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# Metalation of Alkylpyridazines. I. Alkylation of Metalated Alkylpyridazines with Alkyl Halides

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Side-chain lithiation with lithium diisopropylamide and subsequent alkylation of various alkylpyridazines have been investigated. The lithiated side chains of alkylpyridazines were alkylated efficiently with alkyl halides.

**Keywords**——pyridazines; alkylpyridazines; metalation of alkylpyridazines; lithiation of alkylpyridazines; alkylation of methylpyridazines; pyridazinylmethyl anions

No successful result of side-chain alkylation of alkylpyridazines has been reported in spite of many detailed studies concerning the side-chain metalation of methylpyridines,[2] methylpyrazines[3] and methylpyrimidines[4] with alkyllithium, phenyllithium, sodium and potassium amides *etc.*, and the subsequent alkylation.

The difficulty of metalation of alkylpyridazines chiefly comes from high reactivity of pyridazine ring itself towards those metalating agents, resulting in ring substitution as shown in earlier papers[5] and as mentioned in the later part of this paper. Nevertheless, introduction of the alkyl group into the side chain must be the most potential method for the synthesis of substituted pyridazines because a tedious method *via* cyclization or ring-transformation has to be employed for this purpose otherwise.[6]

We found that lithium diisopropylamide (LDA) efficiently lithiated the methyl groups of various alkylpyridazines (I) and the resulting anions were alkylated by alkyl halides (R′-X) in satisfactory yields.

A solution of a lithiated alkylpyridazine was obtained by addition of the corresponding alkylpyridazine in tetrahydrofuran (THF) to a freshly prepared LDA-THF solution (1.2 molar equiv.) under cooling with dry ice.[7] To examine the efficiency of lithiation, an excess deuterium oxide was added to a solution of lithiated 3-methylpyridazine (Ia) under cooling.

1) Location: *Hatanodai, Shinagawa-ku, Tokyo 142, Japan.*
2) R. Levine, D.A. Dimmig, and W.M. Kadunce, *J. Org. Chem.*, **26**, 3834 (1974); N.N Goldberg, L.B. Barkley, and R. Levine, *J. Am. Chem. Soc.*, **73**, 4301, (1951); A.H. Beckett, K.A. Kerridge, P.M. Clark, and W.G. Smith, *J. Pharm. and Pharmacol.*, **7**, 717 (1955); A.H. Beckett and K.A. Kerridge, *J. Chem. Soc.*, **1954**, 2948; E.M. Kaiser and J.D. Petty, *Synthesis*, **1975**, 705; J. Oszczapowicz and H. Pines, *J. Org. Chem.*, **37**, 2799 (1972).
3) B. Klein and P.E. Spoerri, *J. Am. Chem. Soc.*, **72**, 1844 (1950); B. Klein and P.E. Spoerri, *J. Am. Chem. Soc.*, **73**, 2949 (1951); J.D. Behun and R. Levine, *J. Am. Chem. Soc.*, **81**, 5157, 5666 (1959); M.R. Kamal and R. Levine, *J. Org. Chem.*, **27**, 1355, 1360 (1962); S.K. Chakrabartty and R. Levine, *J. Heterocycl. Chem.*, **3**, 265 (1966); G.P. Lizzi, *J. Org. Chem.*, **33**, 1333 (1968) *etc.*
4) .H Yamanaka, H. Abe, T. Sakamoto, H. Hiranuma, and A. Kamata, *Chem. Pharm. Bull.* (Tokyo), **25**, 1821 (1977).
5) R.L. Letsinger and R. Lasco, *J. Org. Chem.*, **21**, 812 (1956); H. Igeta, T. Tsuchiya, and T. Nakai, *Tetrahedron Lett.*, **1969**, 2667; G. Okusa, M. Kumagai, and T. Itai, *Chem. Commun.*, **1969**, 710; I. Crossland and H. Kofod, *Acta Chem. Scand.*, **24**, 751 (1970); I. Crossland, *Acta Chem. Scand.*, **22**, 2700 (1968), and references cited therein.
6) M. Tišler and B. Stanovnik, "*Advances in Heterocyclic Chemistry*," Vol. 9, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, New York and London, 1968, p. 211.
7) The solution was usually purple-colored, and in some runs, the mixture contained finely dispersed dark-brown precipitate which was unstable to moisture or to air.

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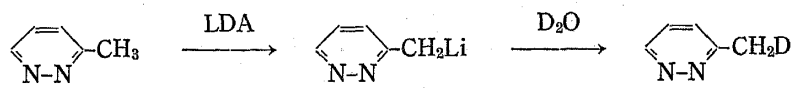
After a usual work-up, recovered Ia showed the $M^+$ peak at *m/e* 95 in the mass spectrum and its nuclear magnetic resonance (NMR) spectrum exhibited a signal at $\delta$ 2.73 which is assignable to the methyl group and its integrated intensity ratio corresponded to two protons. A slight but recognizable broadening of this signal was observed, owing to H-C-D coupling. These observations show that the recovered Ia had the structure of 3-$CH_2D$-pyridazine, thus the metalation of Ia by LDA might proceed (Chart 1).[8]

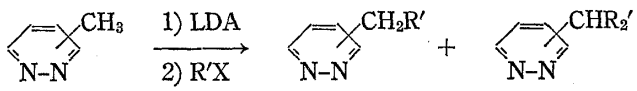



Ia

Chart 1

Thus, alkyl halides(R'-X) were employed as alkylating agents towards the initial reaction mixture obtained from LDA and various alkylpyridazines, as shown in the Tables. The alkylation proceeded in moderate yields (Tables I and II).

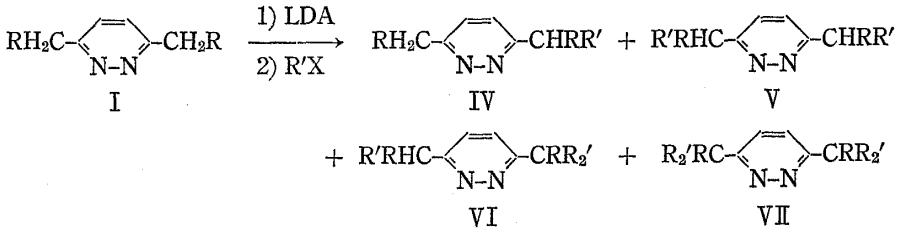
Table I. Alkylation of I (Monomethylpyridazines)




Ia (3-), Ib (4-) IIa, IIb IIIa, IIIb

| Run | I | LDA/I | R'X | II | Yield (%) | III | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | Ia | 1.2 | MeI | IIa-1 | 40 | IIIa-1 | 15 |
| 2 | Ia | 2.2 | MeI | IIa-1 | 38 | IIIa-1 | 27 |
| 3 | Ia | 1.2 | $PhCH_2Cl$ | IIa-2 | 52 | IIIa-2 | 6 |
| 4 | Ib | 1.2 | $PhCH_2Cl$ | IIb-2 | 26 | IIIb-2 | 21 |

Table II. Alkylation of I (3,6-Dialkylpyridazines)[a]




I IV V VI VII

| Run | I | R'X | IV (%) | V (%) | VI (%) | VII (%) |
|---|---|---|---|---|---|---|
| 5 | Ic (R=H) | $PhCH_2Cl$ | IVc-2 (21) | Vc-2 (8) | VIc-2 (1) | (0) |
| 6[b] | Ic | $PhCH_2Cl$ | IVc-2 (15) | Vc-2 (16) | VIc-2 (5) | VIIc-2 (trace) |
| 7 | Id (=IVc-2) | $PhCH_2Cl$ | Vc-2 (38) | VIc-2 (10) | VIIc-2 (3) | — |
| 8 | Ie (=Vc-2) | $PhCH_2Cl$ | VIc-2 (10) | VIIc-2 (25) | — | — |
| 9 | Ic | cyclo-$C_6H_{11}I$ | IVc-3 (27) | Vc-3 (6) | (0) | (0) |

*a*) Used LDA-R'X was 1.2 molar equiv. towards I for all runs in this table.
*b*) Inverse addition of lithiated I to R'X.

Methylpyridazines (Ia and Ib) were alkylated with methyl iodide and with benzyl chloride to give mono-alkylated products (IIa and IIb) together with geminally alkylated products (IIIa and IIIb). The use of an increased amount (2.2 molar equiv.) of LDA resulted in an

8) Deuteration of Ia with $D_2O$ in the presence of 1%-$NaOCD_3$ requires elevated temperature to give $C_4H_{3-n}N_2CH_nD_{3-n}$ ($t_{1/2} \geqq 1$ hr at 100°; see Ref. 9).
9) Y. Kawazoe, Y. Yoshioka, M. Yamada, and H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **15**, 2000 (1967).

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increase in the yield of geminally alkylated product (run 2). The structures of geminally benzylated products IIIa-2 and IIIb-2 were determined as follows. The aliphatic protons of IIIa-2 resonated around $\delta$ 3.2 as an united multiplet in the NMR spectrum in $CDCl_3$ (Fig. Ia).

Meanwhile, in trifluoroacetic acid (TFA), signals due to these protons allowed each of them to be assigned (Fig. Ib). Further, in the NMR spectrum of IIIa-2 (20 mg/0.5 ml $CDCl_3$) with $Eu(FOD)_3$ (50 mg), a shift reagent, these signals separated cleanly into three parts as shown in Fig. 1c, and a spin-spin decoupling technique was enabled. The doublet of doublets at $\delta$ 8.55 (2H) is geminally coupled with a signal at $\delta$ 6.70 ($J$=14 Hz) and with a signal at $\delta$ 9.70 ($J$=9 Hz). The doublet of doublets at $\delta$ 6.70 (2H) is also coupled with a signal at $\delta$ 9.70 ($J$= 6 Hz), thus the signal at $\delta$ 9.70 (1H) attributed to the methine proton forms a complex multiplet being coupled with four protons. These observations show that IIIa-2 has an $(AB)_2C$ spin system in the molecule as shown in Fig. 2.

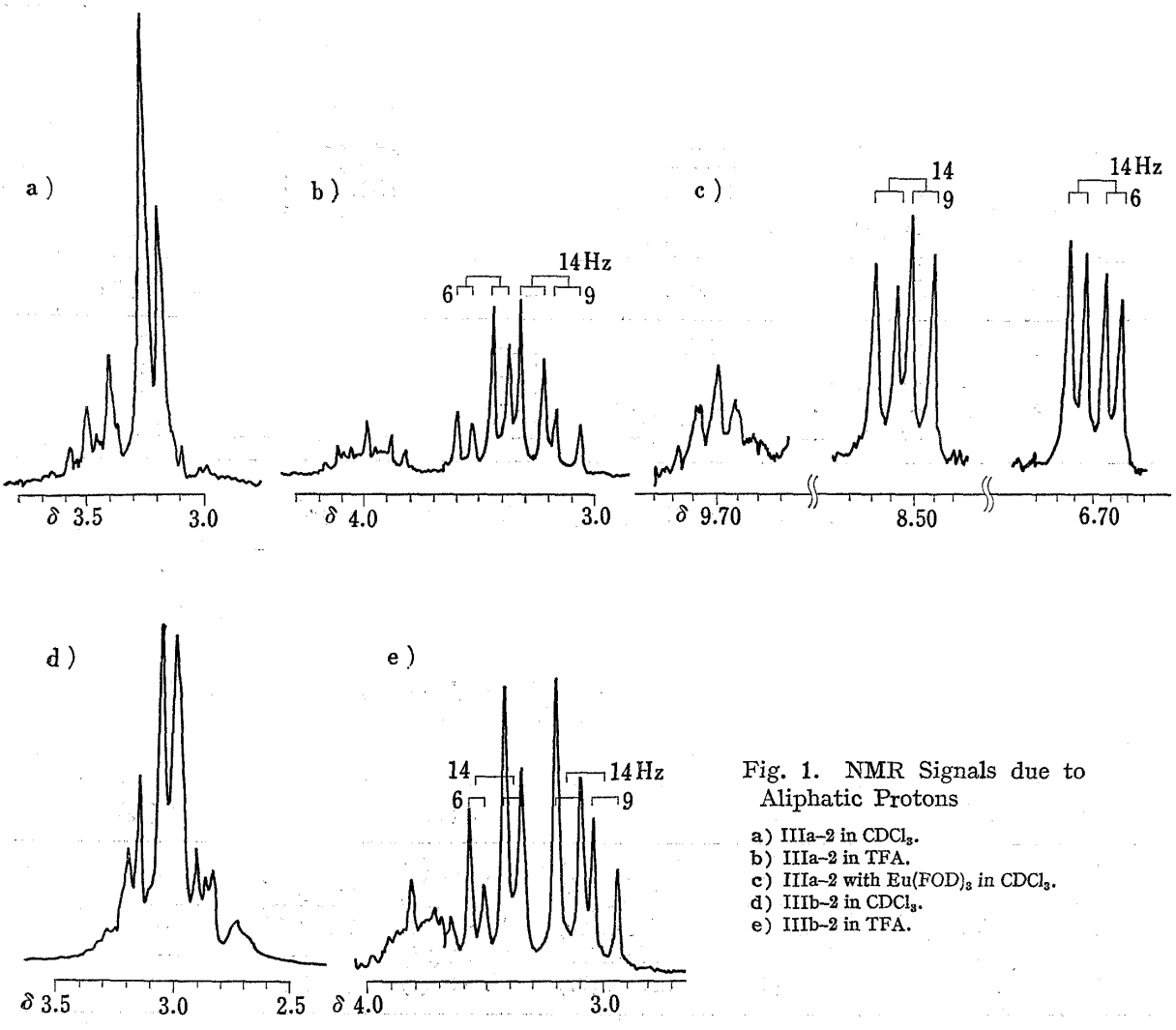



Fig. 1. NMR Signals due to Aliphatic Protons

a) IIIa-2 in $CDCl_3$.
b) IIIa-2 in TFA.
c) IIIa-2 with $Eu(FOD)_3$ in $CDCl_3$.
d) IIIb-2 in $CDCl_3$.
e) IIIb-2 in TFA.

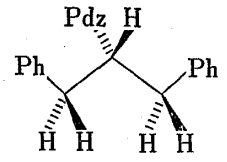
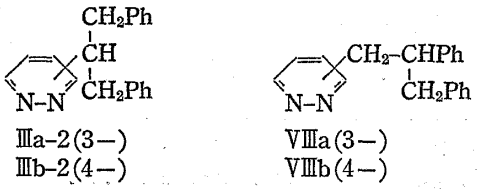



Fig. 2

Pdz represents a pyridazine ring.
Ph=phenyl




IIIa-2(3−) IIIb-2(4−) VIIIa(3−) VIIIb(4−)

Chart 2

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Moreover, $^{13}$C-NMR spectrum exhibited the presence of two kinds of aliphatic carbons ($\delta$ 50.9 and 41.3 ppm from TMS, in $CDCl_3$). This observation also corresponds to the structure of IIIa-2 and quite inconsistent with that of VIIIa (Chart 2). Similarly, the NMR spectrum of IIIb-2 in TFA showed well separated signals (Fig. 1e) corresponding to the aliphatic protons at $\delta$ 3.80 (m), 3.45 (d, d, $J$=14 and 6 Hz), and 3.05 (d, d, $J$=14 and 9 Hz) to which a decoupling technique was applicable. $^{13}$C-NMR spectrum of IIIb-2 showed the presence of two kinds of aliphatic carbons ($\delta$ 47.3 and 41.3 ppm). These observations again support the geminally alkylated structure (IIIb-2).

3,6-Dialkylpyridazines (Ic, Id and Ie) gave mono-alkylated products (IV), binarily alkylated products (V), and geminally-binarily alkylated products (VI and VII). The recovery of I was always accompanied by the formation of the higher (geminally and/or binarily) alkylated products even though 1.2 equiv. of LDA was used in the reaction. The formation of the higher alkylated products may be caused by the metalation of the lower alkylated products with metalated pyridazines (*i.e.*, transferred metalation, Chart 3) in the reaction mixture, although a generation of dianions and subsequent di-alkylation cannot be disproved for the binary alkylation, so far.[10]

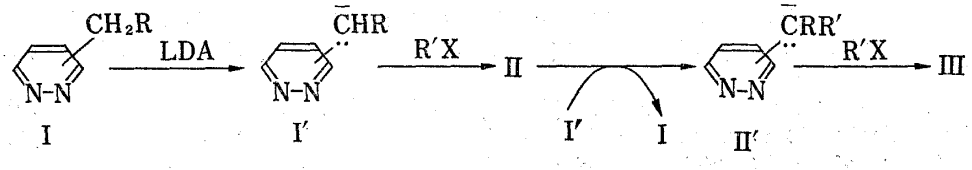


Chart 3

Alkylation with cyclohexyl iodide afforded no isolable amount of geminally alkylated product so long as 1.2 molar equiv. of LDA was used (run 9). Furthermore, to evaluate the relative reactivity of methyl groups in 3- and 4-positions on pyridazine, we have tried an alkylation of a mixture of Ia and Ib (1:1) using 0.5 molar equiv. (towards Ia+Ib) of LDA and benzyl chloride.

IIa-2, IIb-2, IIIa-2 and IIIb-2 were obtained in the yields of 17, 59, 1 and 7% based on LDA, respectively. A simple estimation shows 4-methylpyridazine (Ib) is *ca.* 3.5 times as reactive as 3-methylpyridazine (Ia).

Additionally, when trimethylchlorosilane was employed as electrophilic reagent to the lithiated Ia, 3-(trimethylsilylmethyl)pyridazine (IX) and a geminally (bis)trimethylsilylated product *i. e.*, 3-[bis(trimethylsilyl)methyl]pyridazine (X) were obtained in 8 and 20% yields, respectively, together with 27% of unchanged Ia (Chart 4).

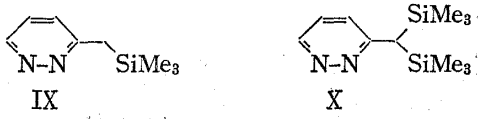


Chart 4

Finally, alkylation of some methylpyridazines were examined using butyllithium (BuLi) as a lithiating agent under similar conditions. The use of BuLi and benzyl chloride afforded 31% of 3-butyl-6-methylpyridazine (XI) and no benzylated product was detected. The use of

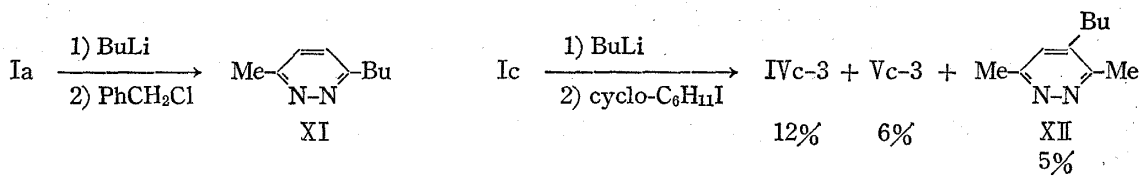


Chart 5

10) The inverse addition of a solution of lithiated Ic to a solution of R'-X resulted in an increase in the ratios of the higher alkylated products compared with the preceding method (run 6).

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BuLi on 3,6-dimethylpyridazine (Ic) lowered the yields of side-chain alkylated products compared with the use of LDA, and led to the formation of 3,6-dimethyl-4-butylpyridazine (XII, Chart 5). Thus, the lithiation of alkylpyridazines using LDA as a metalating agent and the alkylation of the lithiated alkylpyridazines could be a practical method for the preparation of substituted pyridazines.

## Experimental

All melting points are uncorrected. $^1$H–NMR spectra were recorded on Hitachi R-20 (60 Mc) and Hitachi R-22 (90 Mc) instruments. $^{13}$C–NMR spectra were run on a JEOL FX-100 instrument. Mass spectra were recorded on a Hitachi RMS-4 spectrometer.

**Deuteration of Ia**——A solution containing 12.7 mmol of BuLi (15% in hexane) was added dropwise to a solution of (iso-pr)$_2$NH (1.94 ml in 50 ml THF) under $N_2$ atmosphere with stirring and cooling on a dry ice-acetone bath. The mixture was allowed to stand at room temperature for 30 min and then cooled again on a dry ice-acetone bath, and a solution of Ia (1 g, 10.6 mmol, in 10 ml THF) was added dropwise with stirring. Then the mixture was allowed to stand at room temperature for 1 hr and then added with $D_2O$ (2 g in 20 ml THF) dropwise under $N_2$ with stirring. After filtration and evaporation of the solvent *in vacuo*, the residue was purified by silica gel column chromatography ($CH_2Cl_2$) and then by distillation (bp 95—100°/15 mmHg, picrate mp 142°).

Mass spectrum of obtained Ia ($CH_2D$, 710 mg, 70%) (*m/e*): 96 ($M^+$+1, 20%), 95 ($M^+$, Base), 94 ($M^+$−1, 37%), 93 ($M^+$−2, 15%). NMR ($\delta$): 9.12—9.00 (1H, m, 6-H), 7.55—7.40 (2H, m, 4- and 5-H), 2.73 (2H, bs, $CH_2D$).

These data are identical with those of Ia ($CH_2D$) obtained from an alternative method.[11]

**Alkylation of I with R′X: General Procedure**——A solution containing 12.7 mmol (runs 1, 3, 4, 5 and 9) or 23.3 mmol (run 2) of BuLi (15% in hexane) was added dropwise to a solution of (iso-pr)$_2$NH (1.94 ml or 3.8 ml in THF) under $N_2$ atmosphere with stirring and cooling on a dry ice–acetone bath. The mixture was allowed to stand at room temperature for 30 min and then cooled on a dry ice–acetone bath and a solution of I (10.6 mmol, in 10 ml THF) was added dropwise with stirring. The mixture was allowed to stand at room temperature for 1 hr and then again cooled on a dry ice–acetone bath. A solution containing 12.7 mmol (runs 1, 3, 4, 5 and 9) or 23.3 mmol (run 2) of an R′X in 20 ml of THF was added dropwise to that mixture. Then the mixture was stirred for 3 hr at room temperature under $N_2$ and quenched by $H_2O$ (*ca.* 3 ml). After filtering and drying with $MgSO_4$, the solution was evaporated *in vacuo* to dryness. The resulting residue was submitted to isolation procedure described next.

**Alkylation of Ia with MeI (1.2 equiv. LDA: run 1)**——The residue, obtained from the preceding procedure, was submitted to silica gel column chromatography (1:1 ether–$CH_2Cl_2$). IIIa-1 (0.205 g, 15%), IIa-1 (0.46 g, 40%) and 0.05 g (5%) of the starting material (Ia) were isolated in the order of elution, IIa-1: colorless oil. NMR ($\delta$): 9.15—8.98 (1H, m, 6-H), 7.45—7.20 (2H, m, 4- and 5-H), 3.00 (2H, q, $J$=7.8 Hz, $CH_2$), 1.35 (3H, t, $J$=7.8 Hz, $CH_3$). Picrate: prisms from EtOH, mp 134—135°.[12] *Anal.* Calcd. for $C_{12}H_{11}N_5O_7$: C, 42.73; H, 3.26; N, 20.77. Found: C, 43.20; H, 3.36; N, 20.75. IIIa-1: colorless oil. NMR ($\delta$): 9.16—9.00 (1H, m, 6-H), 7.54—7.28 (2H, m, 4- and 5-H), 3.33 (1H, sept, $J$=7.1 Hz, CH), 1.38 (6H, d, $J$=7.1 Hz, $CH_3\times2$). Picrate: needles from EtOH, mp 117—119°. *Anal.* Calcd. for $C_{13}H_{13}N_5O_7$: C, 44.45; H, 3.73; N, 19.94. Found: C, 44.63; H, 3.64; N, 20.07.

**Alkylation of Ia with MeI (2.2 equiv. LDA: run 2)**——A separation of the residue using silica gel column chromatography afforded 0.05 g (5%) of Ia, 0.44 g (38%) of IIa-1 and 0.35 g (27%) of IIIa-1.

**Alkylation of Ia with $PhCH_2Cl$ (run 3)**——The residue was separated by aluminum oxide column chromatography (from 1:1 hexane–ether to ether) to give IIIa-2 (0.17 g, 6%), IIa-2 (1.02 g, 52%) and Ia (0.05 g, 5%) in the order of elution. IIa-2: colorless needles from (iso-pr)$_2$O, mp 32—33°. NMR ($\delta$): 9.00 (1H, dd, $J$=4.5 and 2.2 Hz, 6-H), 7.46—7.01 (7H, m, $C_6H_5$ and 4- and 5-H), 3.40—2.86 (4H, m, $PhCH_2$-$CH_2$). Mass spectrum (*m/e*): 184 ($M^+$). Picrate: needles from EtOH, mp 157—159°. *Anal.* Calcd. for $C_{18}H_{15}N_5O_7$: C, 52.30; H, 3.66; N, 16.94. Found: C, 52.52; H, 3.65; N, 16.84. IIIa-2: colorless needles from (iso-pr)$_2$O, mp 105—105.5°. *Anal.* Calcd. for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 82.88; H, 6.61; N, 10.08. Mass spectrum (*m/e*): 274 ($M^+$). NMR ($\delta$): 8.97 (1H, dd, $J$=4.8 and 1.4 Hz, 6-H), 7.42—6.92 (11H, m, $C_6H_5\times2$ and 5-H), 6.72 (1H, dd, $J$=8.8 and 1.4 Hz, 4-H), 3.68—2.94 (5H, m, $PhCH_2\times2$ and CH).

The $^1$H–NMR signals due to $CH_2$ and CH in TFA and in $CDCl_3$ with Eu(FOD)$_3$ are shown in Figs. 1b and 1c.

11) Authentic Ia ($CH_2D$) has been obtained from a thermal decomposition of 3-[$Ph_2C(OD)CH_2$–]$C_4H_3N_2$ (unpublished, while in preparation).

12) J. Levisalles, *Bull. Soc. Chim. Fr.*, **1957**, 997.

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**Alkylation of Ib with $PhCH_2Cl$ (run 4)**——The obtained residue afforded IIIb-2 (0.60 g, 21%), IIb-2 (0.50 g, 26%) and Ib (0.22 g, 22%) in turn, by silica gel chromatography (1: 1 ether–$CH_2Cl_2$). IIb-2: colorless needles from ether–hexane, mp 66.5—67.5°. *Anal.* Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.42; H, 6.58; N, 15.22. Mass spectrum (*m/e*): 184 ($M^+$). NMR ($\delta$): 8.97—8.84 (2H, m, 3- and 6-H), 7.35—6.82 (6H, m, $C_6H_5$ and 5-H), 2.90 (4H, s, $PhCH_2CH_2$). IIIb-2: colorless oil which distills at *ca.* 200° (bath temp) at 0.01 mmHg. *Anal.* Calcd. for $C_{19}H_{18}N_2$: C, 83.17; H, 6.61; N, 10.21. Found: C, 83.39; H, 6.64; N, 9.95. NMR ($\delta$): 8.95—8.81 (2H, m, 3- and 6-H), 7.46—6.58 (11H, m, $C_6H_5\times2$ and 5-H), 3.40—2.55 (5H, m, $PhCH_2\times2$ and CH). The NMR signals due to $CH_2$ and CH in THF are shown in Fig. 1e.

**Alkylation of Ic with $PhCH_2Cl$ (run 5)**——The mixture was submitted to aluminum oxide column chromatography (from 1: 1 hexane–ether to ether) to give VIc-2 (0.045 g, 1%), Vc-2 (0.25 g, 8%), IVc-2 (0.45 g, 21%) and Ic (0.20 g, 18%) in the order of elution. IVc-2: colorless needles from hexane–$CCl_4$, mp 41—41.5°. Mass spectrum (*m/e*): 198 ($M^+$). NMR ($\delta$): 7.35—6.80 (7H, m, $C_6H_5$ and 4- and 5-H), 3.35—3.92 (4H, m, $PhCH_2CH_2$), 2.57 (3H, s, $CH_3$). *Anal.* Calcd. for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.34; H, 7.27; N, 14.51. Picrate, plates from (iso-pr)$_2$O–MeOH, mp 119—120.5°. Vc-2: colorless plates from hexane–ether, mp 96.5—97.5°. *Anal.* Calcd. for $C_{20}H_{20}N_2$: C, 83.29; H, 6.99; N, 9.71. Found: C, 83.00; H, 7.01; N, 9.97. Mass spectrum (*m/e*): 288 ($M^+$). NMR ($\delta$): 7.34—6.85 (10H, m, $C_6H_5\times2$), 6.80 (2H, s, 4- and 5-H), 3.35—2.85 (8H, m, $PhCH_2CH_2\times2$). VIc-2: colorless needles from hexane–ether, mp 86—87°. *Anal.* Calcd. for $C_{27}H_{26}N_2$: C, 85.67; H, 6.92; N, 7.40. Found: C, 85.76; H, 7.05; N, 7.54. Mass spectrum (*m/e*): 378 ($M^+$). NMR ($\delta$): 7.36—6.64 (15H, m, $C_6H_5\times3$), 6.54 (1H, d, $J$=8.4 Hz, 4- or 5-H), 6.33 (1H, d, $J$=8.4 Hz, 4- or 5-H), 3.48—2.78 (9H, m, $PhCH_2\times2$, $PhCH_2CH_2$ and CH).

**Alkylation of Ic with Cyclo-$C_6H_{11}I$ (run 9)**——The residue was submitted to aluminum oxide column chromatography (1: 1 ether–$CH_2Cl_2$) to give Vc-3 (0.15 g, 6%), IVc-3 (0.47 g, 27%) and Ic (0.60 g, 60%, from 1 g of Ic) in the order of elution. IVc-3: colorless oil which distills at *ca.* 120° (bath temp.) at 0.1 mmHg. Mass spectrum (*m/e*): 190 ($M^+$). NMR ($\delta$): 7.21 (2H, m, 4- and 5-H), 2.83 (2H, d, $J$=6.6 Hz, $CH_2$), 2.70 (3H, s, $CH_3$), 2.01—0.81 (11H, m, cyclo-$C_6H_{11}$). Picrate: mp 101—102°, plates from (iso-pr)$_2$O–MeOH. *Anal.* Calcd. for $C_{18}H_{21}N_5O_7$: C, 51.55; H, 5.05; N, 16.70. Found: C, 51.73; H, 5.03; N, 16.80. Vc-3: colorless needles from hexane, mp 120—121°. *Anal.* Calcd. for $C_{18}H_{28}N_2$: C, 79.36; H, 10.36; N, 10.28. Found: C, 79.09; H, 10.59; N, 10.02. Mass spectrum (*m/e*): 272 ($M^+$). NMR ($\delta$): 7.13 (2H, s, 4- and 5-H), 2.83 (4H, d, $J$=6.6 Hz, $CH_2\times2$), 2.18—0.80 (22H, m, cyclo-$C_6H_{11}\times2$).

**Alkylation of IVc-2 (Id) and Vc-2 (Ie) with $PhCH_2Cl$ (run 7 and 8)**——IVc-2 and Vc-2 were alkylated by the corresponding amounts of LDA and $PhCH_2Cl$ under a similar condition as described above. Alkylated mixture derived from 0.2 g of Vc-2 afforded VIIc-2 (0.080 g, 25%), VIc-2 (0.025 g, 10%) besides the starting material (Vc-2, 0.040 g, 20%). VIIc-2: colorless needles from hexane-$CCl_4$, mp 150—152°. *Anal.* Calcd. for $C_{34}H_{32}N_2$: C, 87.14; H, 6.88; N, 5.98. Found: C, 86.91; H, 7.00; N, 5.99. Mass spectrum (*m/e*): 468 ($M^+$). NMR ($\delta$): 7.42—6.62 (20H, m, $C_6H_5\times4$), 6.23 (2H, s, 4- and 5-H), 3.53—2.91 (10H, m, $PhCH_2\times4$ and $CH\times2$).

**Alkylation of Ic with $PhCH_2Cl$ by Reversed Addition (run 6)**——To a dry ice-cooled mixture of lithiated Ic prepared by the preceding method, an additional amount of THF (*ca.* 50 ml) was added untill all the precipitate had dissolved into the solution with cooling, and the solution was allowed to warm to room temperature.

The solution was then added to a dry ice-cooled solution containing the corresponding amount of $PhCH_2Cl$ (in THF) through an equipped bridge of tubing. The mixture was stirred for 1 hr at room temperature under $N_2$, and submitted to a work-up as described before. The result has been shown in Table II.

**Trimethylsilylation of Ia**——Trimethylchlorosilane (3.3 g, 30 mmol) was added dropwise under $N_2$ atmosphere with stirring and cooling on a dry ice–acetone bath to a solution of lithiated Ia obtained from 1.9 g (20 mmol) of Ia according to the preceding way. The mixture was allowed to warm to room temperature and the solvent was distilled off *in vacuo* under $N_2$. The residue was roughly distilled (40—90°/0.5 mmHg). An oily mixture (*ca.* 2.5 g) containing a little amount of solid was obtained. NMR of this mixture showed the presence of Ia, IX and X in the molar ratio of 18 (15%): 30 (25%): 32 (26%). The crude mixture was separated by aluminum oxide column chromatography (3: 1 hexane–ether) into three major fractions.

The first fraction solidified after evaporation of the solvent (X, 1.00 g 20%). Colorless needles from hexane, mp 86—87°. *Anal.* Calcd. for $C_{11}H_{22}N_2Si_2$: C, 55.46; H, 9.24; N, 11.76. Found: C, 55.61; H, 9.46; N, 11.90. NMR (ppm from TMS in $CCl_4$): 8.83 (1H, dd, $J$=2 and 6 Hz, 6-H), 7.3—6.75 (2H, m, 4- and 5-H), 1.77 (1H, s, CH), 0.10 (18H, s, $SiCH_3\times6$). The second fraction afforded a colorless oil (IX, 0.28 g, 8%) which contained *ca.* 5% of Ia (NMR). Although IX is unstable to the atmospheric moisture, being hydrolyzed to Ia, a quick work-up and nimble chromatography and evaporation of the solvent gave an essentially pure IX (a silica gel chromatography resulted in a complete degradation to Ia). Mass spectrum (*m/e*): 166 ($M^+$). NMR (ppm from TMS in $CCl_4$): 8.80 (1H, dd, $J$=2 and 6 Hz, 6-H), 7.3—6.7 (2H, m, 4- and 5-H), 2.45 (2H, s, $CH_2$), 0.10 (9H, s, $SiCH_3\times3$).

A solution of IX in $CCl_4$ showed a complete change to Ia after standing for 24 hr in contact with the atmosphere.

The last fraction gave 0.51 g (27%) of Ia.

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**An Attempt on Alkylation of Ia with $PhCH_2Cl$ using BuLi**——One gram of Ia was treated as described in the general procedure.

BuLi (12.7 mmol) was used instead of LDA solution. Work-up gave neither IIa-2 nor IIIa-2, while 1.0 g (31%) of XI, and Ia were obtained (separation was carried out by aluminum oxide column chromatography, from 1:1 hexane-ether to ether). XI: colorless oil. Mass spectrum (*m/e*): 150 ($M^+$). NMR ($\delta$): 7.25 (2H, s, 4- and 5-H), 2.92 (2H, t, $J=7.5$ Hz, Pdz.-$CH_2$), 2.63 (3H, s, $CH_3$), 1.98—0.63 (7H, m, $CH_2CH_2CH_3$).

**Alkylation of Ic with Cyclo-$C_6H_{11}I$ using BuLi**——IVc-3, Vc-3 and XII were obtained in the yields of 12, 6 and 5%, respectively. XII: colorless oil. Mass spectrum (*m/e*): 164 ($M^+$). NMR ($\delta$): 7.00 (1H, s, 5-H), 2.60 (8H, m, $CH_3\times2$ and Pdz.-$CH_2$), 1.90—0.70 (7H, m, $CH_2CH_2CH_3$).

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