A Novel Two-Step Synthesis of Hexahydropyrazino[1,2-α]-quinolines

Walter H.N. Nijhuis, Willem Verboom, David N. Reinhoudt*

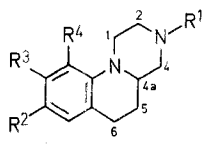
Laboratory of Organic Chemistry, Twente University of Technology, P.O. Box 217, 7500 AE Enschede, The Netherlands

The hexahydropyrazino[1,2-*a*]quinolines **2** were prepared in good yields by reaction of 2-(4-substituted 1-piperazinyl)benzaldehydes **5** with malononitrile and subsequent thermal cyclization of the condensation products **6**; the latter reaction takes place *via* a concerted [1,5] hydrogen transfer and subsequent ring closure by addition of a carbanion to the iminium double bond.

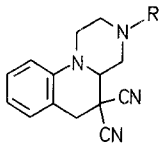
The 2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines **1** comprise a very interesting class of compounds because several representatives show significant biological activities. Hypotensive and CNS depressant properties were recently reported for compounds **1** with R^1, R^2, and R^4 = H and R^3 = CF_3 and for compounds **1** in which R^1 is an alkyl or aryl substituent and R^2-R^4 hydrogen atoms.[1] Several members of this class of heterocycles also exhibit activity against early developing forms of *Schistosoma mansoni*, e.g. when R^1 = H, R^2 = CH_2OH, R^3 = Cl, and R^4 = CH_3.[2]

In the literature, several multi-step syntheses of this class of heterocycles have been described, all starting from the appropriately 2-substituted 1,2,3,4-tetrahydroquinolines, e.g. *via* cyclization of 2-{[(1,2,3,4-tetrahydro-2-quinolinyl)methyl]-amino}ethanol,[3] *via* 2-cyanoquinoline,[4] *via* *N*-[(1,2,3,4-tetrahydro-2-quinolinyl)methyl]benzamide followed by ethylene oxide condensation and hydrogen bromide treatment,[5] or *via* cyclization of 2-{[(6-methyl-2-quinolinyl)methyl]amino}ethanol.[6]

As part of our investigations on the possible applications of the "*tert*-amino effect"[7] in heterocyclic synthesis, viz. the formation of *N*-heterocycles by ring closure of *N,N*-dialkylanilines that have a 2π-substituent at the 2-position, we have previously described the synthesis of pyrrolo[1,2-*a*]indoles,[8] pyrrolo[1,2-*a*]quinolines,[9] benzoxazines,[10] benzothiazines and a quinazoline.[11] In this paper we present an extremely facile two-step route to the 2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline skeleton **2** using this reaction principle.

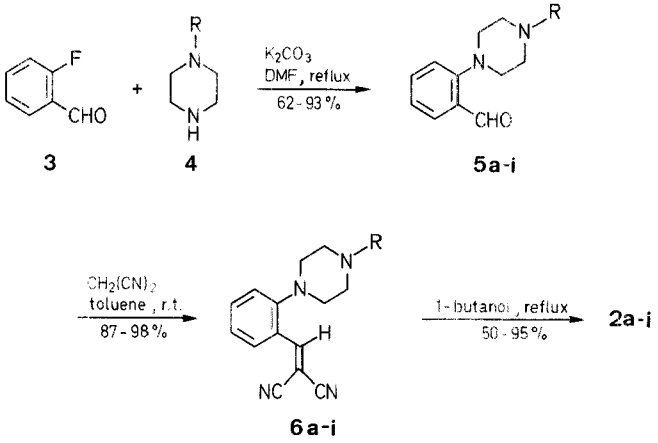


1



2

Reaction of 2-fluorobenzaldehyde (**3**) and suitably *N*-monosubstituted piperazines **4** gave the corresponding piperazinylbenzaldehydes **5** in high yields (Scheme **A**, Table 1) by refluxing in *N,N*-dimethylformamide in the presence of potassium carbonate according to the procedure as described by Niewiadomski and Suschitzky.[12] Knoevenagel condensation of **5** with malononitrile (propanedinitrile) in toluene at room temperature afforded the corresponding {[2-(4-substituted 1-pyrazinyl)-phenyl]methylene}propanedinitriles **6** as yellow-orange solids in high yields (Scheme **A**, Table 2). Heating of **6** in refluxing 1-butanol gave the *N*-substituted 5,5-dicyanohexahydropyrazino[1,2-*a*]quinolines **2** as solid compounds in a very smooth reaction (Scheme **A**, Table 3). All compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, and IR spectroscopy, mass spectrometry and elemental analysis. Characteristic for compounds **2** are for example, the $ArCH_2$ absorptions (singlets) in the ^{1}H-NMR spectra between δ 3.50 and 3.60 and the $C(CN)_2$ (singlets), $ArCH_2$ (triplets) and NCH (doublets) absorptions in the ^{13}C-NMR spectra between δ 34.7–35.2, 37.4–37.5, and 57.7–58.9, respectively.

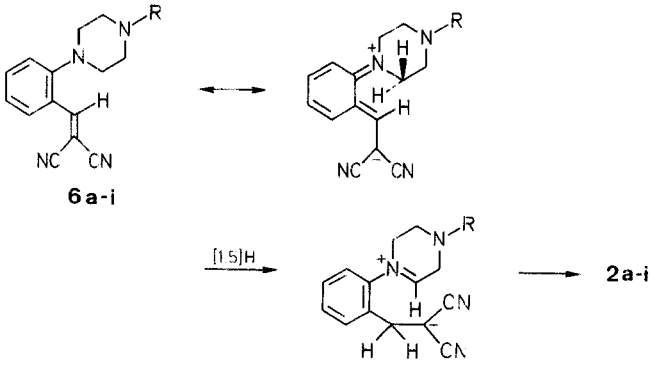


3 **4** **5a-i** **6a-i**

2, 4–6	R	2, 4–6	R	2, 4–6	R
a	CH_3	**d**	C_6H_5	**g**	2-CH_3-5-ClC_6H_3
b	c-C_6H_{11}	**e**	4-FC_6H_4	**h**	3-$CF_3C_6H_4$
c	$C_6H_5CH_2$	**f**	3-ClC_6H_4	**i**	2,6-$(CH_3)_2C_6H_3$

Scheme **A**

The synthesis of **6** can also be performed in a one pot procedure, as illustrated by the preparation of **2c** directly from **5c** and malononitrile. Heating of these two compounds for five days in refluxing toluene gave **2c** in 81 % yield. According to thin layer chromatography the first step (**5c** → **6c**) was completed within ~ 4 h at this higher reaction temperature, while some cyclized product was also already present. In toluene, the cyclization requires a longer time, irrespective of the somewhat lower reaction temperature compared with refluxing 1-butanol, because the reaction proceeds *via* a dipolar intermediate, which will be better stabilized in a more polar solvent. Consequently the reaction will be faster in 1-butanol than in toluene. The first step comprises a thermal suprafacial [1,5] hydrogen shift of one of the α-methylene protons adjacent to nitrogen in **6** producing the zwitterion **7**.[9] Finally, intramolecular addition to the iminium double bond gives the cyclized products **2**.



6a-i **7a-i**

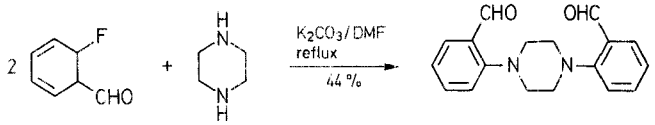
Scheme **B**

We have also tried to synthesize the basic skeleton **2** (R = H) in this way. Reaction of 2-fluorobenzaldehyde (**3**) with piperazine (**4j**, R = H) did not give the desired piperazinylbenzaldehyde **5j** (R = H), but rather the bis-substituted piperazine **8** in 44 % yield.

Table 1. Synthesis of 2-(4-substituted 1-pyrazinyl)benzaldehydes **5a–i**[a]

Product	Yield[b] (%)	m.p.[c] (°C)	Molecular Formula[d]	IR (KBr) ν (cm^{-1})	MS (70 eV) *m/e* (M$^+$, %)	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)	^{13}C-NMR ($CDCl_3$/TMS)[e] δ (ppm)
5a	67	oil	$C_{12}H_{16}N_2O$ (204.1)	1680, 1595	204.127 (55)	2.37 (s, 3H, CH_3); 2.55–2.7, 3.05–3.2 (m, 4H, NCH_2); 7.0–7.2, 7.4–7.9 (m, 2H, ArH); 10.33 (s, 1H, CHO)	45.9 (q, CH_3); 53.8, 55.0 (t, NCH_2); 128.5 (s, ArC-1); 155.5 (s, ArC-2); 191.1 (d, CHO)
5b	71	70–71	$C_{17}H_{24}N_2O$ (272.2)	1680, 1590	272.187 (100)	1.1–2.7 (m, 11H, C_6H_{11}); 2.65–3.2 (m, 8H, CH_2); 7.05–7.9 (m, 4H, ArH); 10.39 (s, 1H, CHO)	25.8, 26.3, 29.0 (t, CH_2); 49.0, 54.5 (t, NCH_2); 63.5 (d, CH); 128.6 (s, ArC-1); 155.7 (s, ArC-2); 191.3 (d, CHO)
5c	81	oil	$C_{20}H_{18}N_2O$ (280.2)	1685, 1595	280.156 (14)	2.45–2.7, 2.9–3.15 (m, 4H, NCH_2); 3.55 (s, 2H, CH_2Ar); 6.9–7.95 (m, 9H, ArH); 10.30 (s, 1H, CHO)	53.0, 53.9 (t, NCH_2); 62.9 (t, CH_2Ar); 128.6 (s, ArC-1); 137.8 (s, ArC); 155.6 (s, ArC-2); 191.1 (d, CHO)
5d	83	114.5–116.5	$C_{17}H_{18}N_2O$ (266.1)	1680, 1590	266.141 (22)	3.1–3.5 (m, 8H, NCH_2); 6.85–7.95 (m, 9H, ArH); 10.39 (s, 1H, CHO)	49.3, 53.9 (t, NCH_2); 128.7 (s, ArC-1); 150.9 (s, ArC); 155.2 (s, ArC-2); 191.0 (d, CHO)
5e	91	86–87	$C_{17}H_{17}FN_2O$ (284.1)	1680, 1600	284.130 (100)	3.27 (bs, 8H, NCH_2); 6.9–7.25 (m, 6H, ArH); 7.45–7.9 (m, 2H, ArH); 10.38 (s, 1H, CHO)	50.3, 53.9 (t, NCH_2); 128.7 (s, ArC-2); 147.7 (s, ArC); 155.2 (s, ArC-1); 157.2 (d, J = 239.6 Hz, ArC-F); 191.0 (d, CHO)
5f	84	146–147	$C_{17}H_{17}ClN_2O$ (300.1)	1680, 1590	300.100 (100)	3.2–3.5 (m, 8H, NCH_2); 6.75–7.95 (m, 8H, ArH); 10.38 (s, 1H, CHO)	48.9, 53.1 (t, NCH_2); 128.7 (s, ArC-1); 152.0 (s, ArC); 155.0 (s, ArC-2); 191.0 (d, CHO)
5g	84	150–151	$C_{18}H_{19}ClN_2O$ (314.1)	1680, 1590	314.116 (100)	2.29 (s, 3H, CH_3); 3.05–3.3 (m, 8H, NCH_2); 6.95–7.3 (m, 5H, ArH); 7.4–7.9 (m, 2H, ArH); 10.39 (s, 1H, CHO)	17.5 (q, CH_3); 51.6, 54.3 (t, NCH_2); 128.7 (s, ArC-1); 130.8, 131.7, 152.1 (s, ArC); 155.4 (s, ArC-2); 191.0 (d, CHO)
5h	93	89.5–90.5	$C_{18}H_{17}F_3N_2O$ (334.1)	1685, 1590	334.128 (100)	3.1–3.6 (m, 8H, CH_2); 7.05–7.95 (m, 7H, ArH); 10.38 (s, 1H, CHO)	48.9, 53.7 (t, NCH_2); 124.4 (q, J = 271.8 Hz, CF_3); 128.8 (s, ArC-1); 131.7 (q, J = 31.5 Hz, ArC–CF_3); 151.2 (s, ArC); 155.0 (s, ArC-2); 191.0 (d, CHO)
5i	62	127–129	$C_{19}H_{22}N_2O$ (294.2)	1680, 1595	294.172 (36)	2.37 (s, 6H, CH_3); 3.0–3.4 (m, 8H, NCH_2); 6.95–7.25 (m, 4H, ArH); 7.45–7.9 (m, 3H, ArH); 10.44 (s, 1H, CHO)	19.7 (q, CH_3); 49.7, 55.4 (t, NCH_2); 128.7 (s, ArC-1); 147.8 (s, ArC); 156.2 (s, ArC-2); 191.3 (d, CHO)

[a] 2-Fluorobenzaldehyde (**3**) and the substituted piperazines **4** are all commercially available.
[b] Yields refer to 2-fluorobenzaldehyde (**3**).
[c] Compounds **5** were recrystallized from petroleum ether (b.p. 60–80 °C)/dichloromethane 5:1.
[d] Satisfactory microanalyses obtained for all crystalline compounds: C ±0.24, H ±0.10, N ±0.23.
[e] The absorptions of the aromatic doublets are not mentioned.



Melting points are uncorrected and are measured with a Reichert microscope. IR spectra were recorded with a Perkin-Elmer 257 spectrophotometer. Mass spectra were recorded with a Varian Mat 311A spectrometer. ^{1}H-NMR spectra were obtained with a Bruker WP 80 spectrometer, while the ^{13}C-NMR spectra were obtained with a Nicolette MT 200-WB spectrometer.

2-(4-Substituted 1-pyrazinyl)benzaldehydes (5a–i); General Procedure:
A mixture of 2-fluorobenzaldehyde (**3**; 4.96 g, 40 mmol), piperazine **4** (47 mmol) and potassium carbonate (6.49 g, 47 mmol) in *N,N*-dimethylformamide (10 ml) is heated for 4 h at 152 °C. Upon cooling, the crude reaction mixture is taken up in water (100 ml) and extracted with ethyl acetate (3 × 75 ml). The combined organic layers are washed with a saturated aqueous solution of ammonium chloride (4 × 75 ml) and subsequently dried with magnesium sulfate. The solvent is removed under reduced pressure and the residue purified by column chromatography [silica gel, dichloromethane (except in the cases of **5a**: ethyl acetate, and **5b**: methanol/ethyl acetate 10/90] to yield **5a–i** (Table 1).

{[2-(4-Substituted 1-pyrazinyl)phenyl]methylene}propanedinitriles (6a–i); General Procedure:
A solution of **5a–i** (20 mmol) and malononitrile (1.32 g, 20 mmol) in toluene (20 ml) is stirred at room temperature for several days (Table 2). After completion of the reaction, the solvent is removed under reduced pressure. The resulting solid is purified by column chromatography [silica gel, dichloromethane (except in the cases of **6a**: ethyl acetate, and **6b**: methanol/ethyl acetate 10/90)].

3-Substituted 2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline-5,5-dicarbonitriles (2a–i); General Procedure:
A solution of **6a–i** (10 mmol) in 1-butanol (10 ml) is heated at 118 °C until, according to TLC, all the starting material has disappeared (Table 3). The solvent is removed under reduced pressure, and the resulting solids are purified by column chromatography [silica gel, dichloromethane (except in the cases of **2a**: ethyl acetate, and **2b**: methanol/ethyl acetate 10/90] yielding the pure **2a–i**.

Table 2. Synthesis of {[2-(4-Substituted-1-pyrazinyl)phenyl]methylene}propanedinitriles **6a–i**

Product	Reaction Time (d)	Yield[a] (%)	m.p. (°C) (CH_3OH)	Molecular Formula[b]	IR (KBr) ν (cm^{-1})	MS (70 eV) m/e (M^+, %)	^{1}H-NMR ($CDCl_3$/TMS)[c] δ (ppm)	^{13}C-NMR ($CDCl_3$/TMS)[d] δ (ppm)
6a	2	87	115–117	$C_{15}H_{16}N_4$ (252.1)	2220, 1595	252.136 (25)	2.39 (s, 3H, CH_3); 7.0–7.3 (m, 2H, ArH); 7.4–7.7 (m, 1H, ArH); 8.0–8.25 (m, 2H, HC=, ArH)	45.9 (q, CH_3); 81.6 (s, =C(CN)$_2$]; 112.7, 114.2 (s, CN); 124.9 (s, ArC-1); 154.4 (s, ArC-2); 157.2 (d, HC=)
6b	2	92	133–135	$C_{20}H_{24}N_4$[e] (320.2)	2230, 1595	320.198 (40)	0.9–2.75 (m, 11H, C_6H_{11}); 6.9–7.7 (m, 3H, ArH); 7.95–8.25 (m, 2H, HC=, ArH)	25.8, 26.3, 29.0 (t, CH_2); 63.5 (d, CH); 81.4 [s, =C(CN)$_2$]; 112.7, 114.3 (s, CN); 124.8 (s, ArC-1); 154.6 (s, ArC-2); 157.3 (d, HC=)
6c	5	98	110–111	$C_{21}H_{20}N_4$ (328.2)	2225, 1595	328.167 (25)	3.61 (s, 2H, CH_2Ar); 7.0–7.7 (m, 8H, ArH); 7.95–8.2 (m, 2H, ArH, HC=)	62.9 (t, CH_2Ar); 81.4 [s, =C(CN)$_2$]; 112.7, 114.2 (s, CN); 124.9 (s, ArC-1); 137.6 (s, ArC); 154.5 (s, ArC-2); 157.0 (d, HC=)
6d	8	97	158.5–160.5	$C_{20}H_{18}N_4$ (314.2)	2200, 1600	314.151 (20)	6.8–7.7 (m, 8H, ArH); 8.0–8.25 (m, 2H, HC=, ArH)	82.1 [s, =C(CN)$_2$]; 112.6, 114.2 (s, CN); 125.1 (s, ArC-1); 150.9 (s, ArC); 154.2 (s, ArC-2); 157.0 (d, HC=)
6e	9	93	194–195	$C_{20}H_{17}FN_4$ (332.1)	2220, 1595	332.142 (34)	6.8–7.75 (m, 7H, ArH); 8.0–8.25 (m, 2H, HC=, ArH)	82.1 [s, =C(CN)$_2$]; 112.6, 114.1 (s, CN); 125.1 (s, ArC-1); 147.5 (s, ArC); 154.1 (s, ArC-2); 157.0 (d, HC=); 157.6 (d, J = 239.4 Hz, ArC–F)
6f	9	97	190–192	$C_{20}H_{17}ClN_4$ (348.1)	2220, 1590	348.111 (39)	6.6–7.75 (m, 7H, ArH); 8.0–8.25 (m, 2H, HC=, ArH)	82.2 [s, =C(CN)$_2$]; 112.7, 114.1 (s, CN); 125.1 (s, ArC-1); 151.9 (s, ArC); 153.9 (s, ArC-2); 156.9 (d, HC=)
6g	9	97	208–210	$C_{21}H_{19}ClN_4$ (362.1)	2225, 1595	362.128 (17)	2.29 (s, 3H, CH_3); 6.9–7.35 (m, 5H, ArH); 7.45–7.7 (m, 1H, ArH); 8.0–8.25 (m, 2H, HC=, ArH)	81.9 [s, =C(CN)$_2$]; 112.6, 114.1 (s, CN); 125.1 (s, ArC-1); 151.8 (s, ArC); 154.3 (s, ArC-2); 157.1 (d, HC=)
6h	9	95	152–153	$C_{21}H_{17}F_3N_4$ (382.1)	2230, 1595	382.138 (50)	6.95–7.75 (m, 7H, ArH); 7.95–8.25 (m, 2H, HC=, ArH)	82.2 [s, =C(CN)$_2$]; 112.5, 114.1 (s, CN); 125.2 (s, ArC-1); 124.3 (q, J = 271.6 Hz, CF_3); 131.9 (q, J = 31.6 Hz, ArC–CF_3); 151.0 (s, ArC); 153.9 (s, ArC-2); 156.9 (d, HC=)
6i	9	96	174–176	$C_{22}H_{22}N_4$ (342.2)	2235, 1590	342.183 (10)	2.38 (s, 6H, CH_3); 6.9–7.35 (m, 5H, ArH); 7.5–7.75 (m, 1H, ArH); 8.0–8.35 (m, 2H, HC=, ArH)	19.7 (q, CH_3); 81.6 [s, =C(CN)$_2$]; 112.7, 114.3 (s, CN); 125.0 (s, ArC-1); 135.1 (s, ArC); 147.6 (s, ArC); 155.0 (s, ArC-2); 157.3 (d, HC=)

[a] Yields refer to compounds **5**.
[b] Satisfactory microanalyses obtained: C ±0.36, H ±0.09, N ±0.19.
[c] The absorptions of the NCH_2 protons are not mentioned.
[d] The absorptions of the NCH_2 carbon atoms and the aromatic doublets are not mentioned.
[e] No satisfactory elemental analyses could be obtained on account of decomposition of **6b**.

2,2′-(1,4-Piperazinediyl)bisbenzaldehyde (8):
A mixture of 2-fluorobenzaldehyde (**3**; 1.24 g, 10 mmol), potassium carbonate (3.65 g, 11.5 mmol), and piperazine hexahydrate (2.23 g, 11.5 mmol) in *N,N*-dimethylformamide (10 ml) is heated at 152 °C for 5 h. After cooling, the crude reaction mixture is taken up in water (25 ml) and extracted with ethyl acetate (3 × 20 ml). The combined organic layers are washed with a saturated aqueous solution of ammonium chloride (3 × 25 ml) and subsequently dried with magnesium sulfate. The solvent is removed under reduced pressure and the residue purified by column chromatography (silica gel, dichloromethane) affording **8**; yield: 0.44 g (26%); m.p. 177–179 °C [dichloromethane/petroleum ether (b.p. 60–80 °C) 1/5].

With 2 equivalents of 2-fluorobenzaldehyde (**3**) and potassium carbonate, after heating for 7 h at 152 °C, **8** is isolated in a yield of 44%.

$C_{18}H_{18}N_2O_2$ (294.4) calc. C 73.45 H 6.16 N 9.52
found 73.08 6.16 9.27

IR (KBr): ν = 1680, 1590 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.31 (s, 8H, NCH_2); 7.0–7.3, 7.4–7.95 (m, 4H$_{arom}$); 10.38 ppm (s, 2H, CHO).

^{13}C-NMR ($CDCl_3$/TMS): δ = 53.9 (t, NCH_2); 119.2, 123.0 (d, ArC); 128.8 (s, ArC); 130.3, 135.0 (d, ArC); 155.1 (s, ArC); 191.1 ppm (d, CHO).

Table 3. Synthesis of 3-Substituted 2,3,4,4a,5,6-Hexahydro-1*H*-pyrazino[1,2-*a*]quinoline-5,5-dicarbonitriles **2a–i**

Product	Reaction Time[a]	Yield[b] (%)	m.p. (°C) (CH_3OH)	Molecular Formula[c]	IR (KBr) ν (cm^{-1})	MS (70 eV) *m/e* (M^+, %)	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)	^{13}C-NMR ($CDCl_3$/TMS)[d] δ (ppm)
2a	13 h	54	166–167	$C_{15}H_{16}N_4$ (252.1)	2250, 1600	252.136 (100)	2.41 (s, 3H, CH_3); 2.1–2.5, 2.7–3.1, 3.2–3.6 (m, 2H, NCH_2); 3.53 (s, 2H, $ArCH_2$); 3.65–3.95 (m, 1H, NCH); 6.7–7.35 (m, 4H, ArH)	35.2 [s, $C(CN)_2$]; 37.4 (t, $ArCH_2$); 43.9 (q, CH_3); 46.4, 54.0, 57.5 (t, NCH_2); 57.7 (d, NCH); 115.6 (s, ArC-6a); 143.9 (s, ArC-10a)
2b	9 h	50	139–141	$C_{20}H_{24}N_4$ (320.2)	2245, 1600	320.196 (9)	0.9–2.3 (m, 11H, C_6H_{11}); 2.25–2.8, 2.85–3.2, 3.25–3.6 (m, 2H, NCH_2); 3.52 (s, 2H, $ArCH_2$); 3.7–4.0 (m, 1H, NCH); 6.65–7.3 (m, 4H, ArH)	25.7, 26.1, 28.6, 29.0 (t, CH_2); 35.0 [s, $C(CN)_2$]; 37.6 (t, $ArCH_2$); 47.0, 47.9, 52.1 (t, NCH_2); 58.4 (d, NCH); 63.4 [d, NCH (c-C_6H_{11})]; 115.6 (s, ArC-6a); 144.1 (s, ArC-10a)
2c	10 h	87	135–136	$C_{21}H_{20}N_4$ (328.2)	2255, 1600	328.167 (34)	2.10–2.65, 2.7–3.15 (m, 2H, NCH_2); 3.25–3.9 (m, 7H, $ArCH_2$, NCH_2, NCH); 6.7–7.45 (m, 9H, ArH)	35.0 [s, $C(CN)_2$]; 37.5 (t, $ArCH_2$); 46.5, 51.6, 55.8 (t, NCH_2); 57.9 (d, NCH); 62.5 (t, N–CH_2Ar); 115.6 (s, ArC-6a); 136.9 (s, ArC); 144.0 (s, ArC-10a)
2d	4 d	79	191–192.5	$C_{20}H_{18}N_4$ (314.2)	2250, 1600	314.151 (2)	2.9–4.3 (m, 7H, NCH, NCH_2); 3.57 (s, 2H, $ArCH_2$); 6.75–7.5 (m, 9H, ArH)	34.8 [s, $C(CN)_2$]; 37.5 (t, $ArCH_2$); 46.6, 49.4, 52.6 (t, NCH_2); 57.9 (d, NCH); 115.7 (s, ArC-6a); 143.8 (s, ArC-10a); 150.0 (s, ArC)
2e	2 d	92	169–170	$C_{20}H_{17}FN_4$ (332.1)	2250, 1600	332.142 (85)	2.75–3.3 (m, 4H, NCH_2); 3.35–3.75 (m, 2H, NCH_2); 3.57 (s, 2H, $ArCH_2$); 3.8–4.15 (m, 1H, NCH); 6.75–7.4 (m, 8H, ArH)	34.8 [s, $C(CN)_2$]; 37.4 (t, $ArCH_2$); 46.7, 50.3, 53.6 (t, NCH_2); 58.0 (d, NCH); 107.2 (s, ArC-6a); 119.3 (d, J = 8.8 Hz, ArC); 143.7 (s, ArC-10a); 146.6 (s, ArC); 158.1 (d, J = 241.3 Hz, ArC–F)
2f	4 d	89	158–159	$C_{20}H_{17}ClN_4$ (348.1)	2245, 1595	348.111 (100)	2.9–4.25 (m, 7H, NCH, NCH_2); 3.56 (s, 2H, $ArCH_2$); 6.75–7.4 (m, 8H, ArH)	34.7 [s, $C(CN)_2$]; 37.4 (t, $ArCH_2$); 46.4, 48.9, 52.0 (t, NCH_2); 57.8 (d, NCH); 115.7 (s, ArC-6a); 135.2 (s, ArC); 143.6 (s, ArC-10a); 151.0 (s, ArC)
2g	4 d	95	208–210	$C_{21}H_{19}ClN_4$ (362.1)	2245, 1590	362.126 (18)	2.30 (s, 3H, CH_3); 2.85–3.8 (m, 6H, NCH_2); 3.57 (s, 2H, $ArCH_2$); 3.85–4.25 (m, 1H, NCH); 6.85–7.45 (m, 7H, ArH)	17.4 (q, CH_3); 34.7 [s, $C(CN)_2$]; 37.4 (t, $ArCH_2$); 47.0, 51.0, 54.4 (t, NCH_2); 58.4 (d, NCH); 115.7 (s, ArC-6a); 130.9, 132.0 (s, ArC); 143.8 (s, ArC-10a); 150.8 (s, ArC)
2h	4 d	95	177–178.5	$C_{21}H_{21}F_3N_4$ (382.1)	2250, 1600	382.139 (37)	3.0–4.3 (m, 7H, NCH, NCH_2); 3.57 (s, 2H, $ArCH_2$); 6.75–7.60 (m, 8H, ArH)	34.8 [s, $C(CN)_2$]; 37.4 (t, $ArCH_2$); 46.5, 49.0, 52.0 (t, NCH_2); 57.9 (d, NCH); 113.4 (d, J = 4.3 Hz, ArC); 115.7 (s, ArC-6a); 117.8 (d, J = 4.3 Hz, ArC); 124.0 (q, J = 271.6 Hz, CF_3); 131.8 (q, J = 32 Hz, ArC–CF_3); 143.5 (s, ArC-10a); 150.2 (s, ArC)
2i	3 d	77	175–177	$C_{21}H_{22}N_4$ (342.2)	2240, 1600	342.184 (100)	2.35 (br s, 6H, CH_3); 2.9–4.05 (m, 7H, NCH, NCH_2); 3.56 (s, 2H, $ArCH_2$); 6.9–7.45 (m, 7H, ArH)	19.4, 20.1 (q, CH_3); 34.7 [s, $C(CN)_2$]; 37.5 (t, $ArCH_2$); 48.0, 49.4, 53.0 (t, NCH_2); 58.9 (d, NCH); 115.8 (s, ArC-6a); 136.1, 137.0 (s, ArC); 144.3 (s, ArC-10a); 146.7 (s, ArC)

[a] Reaction time given in hours (h) or days (d).
[b] Yields refer to compounds **6**.
[c] Satisfactory microanalyses were obtained: C ±0.24, H ±0.14, N ±0.29.
[d] The absorptions of the carbon atoms of the cyano group (singlets) and the aromatic doublets are not mentioned.

This investigation was supported by the Netherlands Foundation of Chemical Research (SON) with financial aid from the Netherlands Organization for Advancement of Pure Research (ZWO).

Received: 22 December 1986

(1) Singh, G.B., Srimal, R.C., Dhawan, B.N. *Arzneim.-Forsch./Drug Res.* **1978**, *28 II*, 1641, and references cited therein.
Saxena, A.K., Murthy, V.A., Jain, P.C., Srimal, R.C., Nityanand, S. *Indian J. Chem.* **1980**, *19B*, 879, and references cited therein.
Huff, J.R., King, S.W., Saari, W.S., Springer, J.P., Martin, G.E., Williams, M. *J. Med. Chem.* **1985**, *28*, 945.
(2) Richards, H.C., in: *Medicinal Chemistry, The Role of Organic Chemistry in Drug Research*, Roberts, S.M., Price, B.J. (eds.), Academic Press, London, **1985**, pp. 271–289, and references cited therein.
(3) Rupe, H., Thommen, W. *Helv. Chim. Acta* **1947**, *30*, 920.
(4) Nagata, M., Yamazaki, T. *Yakugaku Zasshi* **1963**, *83*, 679; *C.A.* **1963**, *59*, 12812.
(5) Rao, V.A., Jain, P.C., Nityanand, S. *Indian J. Chem.* **1969**, *7*, 833.
(6) Baxter, C.A.R., Richards, H.C. *J. Med. Chem.* **1972**, *15*, 351.
(7) Meth-Cohn, O., Suschitzky, H. *Adv. Heterocyclic Chem.* **1972**, *14*, 211.
(8) Reinhoudt, D.N., Visser, G.W., Verboom, W., Benders, P.H., Pennings, M.L.M. *J. Am. Chem. Soc.* **1983**, *105*, 4775.
Dijksman, W.C., Verboom, W., Egberink, R.J.M., Reinhoudt, D.N. *J. Org. Chem.* **1985**, *50*, 3791.
Verboom, W., Lammerink, B.H.M., Egberink, R.J.M., Reinhoudt, D.N., Harkema, S. *J. Org. Chem.* **1985**, *50*, 3797.
(9) Verboom, W., Reinhoudt, D.N., Visser, R., Harkema, S. *J. Org. Chem.* **1984**, *49*, 269.
(10) Verboom, W., van Dijk, B.G., Reinhoudt, D.N. *Tetrahedron Lett.* **1983**, *24*, 3923.
(11) Verboom, W., Hamzink, M.R.J., Reinhoudt, D.N., Visser, R. *Tetrahedron Lett.* **1984**, *25*, 4309.
(12) Niewiadomski, K.B., Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1679.
(13) Rao, V.A., Jain, P.C., Nityanand, S., Srimal, R.C., Dua, P.R. *J. Med. Chem.* **1970**, *13*, 516.