butyltinchloride (2.78 ml; 10.25 mmol) was added. After stirring for 1 hr at −78° the mixture was worked up. The crude product (4.63 g) was a mixture of tri-n-butyltinchloride and **16q**. Distillation at 210°/0.01 torr gave **16q** (3.42 g, 84%), as a pale-yellow oil. IR (CCl_4): 2960, 2930, 2870, 2850, 1675, 1615, 1605, 1580, 1490, 1480, 1465, 1455, 1410, 1375, 1365, 1355, 1340, 1325, 1305, 1280, 1225, 1205, 1175, 1115, 1075, 1040, 1025, 990, 960, 950, 925, 875, 860 cm^{-1}. ^1H-NMR ($CDCl_3$): 0.34–1.60 [m, 27 H, Sn(n-butyl)$_3$], 1.31 (s, 9 H, t-butyl), 2.46–4.29 (m, 4 H,

$-CH_2-CH_2-N$), 5.45 (br s, 1 H, Sn–CH–N), 6.71–7.25 (m, 4 H, aromatic protons). MS *m/e* (%): 507 ($M^+ + 1$, 2), 450 (36), 449 (16), 448 (27), 447 (11), 446 (16), 339 (13), 337 (11), 336 (11), 335 (67), 334 (27), 333 (50), 332 (21), 331 (30), 313 (13), 311 (10), 291 (19), 289 (14), 235 (15), 233 (15), 221 (16), 216 (13), 217 (30), 216 (100), 179 (24), 177 (36), 176 (13), 175 (23), 147 (10), 132 (57), 131 (30), 130 (24), 121 (16), 119 (15), 118 (13), 117 (11), 85 (25), 57 (74), 41 (32), 29 (24). (Found: C, 60.61; H, 9.03; N, 2.72. $C_{26}H_{45}NOSn$ requires: C, 61.67; H, 8.96; N, 2.77%).

D. METALLATION OF 1-METHYL-2-PIVALOYL-TETRAHYDROISOQUINOLINE (16d) AND ALKYLATION WITH IODOMETHANE TO GIVE 18

1,1-Dimethyl-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**18**)

To a cooled soln (−78°) of **16d** (0.53 g; 2.31 mmol) and TMEDA (0.5 ml; 3.33 mmol) in 20 ml THF was added 1.56 M t-BuLi (2.0 ml; 3.12 mmol). The mixture was stirred at −78° for 2 hr before addition of MeI (0.50 ml; 8.0 mmol). After stirring for 30 min the soln was warmed to room temp. and, after 2 hr, hydrolyzed. Separation of the crude product by flash chromatography with hexane–EtOAc (4:1) gave **18** (0.336 g; 59%; 94% with respect to **16d** used) and **16d** (0.205 g; 38%). Recrystallisation from pentane afforded **18** (m.p. 79–79.5°). ^{1}H-NMR ($CDCl_3$): δ 1.33 (s, 9 H, t-butyl), 1.80 (s, 6 H, 2 × CH_3), 2.85 (t, J = 6 Hz, 2 H, Ar–CH_2), 3.67 (t, J = 6 Hz, 2 H, –CH_2N), 7.0–7.4 (m, 4 H, aromatic protons). (Found: C, 78.22; H, 9.49; N, 5.68. $C_{16}H_{23}NO$ requires: C, 78.32; H, 9.45; N, 5.71%).

E. REACTIONS OF THE 1-LITHIO-2-PHOSPHINOYLTETRAHYDROISOQUINOLINE (17b)

2-Bis(dimethylamino) - 1 - methyl-1,2,3,4-tetrahydroisoquinoline (**17d**)

(a) A soln of **17a** (1.38 g; 5.2 mmol) in 50 ml THF was metallated and MeI (0.5 ml; 8 mmol) was added. After stirring for 2 hr at −80° the mixture was worked up (method A). Distillation of the crude product (1.37 g) at 130°/0.005 torr afforded **17d** (0.97 g; 66%) as a slight yellow oil. IR (Film): 3040, 2970, 2920, 2880, 2840, 2800, 1605, 1580, 1490, 1460, 1380, 1350, 2195, 1270, 1215, 1150, 1130, 1095, 1065, 1040, 1020, 990, 880, 820, 760, 750, 740, 710, 665 cm^{-1}. ^{1}H-NMR (CCl_4): δ 1.42 (*d*, *J* = 7 Hz, 3 H, –CH_3), 2.52, 2.57 (2d, J = 9 Hz) (12 H, 2 × $N(CH_3)_2$), 2.68–3.68 (m, 4 H, $-CH_2-CH_2$), 4.54 (pentalet, J = 7 Hz, 1 H, –CHN), 6.96 (s, 4 H, aromatic protons). MS *m/e* (%): 281 (M^+, 7), 267 (8), 266 (52), 236 (11), 146 (35), 145 (10), 135 (100), 132 (7), 130 (8), 92 (7), 45 (7), 44 (22). (Found: C, 59.81; H, 8.57; N, 14.86. $C_{14}H_{24}N_3OP$ requires: C, 59.77; H, 8.60; N, 14.94%).

(b) A soln of **17a** (4.1 g; 15.3 mmol) in 40 ml THF was metallated and Me_2SO_4 (1.8 ml; 19 mmol) was added. After stirring for 1 hr at −80° and warm to −10°, the reaction was worked up (method B). Distillation of the crude product (4.31 g) gave **17d** (2.95 g; 69%).

(c) A soln of **17a** (1.36 g; 5.1 mmol) in 50 ml THF was metallated before addition of methyl tosylate (1.37 g; 7.37 mmol) in 10 ml THF. The mixture was warmed to room temp. overnight and worked up (method C). Distillation of the crude product (1.7 g) gave **17d** (1.24 g; 87%).

2-Bis(dimethylamino)phosphinoyl - 1 - butyl - 1,2,3,4-tetrahydroisoquinoline (**17e**)

A soln of **17a** (1.35 g; 5.0 mmol) in 25 ml THF was metallated. After addition of n-BuCl (0.70 ml; 6.7 mmol), the mixture was stirred for 2 hr at −78° and warmed overnight to room temp. Usual work-up (method A) afforded the crude oil (1.58 g) which was purified by distillation at 165°/0.005 torr to give **17e** (1.40 g; 86%), as a pale-yellow oil. IR (Film): 3060, 3000, 2960, 2940, 2880, 2810, 1495, 1460, 1385, 1300, 1275, 1215, 1150, 1135, 1110, 1080, 995, 980, 950, 770, 745, 715, 675 cm^{-1}. ^{1}H-NMR (CCl_4): δ 0.8–1.04 (m, 3 H, –CH_3), 1.18–1.90 [m, 6 H, –$(CH_2)_3$–], 2.50 [d, J = 10 Hz, 6 H, $N(CH_3)_2$], 2.53 [d, J = 10 Hz, 6 H, $N(CH_3)_2$], 2.60–3.48 [m, 4 H, Ar–$(CH_2)_2$–N], 4.36 (br q, J = 8, 1 H, –CH–N), 6.97 (s, 4 H, aromatic protons). MS *m/e* (%): 323 (M^+, 3), 322 (7), 267 (17), 266 (100), 223 (6), 188 (5), 178 (8), 149 (5), 135 (80), 132 (5), 130 (8), 117 (4), 115 (4), 92 (6), 44 (11). (Found: C, 63.15; H, 9.39; N, 12.80. $C_{17}H_{30}N_3OP$ requires: C, 63.13; H, 9.35; N, 12.99%).

2-Bis(dimethylamino)phosphinoyl-1-neopentyl-1,2,3,4-tetrahydroisoquinoline (**17g**)

A soln of **17a** (2.90 g; 10.8 mmol) in 50 ml THF was metallated and neopentyl bromide (2.8 ml; 22 mmol) was added. After stirring for 4 days at room temp. the reaction was worked up (method B). Flash chromatography of the crude product (3.23 g) on silica gel (ether–MeOH 9:1) afforded **17g** (1.43 g; 39%), as a white solid (m.p. 65–67°).[40] Recrystallization of a sample from CH_2Cl_2/petroleum ether gave **17g** (m.p. 71–72.5°). IR ($CHCl_3$): 3060, 2960, 2800, 1620, 1480, 1460, 1380, 1360, 1295, 1260, 1120, 1085, 1065, 1050, 990, 980, 940 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.03 [s, 9 H, $C(CH_3)_3$], 1.4–2.0 (m, 2 H, CH_2–CH), 2.23–2.90 [m, 14 H, Ar–CH_2 and 2 × $N(CH_3)_2$], 3.17–3.60 (m, 2 H, CH_2–N), 4.6–5.0 (m, 1 H, CH–N), 7.1 (s, 4 H, aromatic protons). MS *m/e* (%): 337 (M^+, < 1), 267 (16), 266 (100), 223 (6), 135 (79), 132 (5), 130 (6), 92 (4), 44 (12). (Found: C, 64.00; H, 9.59; N, 12.40. $C_{18}H_{32}N_3OP$ requires: C, 64.07; H, 9.56; N, 12.45%).

2-Bis(dimethylamino)phosphinoyl-1-allyl-1,2,3,4-tetrahydroisoquinoline (**17h**)

A soln of **17a** (1.36 g; 5.1 mmol) in 25 ml THF was metallated and allyl chloride (0.60 ml; 7.4 mmol) was added. The mixture was stirred for 2 hr at −80°, warmed overnight to room temp. and worked up (method B). Bulb-to-bulb distillation of the crude product (1.51 g) at 155°/0.005 torr gave the pale-yellow oil **17h** (1.36 g; 87%). IR (Film): 3060, 3000, 2980, 2900, 2840, 2800, 1635, 1490, 1460, 1435, 1380, 1300, 1260, 1210, 1150, 1130, 1080, 1030, 980, 960, 910, 885, 820, 740, 670 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.3–3.6 [m, 18 H, Ar–$(CH_2)_2$–N, –CH_2–CH, 2 × $N(CH_3)_2$], 4.57 (q, J = 8 Hz, 1 H, CH–N), 4.8–5.16 (m, 2 H, H_2C=), 5.64–6.14 (m, 1 H, –HC=CH_2), 7.06 (s, 4 H, aromatic protons). MS *m/e* (%): 306 ($M^+ - 1$, 1), 267 (14), 266 (85), 223 (6), 178 (5), 136 (6), 135 (100), 132 (6), 130 (8), 92 (5), 44 (13). (Found: C, 62.61; H, 8.64; N, 13.57. $C_{16}H_{26}N_3OP$ requires: C, 62.52; H, 8.52; N, 13.67%).

2 - Bis(dimethylamino)phosphinoyl-1-benzyl-1,2,3,4-tetrahydroisoquinoline (**17i**)

A soln of **17a** (2.6 g; 9.7 mmol) in 100 ml THF was metallated and benzyl chloride (1.40 ml; 12.2 mmol) was added. After stirring for 2 hr at −78° the mixture was worked up (method A) to give crude **17i** (3.8 g; 100%) as a pale-yellow oil.[40] Purification of a sample by distillation at 165°/10^{-5} torr afforded the colourless oil **17i** in 91% yield. IR (CCl_4): 3060, 3020, 3000, 2920, 2890, 2840, 2800, 1600, 1490, 1450, 1380, 1295, 1270, 1260, 1210, 1145, 1125, 1085, 1070, 1025, 990, 975, 955, 940 cm^{-1}. ^{1}H-NMR (CCl_4): δ 2.41 [d, J = 9 Hz, 6 H, $N(CH_3)_2$), 2.47 (d, J = 9 Hz, 6 H, $N(CH_3)_2$], 2.6–3.45 (m, 6 H, Ar–CH_2– and –CH_2–CH_2–N), 4.7 (br q, J = 7 Hz, 1 H, CH–N), 6.43 [d, J = 8 Hz, 1 H, C(8)–H], 6.72–7.26 (m, 8 H, aromatic protons). MS *m/e* (%): 356 ($M^+ - 1$, < 1), 267 (18), 266 (85), 216 (16), 181 (15), 180 (15), 179 (16), 178 (16), 165 (9), 135 (100), 127 (20), 125 (61), 91 (80), 77 (10), 65 (8), 44 (13). (Found: C, 66.86; H, 8.05; N, 11.52. $C_{20}H_{28}N_3OP$ requires: C, 67.21; H, 7.90; N, 11.76%).

2-Bis(dimethylamino)phosphinoyl-1-isopropyl-1,2,3,4-tetrahydroisoquinoline (**17k**)

A soln of **17a** (1.35 g; 5.0 mmol) in 50 ml THF was metallated and isopropyl iodide (0.7 ml; 7 mmol) was added. The soln was stirred for 2 hr at −80°, warmed up to −20°, and hydrolyzed (method A). The crude product (1.42 g) was purified by distillation at 140°/0.001 torr to give a pale-yellow oil **17k** (1.2 g; 78%). IR (Film): 3060, 3020, 2980,

2930, 2880, 2850, 2800, 1600, 1490, 1460, 1385, 1375, 1300, 1215, 1180, 1140, 1115, 1080, 1040, 995, 980, 945, 910, 845, 770, 740, 680, 635 cm^{-1}. ^1H-NMR (CCl_4): δ 0.87 (d, J = 7 Hz, 3 H, $-CH_3$), 1.07 (d, J = 7 Hz, 3 H, $-CH_3$), 1.65–2.13 [m, 1 H, $-CH(CH_3)_2$], 2.3 [d, J = 9 Hz, 6 H, $N(CH_3)_2$], 2.54 [d, J = 9 Hz, 6 H, $N(CH_3)_2$], 2.67–2.92 (m, 2 H, Ar–CH_2–), 3.16–3.50 (m, 2 H, $-CH_2-N$), 4.05 (dxd, $J_1 \approx J_{PH} = 9$ Hz, 1 H, $-CH-N$), 6.97 (s, 4 H, aromatic protons). MS *m/e* (%): 309 (M^+, < 1), 267 (14), 266 (85), 223 (6), 178 (5), 136 (6), 135 (100), 132 (6), 131 (5), 130 (8), 92 (6), 44 (18).

2-Bis(dimethylamino)phosphinoyl-1-cyclohexyl-1,2,3,4-tetrahydroisoquinoline (**17l**)

A soln of **17a** (2.67 g; 10 mmol) in 30 ml THF was metallated and cyclohexyl iodide (1.7 ml; 13.1 mmol) was added. After stirring for 2 hr at −78° the soln was warmed overnight to room temp. and worked up (method B). Fractional distillation of the crude product (3.86 g) afforded **17a** (0.27 g; 10%) and a mixture (1.99 g; b.p. 160°/10^{-5} torr) of **17a** and **17l**. Flash chormatography (MeOH-ether 1:9) gave **17l** (1.31 g) and **17a** (0.29 g; 11%). Further purification by distillation at 150°/10^{-5} torr gave **17l** (1.23 g; 45% with respect to **17a** used), as a colorless viscous oil. IR ($CHCl_3$): 3060, 2930, 2850, 2800, 1600, 1480, 1450, 1380, 1295, 1175, 1140, 1110, 1090, 1065, 990, 980, 940, 840 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 0.94–2.10 (m, 11 H, H cyclohexyl), 2.38 [d, J = 9 Hz, 6 H, $N(CH_3)_2$], 2.58 [d, J = 9 Hz, 6 H, $N(CH_3)_2$], 2.74–2.96 (m, 2 H, Ar–CH_2), 3.26–3.56 (m, 2 H, $-CH_2N$), 4.09 (t, J = 9, 1 H, CH–N), 6.92–7.15 (m, 4 H, aromatic protons). MS *m/e* (%): 348 ($M^+ - 1$, < 1), 267 (16), 266 (100), 223 (5), 178 (9), 135 (73), 132 (6), 131 (8), 130 (11), 92 (6), 55 (10), 44 (15), 41 (8). (Found: C, 65.23; H, 9.29; N, 11.96. $C_{19}H_{32}N_3OP$ requires: C, 65.30; H, 9.33; N, 12.02%).

2-Bis(dimethylamino)phosphinoyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**17m**)

A soln of **17a** (1.38 g; 5.2 mmol) in 50 ml THF was metallated and benzenetricarbonylchromium (1.3 g; 6.2 mmol) in 10 ml THF was added. The yellow soln was warmed to 0° and stirred for 1 hr. After cooling to −78° iodine (6.16 g; 24.2 mmol) in 15 ml THF was added, the mixture was warmed to room temp. and stirred for 3 hr. After hydrolysis with 2 ml water the soln was diluted with 200 ml ether and washed with brine (including 5% $NaHSO_3$; 4 × 50 ml). Drying over $MgSO_4$ and concentration under reduced pressure afforded a green residue which was purified by flash chormatography on silica gel (ether–MeOH 9:1) and bulb-to-bulb distillation at 190°/10^{-5} torr to give **17m** (0.80 g; 45%) as a pale-yellow oil which crystallized on standing (m.p. 94–95°). Recrystallization of a sample from ether afforded **17m** as a white powder (m.p. 95.5°). IR ($CHCl_3$): 3060, 2980, 2920, 2840, 2800, 1600, 1480, 1450, 1370, 1295, 1125, 1080, 1050, 1020, 995, 980, 945, 930, 860, 830 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 2.36 [d, J = 9 Hz, 6 H, $N(CH_3)_2$], 2.56 [d, J = 9 Hz, 6 H, $N(CH_3)_2$], 2.7–3.4 (m, 4 H, $-CH_2-CH_2N$), 5.95 (d, J = 7 Hz, –CH–N), 6.82–7.3 (m, 9 H, aromatic protons). MS *m/e* (%): 343 (M^+, 11), 266 (11), 209 (17), 208 (100), 207 (9), 206 (13), 179 (7), 178 (8), 135 (35), 132 (5), 130 (6), 92 (6), 91 (6), 45 (8), 44 (13). (Found: C, 66.28; H, 7.66; N, 12.23. $C_{19}H_{26}N_3OP$ requires: C, 66.45; H, 7.63; N, 12.24%).

2-Bis(dimethylamino)phosphinoyl-1-(hydroxycyclopentyl)-1,2,3,4-tetrahydroisoquinoline (**17n**)

A soln of **17a** (2.72 g; 10.2 mmol) in 30 ml THF was metallated and cyclopentanone (1 ml; 11.2 mmol) was added. After stirring for 6 hr at −80°, the reaction was worked up (method C). The crude product (3.35 g) was chromatographed on 130 g of silica gel to give **17n** (1.75 g; 73% with respect to **17a** used) as a solid (m.p. 129–130°) and **17a** (0.888 g; 33%). Recrystallization of a sample from CH_2Cl_2/petroleum ether afforded **17n** (m.p. 131–132°). IR (KBr): 3340, 3060, 3020, 2960, 2930, 2880, 2840, 2800, 1485, 1460, 1385, 1295, 1275, 1200, 1180, 1145, 1130, 1085, 1060, 1035, 1015, 995, 970, 940, 905, 825, 770, 740, 670, 620 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.3–2.06 [m, 8 H, $-(CH_2)_4-$], 2.43 [d, J = 9 Hz, 6 H, $N(CH_3)_2$], 2.64 [d, J = 9 Hz, 6 H, $N(CH_3)_2$], 2.78–3.90 [m, 5 H, Ar–$(CH_2)_2$–N and OH], 4.63 (d, J = 9 Hz, 1 H, –CH–N), 7.09 (s, 4 H, aromatic protons). MS *m/e* (%): 352 ($M^+ + 1$, < 1), 267 (40), 266 (52), 178 (10), 135 (60), 133 (12), 132 (100), 131 (10), 130 (10), 92 (10), 45 (12), 44 (20). (Found: C, 61.27; H, 8.52, N, 11.82. $C_{18}H_{30}N_3O_2P$ requires: C, 61.52; H, 8.60, N, 11.96%).

2-Bis(dimethylamino)phosphinoyl-1-(α-hydroxybenzhydryl)-1,2,3,4-tetrahydroisoquinoline (**17o**)

A soln of **17a** (2.66 g; 9.9 mmol) in 30 ml THF was metallated and benzophenone (2.29 g; 12.6 mmol) in 12 ml THF was added. The mixture was stirred for 2 hr at −78°, warmed up to room temp. overnight and worked up (method B). Recrystallization of the crude product (4.77 g) from CH_2Cl_2/petroleum ether gave **17o** (3.29 g; 74%) as a white powder (m.p. 216°). IR (KBr): 3360, 3060, 3020, 2920, 2900, 2850, 2810, 1600, 1580, 1490, 1455, 1445, 1380, 1295, 1190, 1170, 1125, 1110, 1080, 1060, 1030, 990, 890, 780, 745, 705, 690, 660, 620 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 2.2–3.0 [m, 16 H; $-CH_2-CH_2-$ and 2 × $N(CH_3)_2$], 5.64 (d, J = 9 Hz, 1 H, –CH–N), 5.72 (s, 1 H, OH), 6.15 [d, J = 8 Hz, C(8)–H]; 6.62–6.84 [m, 1 H, C(7)–H], 6.9–7.4 (m, 10 H) and 7.58–7.7 (m, 2 H) (aromatic protons). MS *m/e* (%): 450 ($M^+ + 1$, < 1), 268 (10), 267 (70), 266 (100), 223 (15), 182 (9), 178 (25), 136 (17), 135 (100), 133 (10), 132 (98), 131 (21), 130 (23), 105 (48), 92 (13), 77 (40), 45 (13), 44 (40). (Found: C, 69.26; H, 7.25; N, 9.24. $C_{26}H_{32}N_3O_2P$ requires: C, 69.47; H, 7.18; N, 9.35%).

F. ALKYLATION OF 1-LITHIO-1-METHYL-2-PHOSPHINOYL TETRAHYDROISOQUINOLINE 19b TO 1,1-DIALKYLATED PRODUCTS

2-Bis(dimethylamino)phosphinoyl-1,1-dimethyl-1,2,3,4-tetrahydroisoquinoline (**19d**) *and 2-Bis(dimethylamino)phosphinoyl-1-butyl-1-methyl-1,2,3,4-tetrahydroisoquinoline*[35]

To a cooled (−78°) soln of **19a** (1.87 g; 6.7 mmol) in 40 ml THF was added 1.50 M n-BuLi (4.9 ml; 7.3 mmol). The red soln was stirred for 1 hr before addition of MeI (0.55 ml; 8.8 mmol). After stirring for 3 hr at −78° the mixture was warmed overnight to room temp. and worked up (method B). Chromatography of the crude product (1.93 g) on 120 g silica gel (ether-MeOH 9:1) afforded 2-bis(dimethylamino)phosphinoyl-1-butyl-1-methyl-1,2,3,4-tetrahydroisoquinoline[35] (0.349 g; 18% with respect to **19a** used), **19d** (0.321 g; 19% with respect to **19a** used) as a solid (m.p. 70–71°) and **19a** (0.284 g; 15%). Recrystallization of a sample of **19d** from CH_2Cl_2/petroleum ether afforded a white powder (m.p. 72–73°). IR (KBr): 3060, 3020, 2970, 2940, 2900, 2850, 2800, 1620, 1580, 1490, 1470, 1445, 1390, 1365, 1355, 1305, 1285, 1270, 1240, 1205, 1180, 1160, 1125, 1065, 1040, 1000, 980, 960, 940, 920, 850, 765, 750, 740, 730, 675 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.78 (s, 6 H, 2 × CH_3), 2.52–2.84 [m, 14 H, Ar–CH_2 and 2 × $N(CH_3)_2$], 3.13–3.37 (m, 2 H, $-CH_2N$), 6.96–7.33 (m, 4 H, aromatic protons). MS *m/e* (%): 295 (M^+, 4), 281 (17), 280 (100), 146 (5), 145 (4), 144 (7), 136 (5), 135 (90), 92 (3), 91 (3), 44 (9). (Found: C, 60.91; H, 8.81; N, 14.10. $C_{15}H_{26}N_3OP$ requires: C, 61.00; H, 8.87; N, 14.23%).

Distillation of crude butyl derivative (as described above) at 140°/10^{-5} torr afforded 2-bis(dimethylamino)phosphinoyl-1-butyl-1-methyl-1,2,3,4-tetrahydroisoquinoline[35] (0.33 g; 17% with respect to **19a** used) as a colorless, viscous oil. IR ($CHCl_3$): 3060, 2960, 2920, 2870, 2800, 1600, 1480, 1450, 1370, 1315, 1290, 1270, 1070, 1035, 990, 975, 870, 860 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 0.73 (br t, J = 6 Hz, 3 H, $-CH_2-CH_3$), 0.83–1.50 [m, 6 H, $-(CH_2)_3-$], 1.73 (s, 3 H, $-CH_3$), 2.47–2.87 [m, 14 H, Ar–CH_2, 2 × $N(CH_3)_2$], 3.0–3.4 (m, 2 H, $-CH_2N$), 6.90–7.37 (m, 4 H, aromatic protons). MS

m/e (%): 336 ($M^+ - 1$, < 1), 322 (4), 281 (17), 280 (99), 146 (4), 145 (7), 144 (9), 136 (5), 135 (100), 92 (5), 44 (11). (Found: C, 64.73; H, 9.70; N, 12.18. $C_{18}H_{32}N_3OP$ requires: C, 64.07; H, 9.56; N, 12.45%).

2-Bis(dimethylamino)phosphinoyl-1-benzyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (**19e**)

A soln of **19a** (1.82 g; 6.5 mmol) in 40 ml THF was metallated with n-BuLi (4.7 ml; 7 mmol) and stirred for 1 hr at −78°. After addition of benzyl chloride (1.0 ml; 8.7 mmol) the mixture was stirred for 3 hr at −78°, warmed to room temp. overnight and worked up (method B). Chromatography of the crude product (2.58 g) on 120 g silica gel (ether–MeOH 9:1) gave **19e** (0.809 g; 40% with respect to **19a** used) as a solid (m.p. 109–111°) and **19a** (0.276 g; 15%). Recrystallization of a sample from CH_2Cl_2/petroleum ether afforded **19e** (m.p. 112–113°). IR (KBr): 3060, 3020, 3000, 2900, 2840, 2800, 1490, 1480, 1450, 1300, 1290, 1275, 1205, 1195, 1135, 1120, 1090, 1065, 1055, 995, 985, 960, 920, 910, 855, 765, 750, 740, 730, 700, 675 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.88 (s, 3 H, CH_3), 2.06–3.0 [m, 16 H, Ar–$(CH_2)_2$–N, 2 × $N(CH_3)_2$], 3.19 (d, J = 13 Hz, H_A–C–Ar), 3.98 (d, J = 13 Hz, H_B–C–Ar), 6.72–7.34 (m, 9 H, aromatic protons). MS *m/e* (%): 371 (M^+, < 1), 281 (16), 280 (94), 145 (5), 144 (5), 136 (5), 135 (100), 91 (6), 44 (7). (Found: C, 67.85; H, 8.14; N, 11.38. $C_{21}H_{30}N_3OP$ requires: C, 67.90; H, 8.14; N, 11.31%).

G. HYDROLYSIS OF THE PHOSPHORYLAMIDES

General procedure: 2–3 mmol of the amide in 2 M HCl or in MeOH/EtOH and HCl aq were heated under reflux. The cooled soln (ice bath) was made strongly alkaline with KOH pellets and extracted with ether (3–4 × 50–100 ml). The combined organic phases were dried over K_2CO_3 and concentrated under reduced pressure to give the crude product.

1,2,3,4-Tetrahydroisoquinoline (**15a**). A soln of **17a** (0.545 g; 2.0 mmol) in 10 ml HCl (2.4 M) was heated under reflux for 30 min. Distillation of the crude oil (0.27 g) at 115°/14 torr afforded **15a** in 90% yield.

1-Methyl-1,2,3,4-tetrahydroisoquinoline (**15d**)

A soln of **17d** (0.79 g; 2.8 mmol) in 15 ml HCl (2.0 M) was heated under reflux for 4 hr. Bulb-to-bulb distillation of the crude oil (0.39 g) at 60°/0.005 torr afforded **15d** (0.38 g; 93%), as colorless liquid. Picrate: m.p. 187° (lit.[41], m.p. 187°). IR (Film): 3260, 3060, 3020, 2960, 2920, 2830, 1490, 1445, 1435, 1370, 1305, 1135, 755, 730 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.42 (d, J = 7 Hz, 3 H, CH_3), 1.60 (s, 1 H, NH), 2.57–3.43 [m, 4 H, $-(CH_2)_2-$], 4.03 (q, J = 7 Hz, 1 H, –CH–N), 7.10 (s, 4 H, aromatic protons). MS *m/e* (%): 147 (M^+, 6), 146 (21), 144 (12), 133 (21), 132 (100), 131 (18), 130 (21), 118 (12), 117 (26), 115 (15), 105 (12), 104 (12), 103 (12), 91 (10), 77 (12). (Found (picrate): C, 51.03; H, 4.28; N, 14.88. Calc for $C_{16}H_{16}N_4O_7$: C, 51.06; H, 4.29; N, 14.89%).

1-Butyl-1,2,3,4-tetrahydroisoquinoline (**15e**)

A soln of **17e** (1.03 g; 3.2 mmol) in 15 ml HCl (2.0 M) was heated under reflux for 16 hr. Bulb-to-bulb distillation of the crude oil (0.552 g) at 90°/0.005 torr gave a colorless liquid **15e** (0.505 g; 84%). Oxalate: m.p. 176–177° (EtOH). IR (Film): 3380–3240, 2960, 2940, 2880, 2860, 1495, 1455, 1430, 745 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 0.80–1.04 (m, 3 H, CH_3), 1.16–1.85 [m, 7H, $-(CH_2)_3-$, NH], 2.45–3.25 [m, 4 H, Ar–$(CH_2)_2$–N], 3.82 (br t, J = 8 Hz, 1 H, –CH–N), 6.82–7.00 (m, 4 H, aromatic protons). MS *m/e* (%): 189 (M^+, < 1), 188 (4), 145 (6), 133 (11), 132 (100), 130 (6), 117 (6), 115 (4), 105 (4), 91 (3), 77 (5). (Found (oxalate): C, 64.38; H, 7.60; N, 5.20. $C_{15}H_{21}NO_4$ requires: C, 64.50; H, 7.58; N, 5.01%).

1-Neopentyl-1,2,3,4-tetrahydroisoquinoline (**15g**)

A soln of **17g** (0.922 g; 2.7 mmol) in 10 ml MeOH and 50 ml HCl (2.06 M) was heated under reflux for 31 hr. Distillation of the crude product (0.48 g) at 90°/0.01 torr gave **15g** (0.415 g; 75%), as a colorless liquid. Oxalate: m.p. 181° (EtOH). IR (Film): 3320, 3060, 3020, 2950, 2860, 1490, 1475, 1450, 1430, 1390, 1360, 1240, 1210, 1120, 1040, 980, 950, 870, 830, 780, 745, 710 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.07 [s, 9 H, $C(CH_3)_3$], 1.48 (s, 1 H, NH), 1.7 [d, J = 5 Hz, 2 H, CH_2–CH), 2.6–3.37 [m, 4 H, Ar–$(CH_2)_2$–N], 4.05 (t, J = 5 Hz, 1 H, –CH–N), 7.07 (s, 4 H, aromatic protons). MS *m/e* (%): 203 (M^+, 1), 143 (4), 133 (11), 132 (100), 130 (5), 117 (6), 115 (5), 105 (4), 91 (2), 77 (3), 30 (4). (Found (oxalate): C, 65.17; H, 7.84; N, 4.80. $C_{16}H_{23}NO_4$ requires: C, 65.51; H, 7.90; N, 4.77%).

1-Allyl-1,2,3,4-tetrahydroisoquinoline (**15h**)

A soln of **17h** (0.967 g; 3.1 mmol) in 20 ml HCl (2.0 M) was heated under reflux for 20 hr. Distillation of the brown oil (0.47 g) at 90°/0.100 torr gave **15h** (0.407 g; 75%), as a colorless liquid. Oxalate: m.p. 169° (EtOH). IR (Film): 3300, 3070, 3020, 2920, 2830, 2800, 1635, 1490, 1450, 1430, 1315, 1130, 995, 915, 760, 740, 720 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.97 (s, 1 H, NH), 2.26–3.36 (m, 6 H, 3 × CH_2), 3.93–4.12 (m, 1 H, –CH–N), 4.96–5.26 (m, 2 H, H_2C=), 5.60–6.04 (m, 1 H, CH=CH_2), 6.96–7.18 (m, 4 H, aromatic protons). MS *m/e* (%): 173 (M^+, < 1), 133 (11), 132 (100), 130 (11), 117 (10), 115 (6), 105 (7), 103 (5), 77 (6). (Found (oxalate): C, 63.83; H, 6.49; N, 5.28. $C_{14}H_{17}NO_4$ requires: C, 63.87; H, 6.51; N, 5.32%).

1-Benzyl-1,2,3,4-tetrahydroisoquinoline (**15i**)

A soln of crude **17i** (3.28 g; 9.2 mmol) in 30 ml HCl (2.0 M) was heated under reflux for 23 hr. The cooled soln was diluted with 100 ml ether and worked up as usual. Distillation of the crude oil (1.74 g) at 120°/0.005 torr afforded **15i** (1.56 g; 76%), as a pale-yellow oil. Picrate: m.p. 170° (lit.[42], m.p. 166–167°). IR (Film): 3400–3200, 3060, 3020, 2920, 2830, 2800, 1600, 1490, 1450, 1425, 1315, 1125, 1080, 1030, 960, 805, 780, 755, 735, 715, 700 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.46 (br s, 1 H, NH), 2.53–3.26 (m, 6 H, 3 × $-CH_2-$), 4.07 (dd, J_1 = 10 Hz, J_2 = 4 Hz, CH–N), 6.86–7.32 (m, 9 H, aromatic protons). MS *m/e* (%): 223 (M^+, < 1), 220 (11), 133 (10), 132 (100), 130 (7), 117 (8), 115 (5), 91 (8), 77 (5), 65 (4), 28 (5). (Found (picrate): C, 58.37; H, 4.55; N, 12.36. Calc for $C_{22}H_{20}N_4O_7$: C, 58.40; H, 4.46; N, 12.39%).

1-Isopropyl-1,2,3,4-tetrahydroisoquinoline (**15k**)

A soln of **17k** (1.08 g; 3.5 mmol) in 15 ml HCl (2.0 M) was heated under reflux for 8 hr. Distillation of the crude product (0.59 g) at 50°/0.001 torr gave the colorless liquid **15k** (0.51 g; 83%). Picrate: m.p. 142–142.5° (EtOH). IR (Film): 3440, 3060, 3020, 2980, 2940, 2880, 2840, 2810, 2740, 1495, 1460, 1450, 1440, 1430, 1380, 1365, 1335, 1310, 1300, 1100, 800, 745 cm^{-1}. ^1H-NMR ($CDCl_3$): 0.67 (d, J = 7 Hz, 3 H, CH_3), 1.04 (d, J = 7 Hz, 3 H, CH_3), 1.4 (s, 1 H, NH), 2.04–3.31 [m, 5 H, $HC(CH_3)_2$, $-(CH_2)_2-$], 3.82 (d, J = 4 Hz, 1 H, –CHN), 6.8–7.1 (m, 4 H, aromatic protons). MS *m/e* (%): 175 (M^+, < 1), 133 (11), 132 (100), 130 (8), 117 (7), 105 (5), 77 (5). (Found (picrate): C, 53.36; H, 4.99; N, 13.71. $C_{18}H_{20}N_4O_7$ requires: C, 53.46; H, 4.99; N, 13.85%).

1-Cyclohexyl-1,2,3,4-tetrahydroisoquinoline (**15l**)

A soln of **17l** (0.888 g; 2.5 mmol) in 25 ml MeOH and 40 ml HCl (2.06 M) was heated under reflux for 49 hr. Distillation of the crude product (0.46 g) at 120°/0.005 torr afforded the colorless oil **15l** (0.362 g; 66%). Oxalate: m.p. 181° (EtOH). IR ($CHCl_3$): 3440, 2930, 2850, 2800, 1490, 1450, 1430, 1320, 1295, 1255, 1130, 1120, 1040, 895, 840 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 0.86–2.0 (m, 11 H, H cyclohexyl), 2.47–3.33 [m, 5 H, $-(CH_2)_2$ and NH], 3.8 (d, J = 5 Hz, –CH–N), 6.87–7.13 (m, 4 H, aromatic protons). MS *m/e* (%): 214 ($M^+ - 1$, < 1), 133 (12), 132 (100), 131 (4), 130 (9), 117 (7), 115 (4), 105 (6), 77 (4), 55 (5), 41 (6). (Found (oxalate): C, 66.45; H, 7.27; N, 4.78. $C_{17}H_{23}NO_4$ requires: C, 66.86; H, 7.59; N, 4.59%).

1-Phenyl-1,2,3,4-tetrahydroisoquinoline (**15m**)

A soln of **17m** (0.72 g; 2.1 mmol) in 10 ml MeOH and 50 ml HCl (2.06 M) was heated under reflux for 27 hr. Recrystallization of the solid (0.397 g) from ether afforded **15m** (0.348 g; 79%), as white needles, m.p. 97–98° (lit.[43] m.p. 97°). IR ($CHCl_3$): 3320, 3060, 2950, 2920, 2830, 1490, 1450, 1430, 1365, 1310, 1290, 1120, 1070, 1040, 950, 850 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.83 (s, 1 H, NH), 2.63–3.37 [m, 4 H, $-(CH_2)_2-$], 5.07 (s, 1 H, –CH–N), 6.6–7.4 (m, 9 H, aromatic protons). MS *m/e* (%): 209 (M^+, 27), 208 (37), 180 (10), 179 (17), 178 (11), 133 (11), 132 (100), 77 (7).

1-(-α-Hydroxybenzhydryl)-1,2,3,4-tetrahydroisoquinoline-hydrochloride (**15o**)

A soln of **17o** (1.0 g; 2.2 mmol) in 60 ml EtOH and 50 ml HCl (2.06 M) was heated under reflux for 5 hr. The cooled mixture was concentrated under reduced pressure. Recrystallization of the residue (2 ×) from MeOH gave **15o**. HCl (0.408 g; 52%), as a white powder, m.p. 266° (dec.) IR (KBr): 3420, 3180, 3100, 3060, 3030, 3000, 2940, 2850, 2770, 2750, 2690, 2660, 2630, 2580, 1580, 1490, 1465, 1455, 1430, 1400, 1380, 770, 750, 740, 710, 695, 660, 640 cm^{-1}. ^{1}H-NMR (CD_3OD): δ 2.67–3.21 [m, 4 H, $-(CH_2)_2-$], 5.58 (s, 1 H, –CH–N$^\oplus$), 6.3 [d, J = 8 Hz, 1 H, C(8)–H], 6.68–6.94 [m, 1 H, C(7)–H], 7.00–7.76 (m, 12 H, aromatic protons). MS *m/e* (%): 182 (6), 133 (11), 132 (100), 131 (6), 130 (9), 129 (5), 117 (6), 105 (20), 77 (15), 51 (5), 36 (5), 28 (9). (Found: C, 75.00; H, 6.36; N, 4.06. $C_{22}H_{22}ClNO$ requires: C, 75.09; H, 6.30; N, 3.98%).

1,1-Dimethyl-1,2,3,4-tetrahydroisoquinoline (**19f**)

A soln of **19d** (0.321 g; 1.1 mmol) in 10 ml MeOH and 35 ml HCl (2.06 M) was heated under reflux for 40 hr. Distillation of the crude product (0.161 g) at 125°/12 torr afforded **19f** (0.131 g; 74%), as a colorless liquid (lit.[44] b.p. 125–126°/23 torr). IR (Film): 3280, 3060, 3020, 2960, 2920, 2860, 2820, 1490, 1445, 1425, 1380, 1360, 1290, 1190, 1150, 1125, 1095, 1040, 800, 760, 730, 680 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.38 (s, 6 H, 2 × CH_3), 1.96 (br s, 1 H, NH), 2.67 (t, J = 6 Hz, $-CH_2N$), 3.05 (t, J = 6 Hz, Ar–CH_2), 6.93–7.2 (m, 4 H, aromatic protons). MS *m/e* (%): 161 (M^+, 1), 147 (12), 146 (100), 144 (7), 131 (7), 130 (7), 117 (5), 115 (8), 91 (6), 77 (5), 30 (8).

1-Benzyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (**19g**)

A soln of **19e** (0.794 g; 2.1 mmol) in 25 ml MeOH and 55 ml HCl (2.06 M) was heated under reflux for 41 hr. Distillation of the residue (0.473 g) at 120°/0.005 torr gave **19g** (0.454 g; 89%), as a pale-yellow liquid. Oxalate: m.p. 183° (EtOH). IR (Film): 3330, 3060, 3020, 2960, 2920, 2830, 1600, 1490, 1450, 1425, 1370, 1120, 1090, 1075, 1030, 800, 760, 730, 705, 690 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.37 (s, 3 H, CH_3), 1.47 (s, 1 H, NH), 2.43–3.37 (m, 6 H, 3 × CH_2–), 7.00–7.43 (m, 9 H, aromatic protons). MS *m/e* (%): 237 (M^+, < 1), 222 (10), 147 (13), 146 (100), 144 (7), 131 (7), 130 (7), 115 (6), 91 (12), 77 (4), 65 (7), 51 (4), 39 (7). (Found (oxalate): C, 69.80; H, 6.42; N, 4.31. $C_{19}H_{21}NO_4$ requires: C, 69.71; H, 6.47; N, 4.28%).[45]

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