[Chem. Pharm. Bull. 33(5)1826—1835(1985)]

Aminohaloborane in Organic Synthesis. IX.[1] Exclusive *ortho* Acylation Reaction of *N*-Monoaminoalkylanilines

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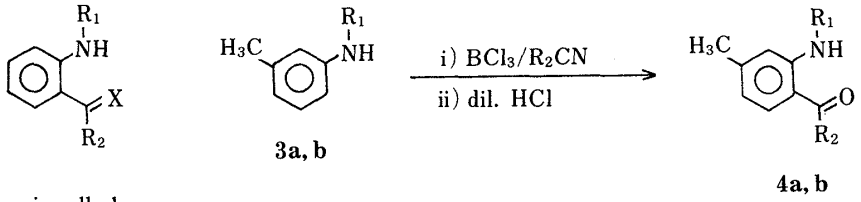
(Received August 1, 1984)

The exclusive *ortho* acylation reaction of aniline derivatives using boron trichloride made possible the one-step synthesis of 2-acyl-*N*-monoaminoalkylanilines (**1**) and the corresponding imines (**2**) from *N*-monoaminoalkylanilines, even in the case of compounds with a bulky substituent at the nitrogen atom. Conventional methods only give **1** *via* elaborate procedures.

Keywords——regioselective reaction; 2-acylaniline derivative; 2-acylaniline-imine derivative; boron trichloride

Continuing our studies on the exclusive *ortho* acylation reaction of anilines using boron trichloride and nitriles,[2] we tried to extend this methodology to the synthesis of 2-acyl-*N*-monoaminoalkylanilines **1** and the corresponding imines **2**, which are unknown in the literature, except for **1** ($R_1=(CH_2)_{2-3}NEt_2$, $R_2=Ph$).[3] Our present study showed that when the group causing the steric hinderance included an aliphatic amine moiety, the reaction proceeded very well. This offered an interesting contrast to our original method, in which 2-benzoylanilines carrying bulky substituents on the nitrogen, such as compounds **4a** and **4b**, were obtained only in moderate yields, 40% and 30%, starting from **3a** and **3b** (Chart 1).



R_1 = aminoalkyl
R_2 = aryl, alkyl, haloalkyl
1: X=O **2**: X=NH

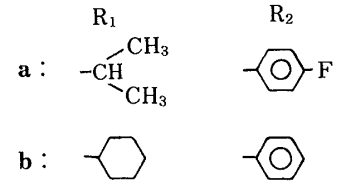


Chart 1

We found that *N*-(1-methyl-4-piperidinyl)aniline (**5a**) gave the desired compound **1a** in almost quantitative yield when **5a** was treated with boron trichloride to give an intermediary anilinodichloroborane **6**, followed by heating with benzonitrile and acidic work-up (method A). The corresponding 2-benzoylanilinine-imine **2a** was also isolated in excellent yield after alkaline work-up (Chart 2).

To test whether the presence of the aliphatic amine moiety would facilitate the reaction, we tried the reaction of **3a** with benzonitrile in the presence of an equimolar amount of *N*-methylpiperidine, but observed no improvement in the yield of **4a**. Thus, the presence of the

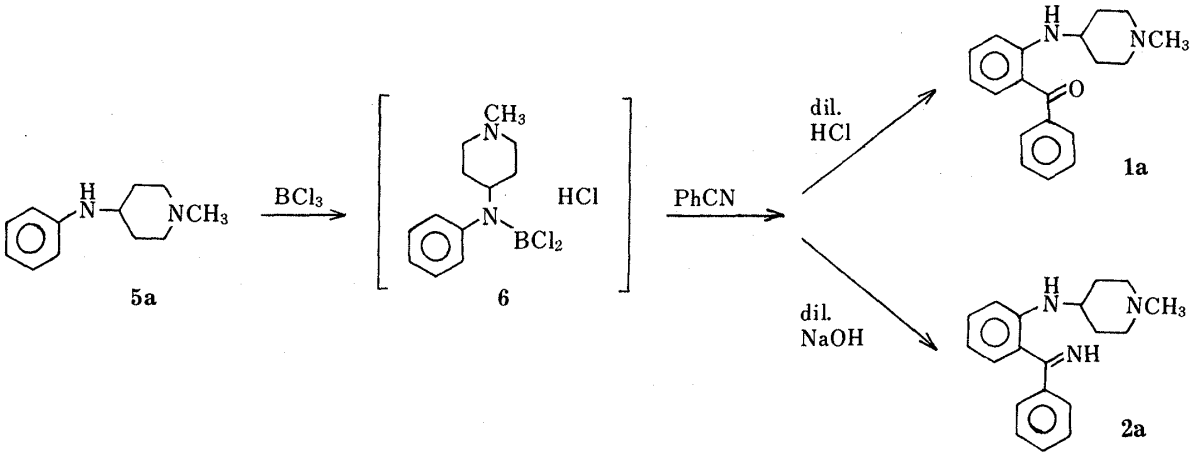
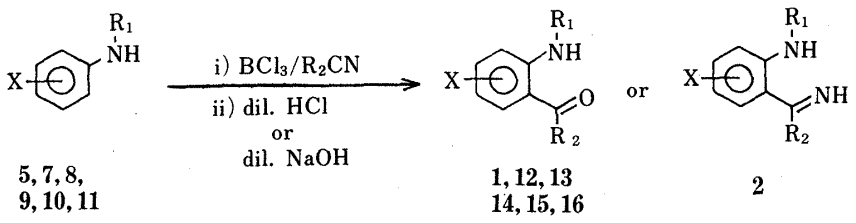


Chart 2

aliphatic amine on the nitrogen atom of aniline activated the reaction in some way. When nitriles having a low boiling point (under 150 °C) or anilines bearing a substituent labile to Lewis acid were used, a solution of aminoalkylanilines, boron trichloride and nitriles in dichloroethane was refluxed (method B). Our method was successfully applied to anilines carrying various aminoalkyl groups on the nitrogen atom, such as **5**, **7**, **8**, **9**, **10**, and **11**; thus, various 2-acylanilines **1**, **12**, **13**, **14**, **15**, **16** and imines **2** could be synthesized in excellent to good yields (Table I). Anilines carrying a secondary amine substituent such as **5j** and **5k** could also undergo the reaction; when the dihydrochlorides of **5j** and **5k** were treated with two molar equivalents of boron trichloride according to method B, **2l** and **2m**, respectively, were obtained (Tables II and III).



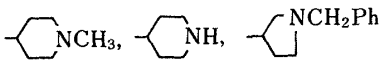
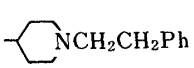
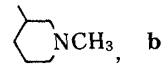
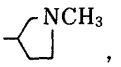
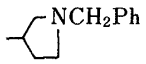
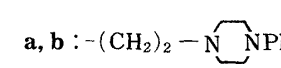
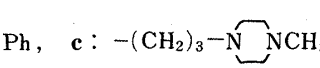
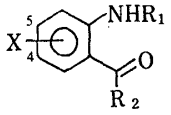
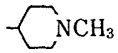
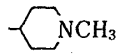
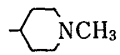
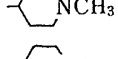
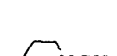
Comp.	R_1	R_2
5, 1, 2		aryl, alkyl
7, 12		aryl, alkyl, α-haloalkyl
8, 13		aryl, alkyl, α-haloalkyl
9, 14	**a**:  , **b**:  , **c**: 	aryl
10, 15	$-(CH_2)_2N(C_2H_5)_2$	aryl
11, 16	**a, b**:  , **c**: 	aryl, alkyl

Chart 3

The advantage of our new method is clear from a comparison of our process for obtaining **1a** with that using a conventional procedure involving Fischer's indole synthesis *via*

TABLE I. 2-Acyl-*N*-monoaminoalkylanilines



Compd.	X	R_1	R_2	mp °C (From)	Method (Time, h)	Yield (%)	^{1}H-NMR[a] ($CDCl_3$ δ)	Formula Analysis[b] (%) Calcd (Found) C H N
1a	H		Ph	193—203 2·HBr (Acetone)	A (3)	99		$C_{19}H_{22}N_2O \cdot 2HBr$ 50.02 5.30 6.14 (50.17 5.36 6.06)
1b	H		2-Cl-Ph	128—129 (Et_2O–hexane)	A (3)	99		$C_{19}H_{21}ClN_2O$ 69.39 6.44 8.52 (69.43 6.36 8.49)
1c	H		2-F-Ph	98—100 (CH_2Cl_2–hexane)	A (3)	97		$C_{19}H_{21}FN_2O$ 73.05 6.78 8.97 (73.02 6.79 9.08)
1d	H		4-F-Ph	152—182 (dec.) 2HCl, $0.5H_2O$ (iso-PrOH–Et_2O)	A (15)	96		$C_{19}H_{21}FNO_2 \cdot 2HCl \cdot 0.5H_2O$ 57.87 6.13 7.10 (57.90 6.14 7.09)
1e	H		*n*-Bu	178—198 (dec.) 2HBr (iso-PrOH–Et_2O)	B (20)	87	1.0 (3H, t, $J=7$ Hz, CH_2CH_3)	$C_{17}H_{28}Br_2N_2O$ 46.80 6.47 6.42 (46.72 6.61 6.42)
1f	4-Cl		Ph	Oil	A (3)	99		c)
1g	4-Cl		2-Cl-Ph	101—102 (Et_2O–hexane)	A (3)	92		$C_{19}H_{20}Cl_2N_2O$ 62.81 5.55 7.71 (62.84 5.46 7.65)
1h	4-Cl		CH_3	226—227 (dec.) 2HCl (CH_3OH)	B (40)	93	2.6 (3H, s, $COCH_3$)	$C_{14}H_{19}ClN_2O \cdot 2HCl \cdot 0.5CH_3OH$ 48.96 6.52 7.88 (48.97 6.25 8.38)
1i	4-Cl		2-F-Ph	Oil	A (3)	99		c)

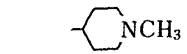
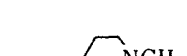
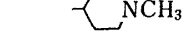
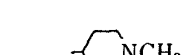
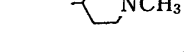
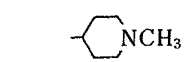
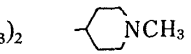
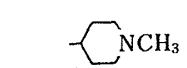
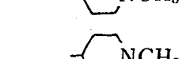
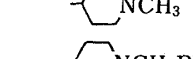
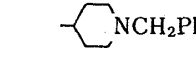
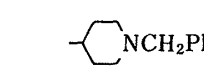
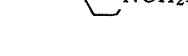
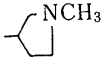
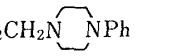
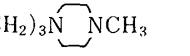
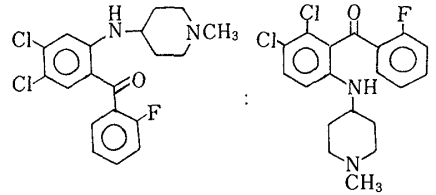
1j	4-Br		2-F–Ph	194—197 $C_2H_2O_4$ (iso-PrOH–Et_2O)	A (3)	97		$C_{19}H_{20}BrFN_2O \cdot C_2H_2O_4$ 52.40 4.60 5.82 (52.11 4.61 5.90)
1k	4-OCH_3		2-F–Ph	117—118 (Et_2O–hexane)	B (12)	56	3.6 (3H, s, OCH_3)	$C_{20}H_{23}FN_2O_2$ 70.15 6.77 8.18 (70.26 6.82 8.10)
1l	4-NO_2		2-Cl–Ph	154—156 (CH_2Cl_2–Et_2O)	A[d] (70)	53		$C_{19}H_{20}ClN_3O_3$ 16.04 5.32 11.24 (61.09 5.28 11.32)
1m	5-F		2-F–Ph	118—120 (CH_2Cl_2–Et_2O)	A (15)	67		$C_{19}H_{20}F_2N_2O$ 69.07 6.10 8.48 (69.27 6.02 8.50)
1n	4-$N(CH_3)_2$		Ph	Oil	A (8)	88	2.6 (6H, s, $N(CH_3)_2$)	c)
1o	4-F		2-F–Ph	Oil	A (3)	99		c)
1p	4,5-di-Cl		2-F–Ph	Oil	A (50)	86[e]		c)
12a	H		Ph	205—210 HCl (CH_2Cl_2–acetone)	A (16)	90	3.5 (2H, s, $-CH_2Ph$)	$C_{25}H_{26}N_2O \cdot HCl$ 73.78 6.69 6.89 (73.58 6.65 6.92)
12b	H		$-CH_2Cl$	167—168 HCl (CH_2Cl_2–acetone)	B[f] (3)	83		$C_{20}H_{23}N_2O \cdot HCl$ 63.32 6.38 7.39 (63.40 6.41 7.37)
13a	H		Ph	223—232 HCl (CH_3OH–acetone)	A (3)	93		$C_{26}H_{28}N_2O \cdot HCl$ 74.18 6.94 6.66 (73.93 6.95 6.66)
13b	H		$-CH_2Cl$	178—179 HCl (CH_2Cl_2–acetone)	B[f] (3)	83	4.7 (s, 2H, $COCH_2Cl$)	$C_{21}H_{25}ClN_2O \cdot HCl$ 64.12 6.66 7.12 (64.29 6.73 7.14)
13c	5-CH_3		Ph	222—228 HCl (CH_2Cl_2–acetone)	A (3)	81		$C_{27}H_{30}N_2O \cdot HCl$ 74.54 7.18 6.44 (74.10 7.25 6.41)
13d	4-Cl		Ph	203—208 HCl (CH_2Cl_2–acetone)	A (3)	91		$C_{26}H_{28}ClN_2O \cdot HCl \cdot 1/2CH_3COCH_3$ 67.78 6.53 5.86 (67.59 6.41 5.89)
14a	4-Cl		2-Cl–Ph	Oil	A (3)	93		c)

TABLE I. (continued)

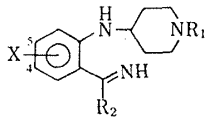
Compd.	X	R_1	R_2	mp °C (From)	Method (Time, h)	Yield (%)	^{1}H-NMR[a] ($CDCl_3$ δ)	Formula Analysis[b] (%) Calcd (Found) C	H	N
14b	4-Cl		2-Cl-Ph	205—209 HCl (CH_2Cl_2–acetone)	A (15)	95		$C_{18}H_{18}Cl_2N_2O\cdot HCl$ 56.05 (56.13)	4.96 (4.88)	7.26 (7.40)
15	H	$-CH_2CH_2N(Et)_2$	Ph	51—53 (*n*-Hexane)	A (3)	88[g]	1.05 (6H, t, J=7 Hz, $-N(CH_2C\underline{H}_3)_2$) 2.4—2.8 (6H, q×2, J=7 Hz, J=6 Hz, $-NCH_2C\underline{H}_2N(C\underline{H}_2CH_3)_2$) 3.3 (2H, q, J=6 Hz, $HNC\underline{H}_2CH_2N(CH_2CH_3)_2$)	$C_{19}H_{24}N_2O$ 76.99 (76.98)	8.16 (8.20)	9.45 (9.52)
16a	H		Ph	205—209 HCl (Acetone)	[h] (2)	97		$C_{25}H_{27}N_2O\cdot 1.5HCl$ 68.21 (68.29)	6.53 (6.61)	9.55 (9.44)
16b	H		CH_3	94—95 (Et_2O–*n*-hexane)	B[i] (20)	94[g]	2.6 (3H, s, $COCH_3$)	$C_{20}H_{25}N_3O$ 74.27 (74.39)	7.79 (7.93)	12.99 (13.11)
16c	H		Ph	Oil	A (15)	61[g]	2.1 (3H, s, NCH_3)	[c]		

IR spectra ($CHCl_3$ or film) of all compounds showed absorptions at *ca.* 3300—3200 cm^{-1} (NH) and at *ca.* 1630—1610 cm^{-1} (C=O). *a*) ^{1}H-NMR spectra ($CDCl_3$, δ) of all compounds showed absorptions at *ca.* 1.5—3.8 (m, aliph. H), at *ca.* 6.4—7.8 (m, arom. H) and at *ca.* 8.5—9.0 (d, J=6 Hz, NH). Besides these absorptions, **1** and **14** showed absorptions at *ca.* 2.3—2.4 (s, 3H, NCH_3). Values of other characteristic absorptions are also given in the table. *b*) Analytical values of halogens were within ±0.4% of the calculated values. *c*) Not analyzed. *d*) BCl_3 was added to a solution of *N*-(1-methyl-4-piperidinyl)-4-nitroaniline and PhCN in dichloroethane and the mixture was treated according to Method A.

e)  =3:1 from the peak height of NCH_3 (δ, 2.30 and 2.32) in the NMR spectrum.

f) The reaction mixture was worked up with dil. HCl according to the general method and the acidic layer was extracted with CH_2Cl_2. Evaporation of the solvent gave the hydrochloride of **12b** or **13b**. *g*) The crude product was purified on SiO_2 using CH_2Cl_2 containing 1—5% CH_3OH or $CH_3COOC_2H_5$. *h*) A mixture of *N*-[2-(4-phenyl-1-piperazinyl)ethyl]aniline·3HCl (5 mmol), BCl_3 (5×1.2 mmol) and PhCN (5×20 mmol) in toluene was heated at 145 °C for 2 h. *i*) *N*-[2-(4-Phenyl-1-piperazinyl)ethyl]aniline·3HCl was used.

TABLE II. 2-Acyl-*N*-(4-piperidinyl)aniline-imines



Compd.	X	R_1	R_2	mp C (From)	Yield (%)	^{1}H-NMR[a] ($CDCl_3$ δ)	Formula Analysis[b] (%) Calcd (Found) C H N
2a	H	CH_3	Ph	117—118 (EtOH)	90		$C_{19}H_{23}N_3$ 77.77 7.80 14.32 (78.00 7.91 14.26)
2b	H	CH_3	CH_3	101—102 (Et_2O)	83	2.5 (3H, s, HN=C$\underline{CH_3}$)	$C_{14}H_{21}N_3$ 72.68 9.15 18.17 (72.94 9.01 18.30)
2c	4-Cl	CH_3	Ph	115—117 (Et_2O)	98		$C_{19}H_{22}ClN_3$ 69.60 6.77 12.82 (69.64 6.49 12.74)
2d	4-Cl	CH_3	CH_3	125—127 (Et_2O)	55	2.5 (3H, s, HN=C$\underline{CH_3}$)	$C_{14}H_{20}ClN_3$ 63.26 7.59 15.81 (63.26 7.44 15.54)
2e	4-Cl	CH_3	2-F-Ph	145—146 (Et_2O)	92		$C_{19}H_{21}ClFN_3$ 65.98 6.12 12.15 (65.75 5.92 12.02)
2f	4-F	CH_3	Ph	130—131 (CH_2Cl_2–Et_2O)	87		$C_{19}H_{22}FN_3$ 73.28 7.12 13.49 (73.36 7.21 13.40)
2g	4-F	CH_3	2-F-Ph	131—132 (CH_2Cl_2–Et_2O)	96		$C_{19}H_{21}F_2N_3$ 69.28 6.43 12.76 (69.68 6.36 12.80)
2h	4-CH_3	CH_3	2-Cl-Ph	111—113 (Et_2O)	90	2.1 (3H, s, CCH_3)	$C_{20}H_{24}ClN_3$ 70.28 7.08 12.29 (69.85 6.76 12.11)
2i	4-OCH_3	CH_3	2-F-Ph	132—134 (Et_2O)	50	3.55 (3H, s, OCH_3)	$C_{20}H_{24}FN_3O$ 70.36 7.09 12.31 (70.27 6.98 12.29)
2j	4-Br	CH_3	Ph	110—112 (CH_2Cl_2–Et_2O)	92		$C_{19}H_{22}BrN_3$ 61.29 5.96 11.29 (61.13 5.81 11.28)
2k	4-Cl	CH_3	2-Cl-Ph	157—159 (Et_2O–hexane)	97		$C_{19}H_{21}Cl_2N_3$ 62.99 5.84 11.60 (62.96 5.84 11.59)
2l	4-F	CH_3	2-Cl-Ph	138—139 (C_6H_6–hexane)	97		$C_{19}H_{21}ClFN_3$ 65.98 6.12 12.15 (66.23 6.19 12.19)
2m	H	H	Ph	Oil	99[d]	1.2—3.8 (m, aliph. H) 6.3—7.6 (m, arom. H) 9.4 (2H, br s, –NH and =NH)	[c]
2n	4-Cl	H	2-F-Ph	Oil	99[d]	1.2—3.8 (m, aliph. H) 6.6—7.5 (m, arom. H) 9.5 (1H, s, =NH) 9.8 (1H, d, J=7 Hz, –NH–<)	[c]
2o	4-Cl	[e]	2-F-Ph	Oil	99	1.5—4.0 (m, aliph. H) 3.63 (s, N$\underline{CH_2}$Ph) 6.5—7.6 (m, arom. H) 9.50 (1H, s, =NH) 9.8 (1H, d, J=7 Hz, –NH–<)	[c]

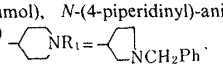
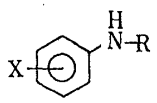
IR spectra ($CHCl_3$ or film) of all compounds showed absorptions at *ca.* 3300—3200 cm^{-1} (NH) and 1610—1600 cm^{-1} (=NH). *a*) ^{1}H-NMR spectra ($CDCl_3$, δ) of all compounds except **2l**, **2m** and **2n** showed at *ca.* 1.5—3.8 (m, aliph. H) at *ca.* 2.3 (s, NCH_3), at *ca.* 6.5—7.5 (m, arom. H) at *ca.* 9.3—9.9 (1H, d, J=7 Hz, –NH–<) and at *ca.* 9.3—9.5 (1H, s, =NH). The values of other characteristic absorptions are given in the table. *b*) Analytical values of halogens were within ±0.4% of the calculated values. *c*) Not analyzed. *d*) A mixture of BCl_3 (12×2.2 mmol), *N*-(4-piperidinyl)-aniline·2HCl (12 mmol) and PhCN (12×1.2 mmol) in dichloroethane (40 ml) was refluxed for 36 h. *e*) 

TABLE III. *N*-Azacycloalkylanilines



Compd.[a]	X	R	mp °C[b] or bp °C	Yield[c] (%)
5a[5]	H		82—83	78
5b[5]	4-Cl		91—92	78
5c[5]	4-F		92—93	79
5d[d]	4-Br		85—87	58
5e[5]	4-CH_3		125—127 (1 mm)	67
5f	4-OCH_3		130—145 (1 mm)	82
5g	4-NO_2		153—155	56
5h[5]	3,4-diCl		80—81	63
5i	4-$N(CH_3)_2$		139—141 (1 mm)	66
5j	H		226—240[e]	69
5k	4-Cl		279—280[e]	69
7	H		87—88	82
8a	H		96—98	81
8b	3-CH_3		Oil	86
9a	4-Cl		Oil	49
9b	4-Cl		50—51	57
9c[f]	4-Cl		178 (1 mm)	77

a) All compounds gave reasonable elemental analysis values (C, H, N). *b*) Recrystallized from Et_2O–*n*-hexane. *c*) Based on the *N*-substituted-3- or -4-oxo-piperidine or -pyrrolidine used. *d*) Prepared by using a Dean–Stark apparatus charged with SiO_2. *e*) Melting point °C (dec.) of dihydrochloride (EtOH). *f*) Prepared by heating 1-benzyl-3-chloropyrrolidine hydrochloride[9] (30 mmol) with *p*-chloroaniline (0.15 mol) at 160 °C for 2 h.

17 and **18** (37% yield over four steps). Another example is compound **19**, which was previously accessible only by an elaborate route including acylation, reduction, and back oxidation[3] (Chart 4).

The starting materials **5**, **7**, **8**, **9**, **10**, and **11** were synthesized in a conventional manner with some modification; **5**, **7**, and **8** were obtained by treatment of the anilines with the corresponding 1-alkyl-4-oxo-piperidine in the presence of molecular sieve[4] followed by $NaBH_4$ reduction.[5] However, *N*-(1-methyl-4-piperidinyl)-4-nitroaniline (**5g**) was synthesized by heating of 4-fluoronitrobenzene with 4-amino-1-methylpiperidine. Compounds **5j** and **5k** were synthesized by treatment of anilines with 1-ethoxycarbonyl-4-oxo-piperidine followed by

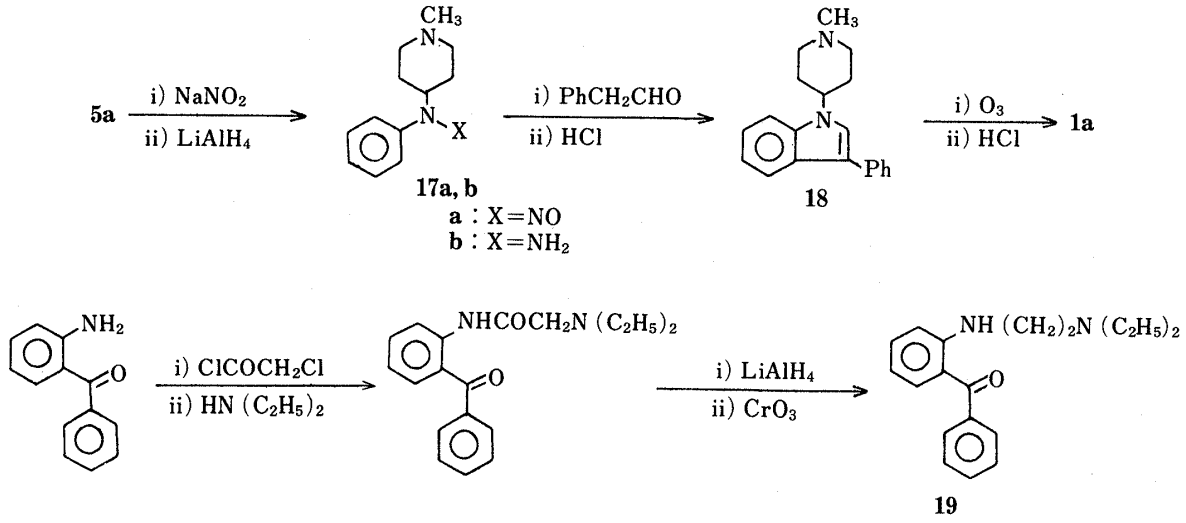


Chart 4

$NaBH_4$ reduction and hydrolysis with 6 N HCl. Compound **9** was obtained by condensation of the anilines with 1-ethoxycarbonyl-3-mesyloxy-piperidine or -pyrrolidine followed by reduction with lithium aluminum hydride (Chart 5 and Table III). Compounds **10** and **11** were synthesized according to the known methods.[6-8]

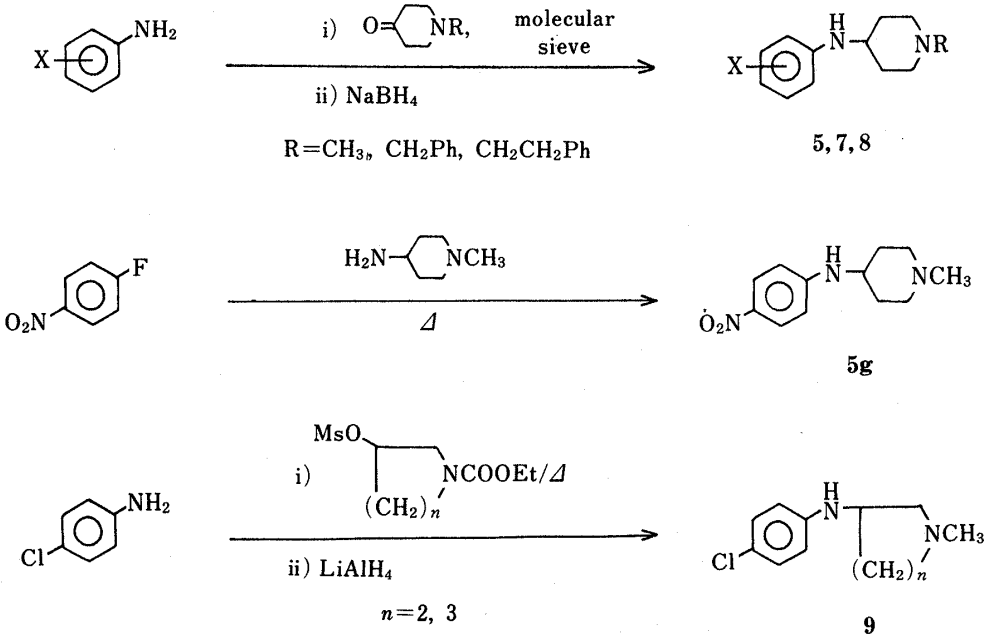


Chart 5

Thus, our method for synthesizing **1** and the corresponding imine **2** by using the exclusive *ortho* acylation reaction of *N*-monoaminoalkylanilines is a simple one, and may be suitable for obtaining intermediates for some pharmacologically interesting compounds.

Experimental

Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected. Infrared (IR) spectra were recorded in $CHCl_3$ solution with a Hitachi 260-10 IRS spectrophotometer. Wave numbers are expressed

in reciprocal centimeters. Nuclear magnetic resonance (NMR) spectra were taken in $CDCl_3$ solution on a Varian EM-390 or T-60 spectrophotometer. Chemical shifts are expressed as δ values (parts per million) from tetramethylsilane. Column chromatography was conducted using silica gel (E. Merck, 70—230 mesh ASTM) and aluminum oxide (E. Merck, Standardisiert). Silica gel GF and aluminum oxide F254 (E. Merck) were used for analytical thin-layer chromatography (TLC). In cases where products were isolated by solvent extraction, the procedure generally followed was to extract the aqueous layer with two to three portions of the indicated solvent, then to wash the organic layer with saturated NaCl–H_2O or H_2O and dry it over Na_2SO_4 or $MgSO_4$.

2-Acyl-*N*-monoaminoalkylaniline (1) and the Corresponding Imine (2) General Procedure——Method A: To a stirred solution of BCl_3 (25 × 1.2 mmol) in toluene (15 ml) was added a solution of a *N*-monoaminoalkylaniline **5** (25 mmol) in toluene (40 ml) under ice cooling. The resulting mixture was refluxed for 1 h and then the solvent was distilled off. To the resulting syrup, a nitrile (25 × 2 mmol) was added, and the mixture was heated at 150 °C (bath temperature) for 3 to 20 h under stirring. The progress of the reaction was monitored by TLC (Al_2O_3, CH_2Cl_2), which showed a yellow spot of 2-acylaniline. After cooling, ice and 1 N HCl (15 ml) were added and the mixture was warmed at 100 °C for 20 min under stirring to hydrolyze the corresponding ketimine. If the hydrochloride of compound **1** crystallized, it was filtered off and recrystallized. Otherwise, the acid layer was washed with ether or CH_2Cl_2 and alkalized with conc. NH_4OH or K_2CO_3. The mixture was extracted with CH_2Cl_2. In most cases the product showed a single spot on TLC and was used directly as the starting material for the next step. When some polar fractions had to be removed, filtration of a solution of the crude product in CH_2Cl_2 over Al_2O_3 was effective. To obtain the corresponding imine **2**, a solution of NaOH (20 g) in H_2O (40 ml) and CH_3OH (70 ml) was added to the cooled reaction mixture and the mixture was stirred at room temperature for 2 h. Extraction with CH_2Cl_2 and evaporation of the extract after drying gave almost pure **2**.

Method B: To a stirred solution of BCl_3 (20 × 1.2 mmol) in dichloroethane (12 ml) was added a solution of *N*-monoaminoalkylaniline **5** (20 mmol) in the same solvent (38 ml) under ice cooling. A nitrile was added and the mixture was refluxed for 20 h. Work-up as described in method A gave **1** (Tables I and II).

2-(4-Fluorobenzoyl)-*N*-isopropyl-5-methylaniline (4a)——According to the general method A and work-up described in the literature,[2] **4a** was obtained from *N*-isopropyl-3-methylaniline (prepared from 3-methylaniline and isopropyliodide by refluxing for 45 min in the presence of $NaHCO_3$, bp 106—109 °C (15 mmHg), 77%) and 4-fluorobenzonitrile after purification by chromatography (SiO_2, benzene) in 40% yield. Oil, IR ν_{max}^{film} cm^{-1}: 3300, 1620. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (6H, d, J=7 Hz), 2.3 (3H, s), 3.8 (1H, q, J=7 Hz), 6.2—7.7 (7H, m, including ABX pattern), 8.5 (1H, br s). 2-(4-Fluorobenzoyl)-*N*-isopropyl-3-methylaniline was also obtained as a more polar fraction in 3% yield. Oil, IR ν_{max}^{film} cm^{-1}: 3400, 1660. ^{1}H-NMR ($CDCl_3$) δ: 1.1 (6H, d, J=7 Hz), 2.0 (3H, s), 3.6 (1H, q, J=7 Hz), 4.0 (1H, br s), 6.5—8.0 (7H, m).

2-Benzoyl-*N*-cyclohexyl-5-methylaniline (4b)——By using a procedure similar to that described for **4a**, **4b** was obtained from *N*-cyclohexyl-3-methylaniline (prepared from 3-methylaniline and cyclohexanone followed by reduction with $NaBH_4$, bp 104 °C (2 mmHg), 70%) and benzonitrile in 31% yield. Oil, IR ν_{max}^{film} cm^{-1}: 3270, 1610. ^{1}H-NMR ($CDCl_3$) δ: 1.0—2.2 (10H, m), 2.3 (3H, s), 3.5 (1H, br s), 6.2—7.7 (8H, m, including ABX pattern). 8.8 (1H, d, J=8 Hz).

***N*-(1-Methyl-4-piperidinyl)-*N*-nitrosoaniline (17a)**——To a stirred solution of *N*-(1-methyl-4-piperidinyl)aniline (3.8 g, 20 mmol) in EtOH (15 ml) containing conc. HCl (42 ml, 20 × 2.5 mmol) was added a solution of $NaNO_2$ (1.52 g, 20 × 1.1 mmol) in H_2O dropwise at −10 °C, and the solution was stirred at the same temperature for 1 h. After the addition of K_2CO_3, the whole was extracted with CH_2Cl_2. The extract was evaporated and the residue was crystallized from Et_2O and petroleum-ether, giving **17a** (4.25 g, 97%, mp 78—79 °C). *Anal.* Calcd for $C_{12}H_{17}N_3O$: C, 65.72; H, 7.81; N, 19.16. Found: C, 65.94; H, 7.79; N, 19.18. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1451 (N–NO).

***N*-Amino-*N*-(1-methyl-4-piperidinyl)aniline (17b)**——To a stirred solution of **17a** (3.9 g, 17.8 mmol) in dried Et_2O (80 ml) was added $LiAlH_4$ (0.74 g, 17.8 × 1.1 mmol, recrystallized from dried Et_2O) at 5 °C, and the mixture was stirred at room temperature. Further, $LiAlH_4$ (three 0.3 g portions) was added at 1 h intervals. After quenching of excess $LiAlH_4$ with wet Et_2O, the precipitate was filtered off and washed with Et_2O. The filtrate was concentrated and the residue was crystallized from Et_2O and *n*-hexane, giving **17b** (2.8 g, 77%, mp 64—65 °C). *Anal.* Calcd for $C_{12}H_{19}N_3$: C, 70.20; H, 9.33; N, 20.47. Found: C, 70.23; H, 9.25; N, 20.40. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3368, 1599.

***N*-(1-Methyl-4-piperidinyl)-3-phenylindole (18)**——A mixture of **17b** (2.48 g, 12.1 mmol) and phenylacetoaldehyde (1.74 g, 12 × 1.2 mmol) was heated at 100 °C for 1 h. After removal of the excess reagent, the resulting oily phenylhydrazone (3.7 g) was heated in 1.35 N HCl gas/EtOH (60 ml) at reflux for 1 h. After removal of the solvent, ice water and K_2CO_3 were added and the mixture was extracted with CH_2Cl_2. Recrystallization of the product from Et_2O–*n*-hexane gave **18** (2.73 g, 78%, mp 112—114 °C). *Anal.* Calcd for C, 82.72; H, 7.64; N, 9.65. Found: C, 82.76; H, 7.55; N, 9.21. ^{1}H-NMR ($CDCl_3$) δ: 4.2 (1H, m, ) 7.0—8.0 (9H, m, arom. H).

2-Benzoyl-*N*-(1-methyl-4-piperidinyl)aniline (1a) from Compound 18——Dry ozone was bubbled (100 l/h O_2-stream) into a solution of **18** (290 mg) in AcOH (3 ml) at room temperature for 5 min. After the excess ozone had been expelled by flushing with dry N_2, ice and dil. NH_4OH were added, and the mixture was extracted with Et_2O. The oily

extract, 2-benzoyl-*N*-(1-methyl-4-piperidinyl)-*N*-formylaniline, was dissolved in 6 N HCl (4 ml) and the solution was refluxed for 1.5 h. After cooling, ice and K_2CO_3 were added, and the mixture was extracted with CH_2Cl_2. The extract was purified on SiO_2 using CH_2Cl_2 and CH_2Cl_2 containing 1% CH_3OH, giving oily **1a** (185 mg, 63%).

(1-Alkyl-4-piperidinyl)aniline (5, 7, 8)——A solution of an aniline (30 × 1.2 mmol) and 1-alkyl-4-oxo-piperidine (30 mmol) in benzene (12 ml) was refluxed (20 h) or stirred at room temperature (50—70 h) in the presence of molecular sieve 4A (6 g). Et_2O was added, then the molecular sieve was filtered off and washed with Et_2O. The filtrate and washing were combined and concentrated, and the residue was dissolved in 95% EtOH (50 ml). To the stirred solution was added $NaBH_4$ (15 mmol) and the solution was stirred at room temperature for 5 h. After removal of EtOH, H_2O was added and the mixture was extracted with CH_2Cl_2. The extract was evaporated and the residue was crystallized from Et_2O–petroleum-ether or distilled under reduced pressure.

1-(Methyl-4-piperidinyl)-4-nitroaniline (5g)——A mixture of 4-amino-1-methylpiperidine (4.82 g, 32.3 mmol) and 4-fluoronitrobenzene (4.56 g, 32.3 mmol) was warmed at 100 °C for 7 h. After cooling, 1 N HCl (40 ml) was added and the mixture was washed with Et_2O. The acidic layer was alkalized with conc. NH_4OH and extracted with CH_2Cl_2. Recrystallization of the extract from Et_2O–petroleum-ether gave **5g** (4.27 g, 56%, mp 153—155 °C).

4-Chloro-*N*-(4-piperidinyl)aniline (5k) and *N*-(4-Piperidinyl)aniline (5j)——A solution of 4-chloroaniline (7.65 g, 60 mmol) and 1-ethoxycarbonyl-4-oxo-piperidine (8.56 g, 50 mmol) in benzene (20 ml) was refluxed for 20 h in the presence of molecular sieve 4A (20 g) under stirring. Subsequent reduction and work-up ($NaBH_4$; 950 mg, 25 mmol, 95% EtOH; 75 ml) in the same manner as above gave 4-chloro-*N*-(1-ethoxycarbonyl-4-piperidinyl)aniline (mp 118—120 °C, 10.5 g, 74%). *Anal.* Calcd for $C_{14}H_{19}ClN_2O_2$: C, 59.46; H, 6.77; Cl, 12.53; N, 9.91. Found: C, 59.17; H, 6.63; Cl, 12.36; N, 9.93. 4-Chloro-*N*-(1-ethoxycarbonyl-4-piperidinyl)aniline (10 g) was refluxed for 16 h in 6 N HCl (50 ml). After removal of HCl, the residue was crystallized from 99% EtOH, giving **5k**·2 HCl (mp 279—280 °C (dec.) 92%). *N*-(4-Piperidinyl)aniline (**5j**) was obtained in a similar manner.

4-Chloro-(1-methyl-3-piperidinyl)aniline (9a) and 4-Chloro-(1-methyl-3-pyrrolidinyl)aniline (9b)——1-Ethoxycarbonyl-3-mesyloxypiperidine, prepared by $NaBH_4$ reduction of 1-ethoxycarbonyl-3-oxo-piperidine followed by mesylation using MsCl and pyridine (8.7 g, 35 mmol, oil, IR ν_{max}^{film} cm^{-1}: 1690 (NCOOEt), 1350, 1180 (OSO_2), ^{1}H-NMR ($CDCl_3$) δ: 3.05 (3H, s, SO_3CH_3)), was heated with 4-chloroaniline (13.3 g, 35 × 3 mmol) at 160 °C for 5 h. After cooling, ice water was added and the mixture was extracted with Et_2O. After removal of excess 4-chloroaniline from the extract at reduced pressure, purification of the residue on a Lobar column B ($CHCl_3$: EtOAc = 10 : 1) gave oily 4-chloro-(1-ethoxycarbonyl-3-piperidinyl)aniline (4.87 g, 49%). To a stirred suspension of $LiAlH_4$ (1.96 g, 17.2 × 3 mmol) in Et_2O (50 ml) was added dropwise a solution of 4-chloro-(1-ethoxycarbonyl-3-piperidinyl)aniline (4.87 g), and the mixture was refluxed for 30 min under stirring. After cooling, wet Et_2O was added and the precipitate was filtered off and washed with Et_2O. Concentration of the filtrate gave oily **9a** (3.91 g). ^{1}H-NMR ($CDCl_3$) δ: 1.2—4.0 (m, aliph. H). 2.3 (s, NCH_3), 6.4—7.3 (m, arom. H). Compound **9b** was obtained in a manner analogous to that described for **9a**.

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