Synthesis of Spiro[2*H*-1,3-benzoxazine-2,4′-piperidines] from *N,N′*-Dibenzylidenephenylmethanediamines and 2,6-Diaryl-4-piperidones

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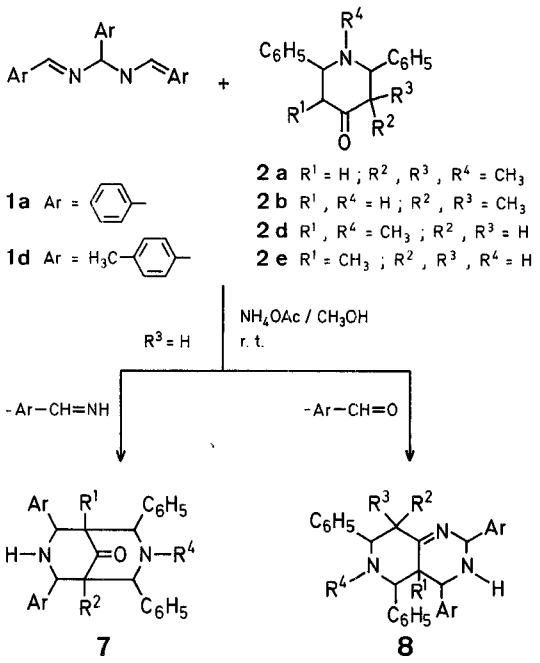
1,3-Oxazines demonstrate analgesic antiinflammatory, vasodilator, diuretic, spasmolytic, analeptic, anticonvulsant, antidepressant, sedative, antiulcer, antitumor, and antihypertensive activities[1-14] and this has motivated us to synthesize several 1,3-benzoxazines and other nitrogen-containing heterocyclic compounds.

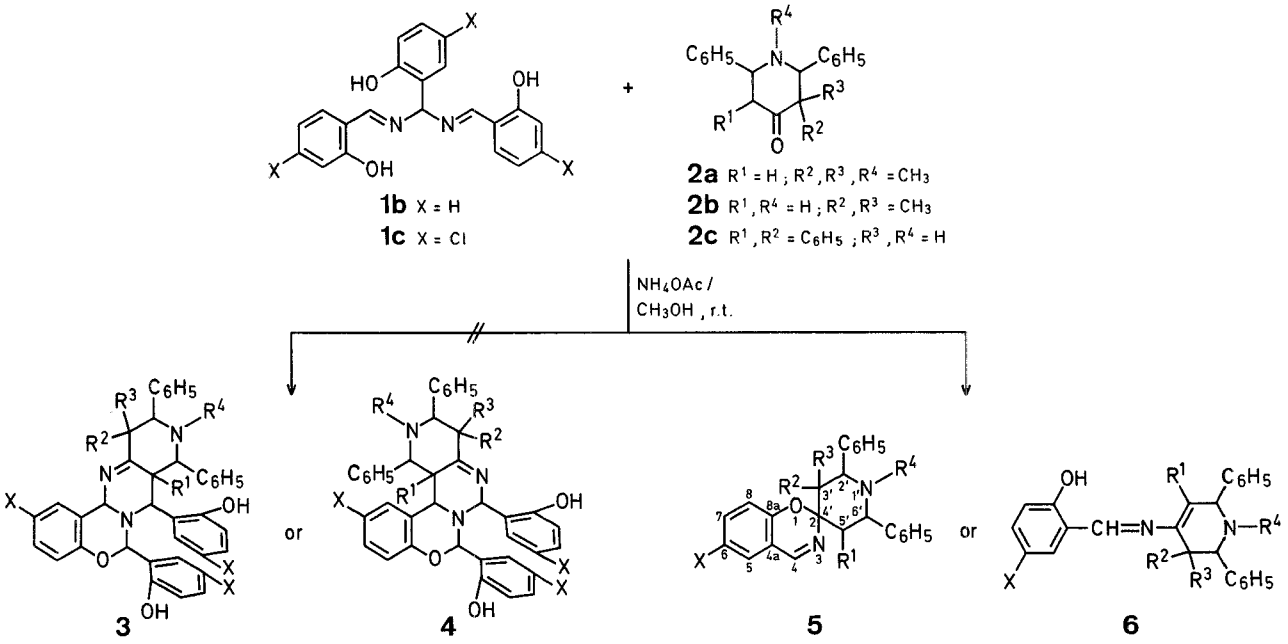
In continuation of our work[15] on the synthetic potential of *N,N′*-dibenzylidenephenylmethanediamines **1** as starting material for novel heterocyclic systems, we report here further reactions of **1** with the 4-piperidones **2**. In analogy with our earlier work[15] on the reaction of **1** with aryl methyl ketones, it was expected that **1b** and **1c** would react with 4-piperidones **2** to give pyrido[4,3-*d*]pyrimido[1,2-*c* or 3,4-*c*][1,3]benzoxazine derivatives **3** and **4**. However, we obtained from the above-mentioned reaction, spiro[2*H*-1,3-benzoxazine-2,4′-piperidines] **5** and 4-tetrahydropyridinopyrimidino-2-arylmethyleneamines **6** (Scheme **A**).

On the other hand, **1a** or **1d** and 4-piperidones **2** condense to give 3,7-diazabicyclo[3.3.1]nonan-9-ones **7** or octahydropyrido[4,3-*d*]pyrimidines **8** (Scheme **B**).



	Ar	R^1	R^2	R^3	R^4
7a	C_6H_5	CH_3	H	H	CH_3
7b	$H_3C-C_6H_4$	CH_3	H	H	H
8a	C_6H_5	H	CH_3	CH_3	CH_3
8b	$H_3C-C_6H_4$	H	CH_3	CH_3	H

Scheme **B**



	X	R^1	R^2	R^3	R^4
5a	H	H	CH_3	CH_3	CH_3
5b	H	H	CH_3	CH_3	H
5c	Cl	H	CH_3	CH_3	H
6a	H	C_6H_5	C_6H_5	H	H
6b	Cl	C_6H_5	C_6H_5	H	H

Scheme **A**

Spiro[2*H*-1,3-benzoxazine-2,4′-(1′,3′,3′-trimethyl-2′,6′-diphenyl)-piperidine] (5a):

A mixture of **1b** (Ar = 2-HO—C_6H_4, 0.23 g, 0.7 mmol), 1,3,3-trimethyl-2,6-diphenyl-4-piperidone (**2a**; 0.29 g, 1 mmol), and ammonium acetate (0.3 g, 4 mmol) in methanol (3 ml) is magnetically stirred at ambient temperature for three days. The pale yellow precipitate deposited is collected and recrystallized from tetrahydrofuran/methanol (1 : 1) to give spongy white crystals; yield: 230 mg (58%); m.p. 208–209 °C.

$C_{27}H_{28}N_2O$	calc.	C 81.78	H 7.12	N 7.07
(396.5)	found	81.90	7.28	7.00

I.R. (Nujol): ν = 1637 (C=N), 1275 (C—O), 760, 708 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 8.30 (s, 1 H, N=CH); 7.8–6.6 (m, 14 H_{arom}); 3.97 (s, 1 H, N—CH—C); 3.62 (t, 1 H, CH_2—CH, J = 8.5 Hz); 2.4–1.9 (m, 2 H, CH_2—CH); 1.82, 1.34, 0.77 ppm (3 s, 3 H each, CH_3).

Spiro[2*H*-1,3-benzoxazine-2,4′-(3′,3′-dimethyl-2′,6′-diphenyl)-piperidine] (5b):

A mixture of **1b** (0.7 g, 2 mmol), 3,3-dimethyl-2,6-diphenyl-4-piperidone (**2b**; 1.68 g, 6 mmol), and ammonium acetate (0.77 g, 10 mmol) in methanol (5 ml) is allowed to react and then worked up as above to give white crystals; yield: 1.34 g (58%); m.p. 178–179 °C.

$C_{26}H_{26}N_2O$	calc.	C 81.64	H 6.85	N 7.32
(382.5)	found	81.43	6.93	7.15

I.R. (Nujol): ν = 3320 (NH), 1262 (C—O), 775, 760, 710 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 8.21 (s, 1 H, N=CH); 7.6–6.6 (m, 14 H_{arom}); 4.57 (s, 1 H, N—CH—C); 4.30 (q, 1 H, CH_2—CH, J = 7.0, 8.5 Hz); 2.5–2.1 (m, 2 H, CH_2—CH); 1.71 (s, 1 H, NH); 1.26, 0.85 ppm (2 s, 3 H each, CH_3).

^{13}C-N.M.R. ($CDCl_3$): δ = 154.4 (s, C-8a); 154.1 (d, C-4); 154.0 (d, C-5); 144.7 (s, C-1 of C_6H_5 at C-2′); 141.4 (s, C-1 of C_6H_5 at C-6′); 133.7 (d, C-7); 128.3, 129.3, 127.3, 127.1, 126.8 (5 d, 2 C each, C-2 to C-6 of C_6H_5 at C-2′ and C-6′); 127.2 (s, C-4a); 120.7 (d, C-6); 116.2 (d, C-8); 95.8 (s, C-2); 65.2 (d, C-6′); 57.1 (d, C-2′); 43.2 (s, C-3′); 42.3 (t, C-5′); 20.7, 16.1 ppm (2 q, CH_3 each).

M.S. (70 eV): *m/e* (relative intensity) = 382 (M^+, 32), 277 (28), 262 (25), 236 (14), 195 (39), 194 (100), 188 (55), 173 (16), 104 (17), 91 (18), 77 (16), 28 (20).

6-Chloro-spiro[2*H*-1,3-benzoxazine-2,4′-(3′,3′-dimethyl-2′,6′-diphenyl)-piperidine] (5c):

A mixture of **1c** (Ar = 2-HO, 5-Cl—C_6H_3, 0.9 g, 2 mmol), **2b** (1.68 g, 6 mmol), and ammonium acetate (0.77 g, 10 mmol) in methanol (5 ml) magnetically stirred at ambient temperature for one day, then methanol (15 ml) is added, stirring is continued for four days, and the mixture is allowed to stand for one day. The precipitate formed is collected and recrystallized from tetrahydrofuran/methanol (1 : 1) to give **5c** as white crystals; yield: 1.3 g (52%); m.p. 170–171 °C.

$C_{26}H_{25}ClN_2O$	calc.	C 74.90	H 6.04	N 6.72
(416.9)	found	74.81	6.07	6.65

I.R. (Nujol): ν = 3330 (NH), 1632 (C=N), 1263 (C—O), 766, 707 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 8.18 (s, 1 H, N=CH); 7.8–6.6 (m, 13 H_{arom}); 4.52 (s, 1 H, N—CH—C); 4.25 (t, 1 H, CH_2—CH, J = 8 Hz); 2.4–1.9 (m, 2 H, CH_2—CH); 1.7 (br., 1 H, NH); 1.25, 0.82 ppm (2 s, 3 H each, CH_3).

2,3,5,6-Tetraphenyl-*N*-(2-hydroxybenzyliene)-1,2,5,6-tetrahydropyrid-4-ylamine (6a):

A mixture of **1b** (0.35 g, 1 mmol), **2c** (0.40 g, 1 mmol), and ammonium acetate (0.77 g, 10 mmol) in methanol (3 ml) is reacted for ten days in the same way as above. The deposited precipitate is collected and recrystallized from tetrahydrofuran/methanol (1 : 1) to give pale yellow crystals; yield: 0.30 g (59%); m.p. 219–221 °C.

$C_{36}H_{30}N_2O$	calc.	C 85.34	H 5.97	N 5.53
(506.6)	found	85.34	6.04	5.45

I.R. (Nujol): ν = 3325 (NH), 1630, 1600, 1560, 755, 700 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 12.17 (s, 1 H, OH); 8.07 (s, 1 H, CH=N); 7.5–6.5 (m, 24 H_{arom}); 5.26 (s, 1 H, NH—CH); 4.74, 4.00 (2 d, 1 H each, CH—CH, J = 3.5 Hz); 2.0 ppm (br, 1 H NH).

2,3,5,6-Tetraphenyl-*N*-(5-chloro-2-hydroxybenzylidene)-1,2,5,6-tetrahydropyrid-4-ylamine (6b):

A mixture of **1c** (0.45 g, 1 mmol), **2c** (0.81 g, 2 mmol), and ammonium acetate (0.77 g, 10 mmol) in methanol (5 ml) is worked up as above for ten days, and the deposited precipitate (1.05 g) is recrystallized from acetonitrile to give yellow crystals; yield: 0.88 g (81%); m.p. 203–204 °C.

$C_{36}H_{29}ClN_2O$	calc.	C 79.91	H 5.40	N 5.18
(541.1)	found	79.96	5.47	5.31

I.R. (Nujol): ν = 3325 (NH), 1625, 1595, 1555, 1280, 815, 745, 695 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 12.12 (s, 1 H, OH); 7.84 (s, 1 H, CH=N); 7.4–6.5 (m, 23 H_{arom}); 5.23, 4.22 (2 d, 1 H each, CH—CH, J = 3 Hz); 4.20 (s, 1 H, N—CH—C); 2.20 ppm (br, 1 H NH).

1,3-Dimethyl-2,4,6,8-tetraphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (7a):

A mixture of **1a** (1.04 g, 3.5 mmol), 1,3-dimethyl-2,6-diphenyl-4-piperidone (**2d**; 1.40 g, 5 mmol), and ammonium acetate (0.4 g, 5 mmol) in methanol (3 ml) is magnetically stirred at ambient temperature for ten days, then methanol (5 ml) added, and stirring is continued for a further half day and allowed to stand for three days until no furthrer white precipitate is produced from the viscous reaction solution. The deposited precipitate is collected and recrystallized from tetrahydrofuran/methanol to give **7a** as a white crystalline matter; yield: 0.73 g (31%); m.p. 217–219 °C.

$C_{33}H_{32}N_2O$	calc.	C 83.86	H 6.83	N 5.93
(472.6)	found	83.60	6.85	6.14

I.R. (Nujol): ν = 3320 (NH), 1710 (C=O), 763, 702 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 6.9–6.2 (m, 20 H_{arom}); 4.63, 3.80 (2 s, 1 H each, N—CH—C); 4.26, 4.08 (2 d, 1 H each, N—CH—CH, J = 3 Hz); 2.96 (t, 1 H, CH—CH—CH, J = 3 Hz); 2.1 (br, 1 H, NH); 1.70, 0.58 ppm (2 s, 3 H each, CH_3).

1-Methyl-2,4-diphenyl-6,8-bis[4-methylphenyl]-3,7-diazabicyclo[3.3.1]nonan-9-one (7b):

A mixture of *N,N′*-bis[4-methylbenzylidene]-4-methylphenylmethanediamine **1d** (Ar = 4-$CH_3C_6H_4$, 1.36 g, 4 mmol), 3-methyl-2,6-diphenyl-4-piperidone (**2e**; 1.59 g, 6 mmol), and ammonium acetate (0.77 g, 10 mmol) in ethanol/acetic acid (1 : 1 volume ratio, 5 ml) is worked up as above for ten hours and allowed to stand for a over night. The precipitate is collected and recrystallized from tetrahydrofuran/methanol to give **7b** as a white crystalline matter; yield: 0.58 g (20%); m.p. 213–214 °C.

$C_{34}H_{34}N_2O$	calc.	C 83.91	H 7.04	N 5.76
(486.6)	found	83.82	6.95	5.76

I.R. (Nujol): ν = 3330 (NH), 1712 (C=O), 762, 718, 701 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 7.8–6.5 (m, 18 H_{arom}); 5.21, 3.74 (2 s, 1 H each, N—CH—C); 4.67, 4.25 (2 d, 1 H each, N—CH—CH, J = 2, 3.5 Hz); 2.93 (q, 1 H, CH—CH—CH, J = 2.0, 3.5 Hz); 2.40, 2.17, 0.63 (3 s, 3 H each, CH_3); 2.00, 1.41 ppm (2 s, 1 H each, NH).

6,8,8-Trimethyl-2,4,5,7-tetraphenyl-2,3,4,4a,5,6,7,8-octahydropyrido[4,3-*d*]pyrimidine (8a):

A mixture of **1a** (0.21 g, 0.7 mmol), 1,3,3-trimethyl-2,6-diphenyl-4-piperidone (**2f**; 0.293 g, 1 mmol), and ammonium acetate (0.154 g, 2 mmol) in methanol (1 mml) is stirred in the same way as above for two days. The deposited precipitate is recrystallized from tetrahydrofuran/methanol (1:1) to give white crystals; yield: 180 mg (37%); m.p. 184–185 °C.

$C_{34}H_{35}N_3$	calc.	C 84.08	H 7.26	N 8.65
(485.6)	found	84.19	7.37	8.64

I.R. (Nujol): ν = 3300 (NH), 1659 (C=N), 758, 703 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 7.7–6.6 (m, 20 H_{arom}); 5.39, (d, 1 H, N—CH—N, J = 2.0 Hz); 3.74 (s, 1 H, N(CH_3)—CH—C); 3.8–2.8 (m, CH—CH—CH); 1.7 (br, 1 H, NH); 1.62, 1.42, 1.08 ppm (3 s, 3 H each, CH_3).

8,8-Dimethyl-2,4-bis[4-methylphenyl]-5,7-diphenyl-2,3,4,4a,5,6,7,8-octahydropyrido[4,3-*d*]pyrimidine (8b):

A mixture of **1d** (1.36 g, 4 mmol), 3,3-dimethyl-2,6-diphenyl-4-piperidone (**2g**; 1.68 g, 6 mmol), and ammonium acetate (0.77 g, 10 mmol)

in methanol (5 ml) is worked up as above to give white crystals, yield: 540 mg (18%); m.p. 177–178 °C.

$C_{35}H_{37}N_3$	calc.	C 84.13	H 7.46	N 8.41
(499.7)	found	84.18	7.55	8.32

I.R. (Nujol): $\nu = 3320$ (NH), 1652 (C=O), 783, 724 cm^{-1}.

^1H-N.M.R. ($CDCl_3$): $\delta = 7.0$–6.6 (m, $18H_{arom}$); 5.44, (d, 1H, N—CH—N, $J = 2.0$ Hz); 3.88 (s, 1H, N—CH—C); 4.0–2.7 (m, 3H, CH—CH—CH); 2.30, 2.15, 1.33, 1.13 (4s, 3H each, CH_3); 1.65 ppm (s, 2H, NH).

Received: December 28, 1982

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