Chem. Pharm. Bull. 24(10)2494—2499(1976)

UDC 547.415.1.04 : 547.333.3.04

Reaction of N-(Butoxymethyl)dialkylamines and N,N'-Methylenebis(dialkylamine)s with N-(1-Cyclohexen-1-yl)dialkylamines

Osamu Matsuda and Minoru Sekiya

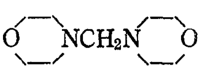
Shizuoka College of Pharmacy[1]

(Received January 31, 1976)

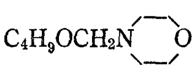
We have now found that reactions of N-dialkylaminomethyl-dialkylamines and -imide, and O-dialkylaminomethyl ethers with N-(1-cyclohexen-1-yl)dialkylamines result in electrophilic substitution at α and α' positions of the enamine to give N-(2-dialkylaminomethyl-6-methylene-1-cyclohexen-1-yl)dialkylamines. Features and generalization of the reactions are described.

The methylene compounds linking two N- and O-functional groups have an affinity for nucleophiles resulting in substitution.[2] The present paper relates an attempt to carry out the reaction of these types of the compounds with enamines, none of analogous reactions having appeared in the literature.

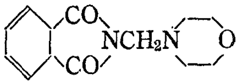
Three N- and O-morpholinomethyl compounds, I, II, and III (see below), possessing different leaving groups in nucleophilic substitution were first allowed to react with 4-(1-cyclohexen-1-yl)morpholine (IV) on refluxing in toluene to give the same plates, mp 77—80° and bp 156—158° (1.5 mmHg), in 43%, 43%, and 30% yield, respectively.



I

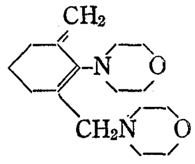


II

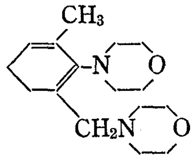


III

Based on analytical, ultraviolet(UV), infrared(IR) and mass spectral data the product was assigned as either of the following two structures.



V



VI

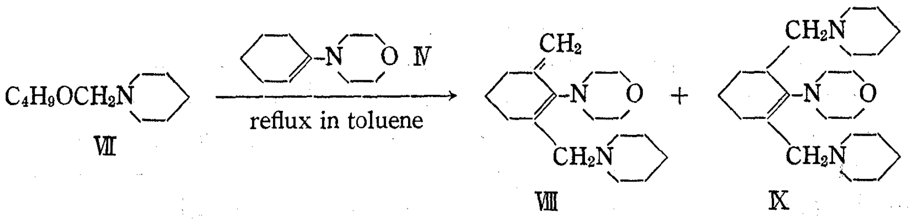
A nuclear magnetic resonance (NMR) spectrum of this product in deuteriochloroform exhibited a clear evidence for the former, 4-(6-methylene-2-morpholinomethyl-1-cyclohexen-1-yl)morpholine(V), where the terminal methylene protons appeared at δ 5.16—5.30 (1H) and at δ 4.75—4.92 (1H) as multiplets and the singlet methyl protons of the latter (VI) were hardly observed.

Next, 1-(butoxymethyl)piperidine(VII) was allowed to react with IV under the same condition, whereupon, in addition to the same type of the product, 4-(6-methylene-2-piperidinomethyl-1-cyclohexen-1-yl)morpholine(VIII), 4-[2,6-bis(piperidinomethyl)-1-cyclohexen-1-yl]morpholine (IX) was obtained in 37% yield.

---

[1] Location: *2-2-1 Oshika, Shizuoka.*

[2] *a*) M. Sekiya and Y. Terao, *Chem. Pharm. Bull.* (Tokyo), **18**, 947 (1970); *b*) K. Ito, H. Oba and M. Sekiya, *ibid.*, **20**, 2112 (1972); *c*) H. Sakai, K. Ito and M. Sekiya, *ibid.*, **21**, 2257 (1973); *d*) O. Matsuda, K. Ito and M. Sekiya, *ibid.*, **22**, 1119 (1974); *e*) K. Shimizu, K. Ito and M. Sekiya, *ibid.*, **22**, 1256 (1974); *f*) M. Sekiya, O. Matsuda and K. Ito, *ibid.*, **23**, 1579 (1975), *etc.*



The structure, IX, was assigned on the basis of the formation of the previously known 2,6-bis-(piperidinomethyl)cyclohexanone[3] by hydrolysis with hydrochloric acid, in addition to its IR, NMR and mass spectral data. Conversion of IX into VIII to a considerable extent was realized on refluxing in toluene. Therefore, IX is probably regarded as an precursor in the formation of VIII. When we speculate on a mechanism of the reaction, a plausible path can be written as shown in Chart 1.

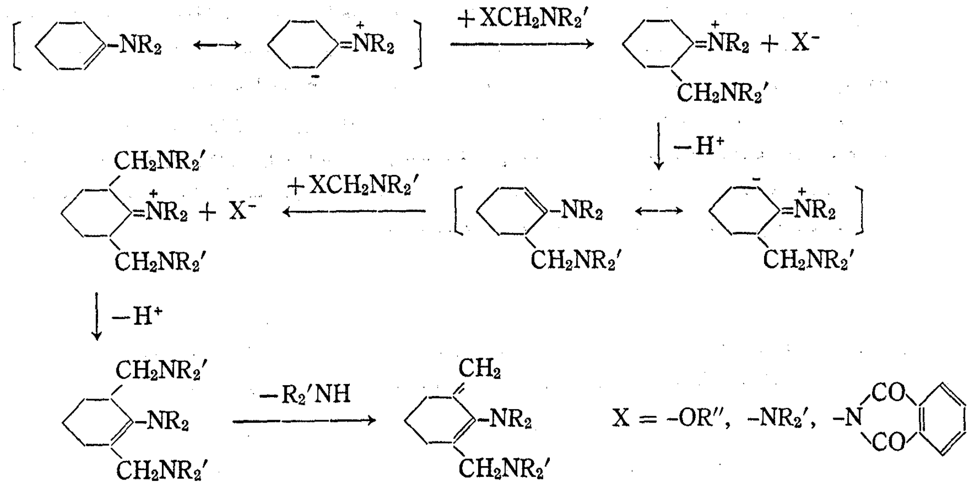
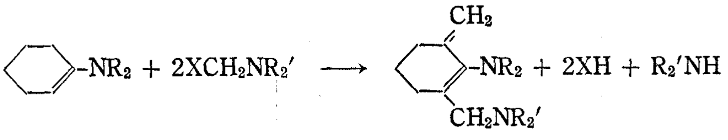


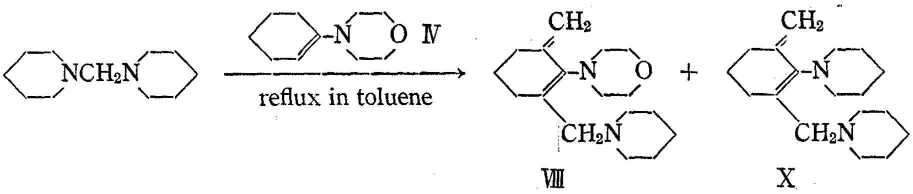
Chart 1

In view from the overall reaction equation according with the following (Eq.1), there seemed a fear of an exchange of amine moiety of the enamine by the dialkylamine generated as the reaction proceeded, as presumed from the previously known reaction of enamine.[4]


(1)

$$\text{C}_6\text{H}_9\text{-NR}_2 + 2\text{XCH}_2\text{NR}_2' \longrightarrow \text{C}_6\text{H}_7(=\text{CH}_2)(\text{CH}_2\text{NR}_2')\text{-NR}_2 + 2\text{XH} + \text{R}_2'\text{NH} \qquad (1)$$

As long as the use of N,N′-methylenebis(dialkylamine) ($X=NR'_2$) the reaction brings about generation of even three molar equivalent of the dialkylamine (R'_2NH) which tends to give the enamine product possessing NR'_2 in place of NR_2 through the amine exchange reaction. This was demonstrated by carrying out the reaction of 1,1′-methylenedipiperidine with IV.



An amine fraction, bp 133—135° (1.5 mmHg), obtained by vacuum distillation was confirmed to be a mixture of VIII and 1-(6-methylene-2-piperidinomethyl-1-cyclohexen-1-yl)piperidine

---

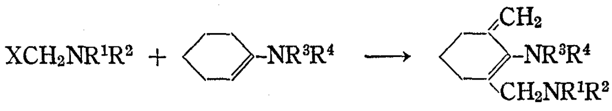
3) F.F. Blicke and F.J. McCarty, *J. Org. Chem.*, **24**, 1069 (1959).
4) J.S. Marchese, *C.A.*, **63**, 2862 (1965).

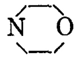
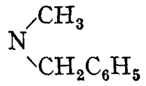
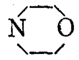
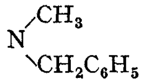
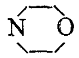
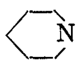
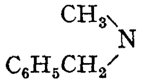
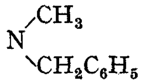
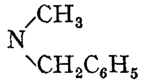
(X) by the following data. The compound, X, was separately synthesized by the reaction between 1-(1-cyclohexen-1-yl)piperidine and VII as described later (see Table I). A thin-layer chromatogram, a mass spectrum and a NMR spectrum of the liquid material evidenced the mixture composed of VIII and X, exhibiting both the corresponding two patterns. Nearly equimolar proportion of the two was suggested from the NMR spectrum and an elemental analysis data. In view from the above the leaving NR'$_2$ of N,N'-methylenebis(dialkylamine) as a reactant should be equal to the amine moiety (NR$_2$) of the starting enamine in order to exclude the amine exchange reaction.

The reaction of VII with IV described in the foregoing corresponds to that of Eq. 1 where $X=OC_4H_9$. In this reaction the amine exchange of the product induced by equimolar amount of the generated dialkylamine was shown to be almost negligible by no detection of X in the reaction mixture.

Several extensions of the reaction of N-(1-cyclohexen-1-yl)dialkylamines were examined with N-(butoxymethyl)dialkylamines and with N,N'-methylenebis(dialkylamine)s. Because of lower reactivity and laborious isolation of the products N-(dialkylaminomethyl)phthalimides were not used for extension. As can be seen in Table I, general synthesis of the α,α'-disubstituted enamines, which have not been described in the literature, was successfully performed by this reaction. For synthesis of the enamines possessing different two amine residues N-(butoxymethyl)dialkylamines were conveniently used as reactants, while N,N'-methylenebis(dialkylamine)s for that possessing the same two amine residues.

Table I. Reaction[a] of N-(Butoxymethyl)dialkylamines and N,N'-Methylenebis(dialkylamine)s with N-(1-Cyclohexen-1-yl)dialkylamines

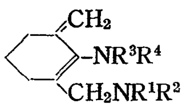


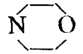
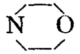
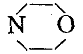
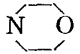
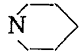
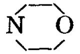
X	NR¹R²	NR³R⁴	Yield[b] (%)
C_4H_9O			47
C_4H_9O			47
C_4H_9O			38
C_4H_9O		 $N(CH_3)CH_2C_6H_5$	39
C_4H_9O			41
C_5H_9O	 $N(CH_3)CH_2C_6H_5$		43
			46
			46
 $CH_3(C_6H_5CH_2)N$	 $N(CH_3)CH_2C_6H_5$	 $N(CH_3)CH_2C_6H_5$	34

a) molar proportion: substrate: enamine (0.05 mole)=2.5: 1, solvent: toluene (70 ml), refluxing time: 5 hr

b) based on the starting enamine

TABLE II. N-(2-Dialkylaminomethyl-6-methylene-1-cyclohexen-1-yl)dialkylamines



NR^1R^2	NR^3R^4	bp[°C(mmHg)]	n_D^{17}	Formula	Analysis (%) Found (Calcd) C	H	N	UV λ_{max} mμ (log ε)	IR, cm^{-1} (liquid) $\nu_{>C=C<}$	$\delta_{>C=CH_2}$	NMR, δ (ppm) $>C=CH_2$ (2×1H, m)	$>CCH_2N<$ (2H, s)	Ref.
		156—158(1.5) mp 77—78° plates(ether)	—	$C_{16}H_{26}O_2N_2$	69.08 (69.03)	9.46 (9.41)	10.01 (10.06)	238(4.26) 286(3.30)	1620 1600	880	4.75—4.92 5.16—5.30	3.14	a)
		135—136(0.4)	1.5340	$C_{18}H_{30}N_2$	78.99 (78.77)	11.00 (11.02)	10.08 (10.21)	237(4.24) 290(3.26)	1620 1600	886	4.66—4.80 5.10—5.26	3.07	b)
		124—125(0.7)	1.5382	$C_{16}H_{26}N_2$	78.03 (77.99)	10.41 (10.64)	10.86 (11.39)	239(4.18) 295(3.01)	1622 1602	880	4.66—4.90	3.22	
$N(CH_3)CH_2C_6H_5$	$N(CH_3)CH_2C_6H_5$	180—181(0.5)	1.5750	$C_{24}H_{30}N_2$	83.51 (83.19)	8.72 (8.73)	8.04 (8.09)	238(4.27) 289(3.36)	1620 1602	878	4.80—4.94 5.04—5.18	3.20	
		143—144(0.6) mp 40—41° plates(ether)	—	$C_{17}H_{28}ON_2$	73.91 (73.86)	10.18 (10.21)	10.22 (10.14)	238(4.21) 291(3.22)	1622 1601	887	4.64—4.84 5.07—5.24	3.14	c)
		145—147(0.4) mp 48—50° plates(ether)	—	$C_{17}H_{28}ON_2$	74.22 (73.86)	10.15 (10.21)	9.80 (10.14)	238(4.22) 285(3.27)	1621 1600	890	4.74—4.90 5.15—5.30	3.07	d)
		140—141(2.0)	1.5364	$C_{17}H_{28}N_2$	78.52 (78.40)	10.43 (10.83)	10.54 (10.76)	240(4.02) 296(2.97)	1620 1600	878	4.64—4.85	3.02	
	$N(CH_3)CH_2C_6H_5$	155—157(0.4)	1.5570	$C_{21}H_{30}N_2$	80.83 (81.23)	9.51 (9.76)	8.82 (9.02)	238(4.16) 286(3.26)	1620 1600	888	4.74—4.94 5.04—5.20	3.10	
		140—142(0.6)	1.5320	$C_{16}H_{26}ON_2$	73.42 (73.24)	9.83 (9.99)	10.70 (10.68)	238(4.01) 287(3.14)	1622 1600	880	4.64—4.85 5.12—5.25	3.28	
$N(CH_3)CH_2C_6H_5$		164—165(0.3)	1.5600	$C_{20}H_{28}ON_2$	76.57 (76.88)	8.78 (9.03)	8.80 (8.97)	238(4.22) 285(3.26)	1622 1600	884	4.72—4.85 5.12—5.27	3.20	

a) mass spectrum m/e: 278 (M^+); IR cm^{-1} (KBr) b) mass spectrum m/e: 274 (M^+) c) IR cm^{-1} (KBr) d) mass spectrum m/e: 276 (M^+); IR cm^{-1} (KBr)

Experimental[5]

Reaction of N-(Butoxymethyl)dialkylamines and N,N′-Methylenebis(dialkylamine)s with N-(1-Cyclohexen-1-yl)dialkylamines——General Procedure: The following eight N- and O-dialkylaminomethyl compounds shown with their boiling points were used as substrate: 4,4′-methylenedimorpholine(I),[6] bp 127—129° (18 mmHg); 1,1′-methylenedipiperidine,[7] bp 110—111° (15 mmHg); 1,1′-methylenedipyrrolidine,[8] bp 87—88° (14 mmHg); N,N′-methylenebis(N-methylbenzylamine),[9] bp 153—154° (2 mmHg); 4-(butoxymethyl)morpholine(II),[10] bp 105—108° (14 mmHg); 1-(butoxymethyl)piperidine(VII),[11] bp 98—99° (19 mmHg); 1-(butoxymethyl)pyrrolidine,[12] bp 84—85° (18 mmHg); N-(butoxymethyl)-N-methylbenzylamine,[2b] bp 132—137° (18 mmHg). Four N-(1-cyclohexen-1-yl)dialkylamines shown with their boiling points were used as enamines: 4-(1-cyclohexen-1-yl)morpholine(IV),[13] bp 139—140° (35 mmHg); 1-(1-cyclohexen-1-yl)piperidine,[13] bp 117—118° (15 mmHg); 1-(1-cyclohexen-1-yl)pyrrolidine,[13] bp 110—111° (15 mmHg); N-(1-cyclohexene-1-yl)-N-methylbenzylamine, bp 156—157° (15 mmHg), n_D^{17} 1.5530. IR ν_{max}^{liquid} cm^{-1}: 1638 (C=C). NMR δ: 7.25 (5H, s, C_6H_5), 4.44—4.67 (1H, m, -CH=C$<$), 4.08 (2H, s, CH_2), 2.49 (3H, s, CH_3), 1.40—2.40 (8H, m, -$(CH_2)_4$-). *Anal.* Calcd. for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.14; H, 9.39; N, 7.03.

A solution of 0.125 mole of the substrate and 0.05 mole of the enamine in 70 ml of toluene was refluxed for 5 hr with stirring. The reaction solution was concentrated under reduced pressure to remove solvent and the unreacted materials. Distillation of the oily residue under reduced pressure gave the corresponding product as a liquid or solid distillate. Physical, spectral and analytical data and yields of all the products are listed in Tables I and II.

The following, a) and b), describes the procedure in the runs in which two kinds of the products were obtained.

a) The reaction solution obtained from VII (21.4 g, 0.125 mole) and IV (8.4 g, 0.05 mole) in 70 ml of toluene was concentrated under reduced pressure. Crystals deposited in the oily residue was collected by filtration, and the filtrate was submitted to distillation under reduced pressure to give 1.7 g (12%) of 4-(6-methylene-2-piperidinomethyl-1-cyclohexen-1-yl)morpholine (VIII), physical, spectral and analytical data of which are recorded in Table II. The foregoing crystals, weighing 6.6 g (37%), were found to be 4-[2,6-bis(piperidinomethyl)-1-cyclohexen-1-yl]morpholine(IX), prisms from EtOH, mp 122—123°. IR ν_{max}^{KBr} cm^{-1}: 1650 (C=C). UV $\lambda_{shoulder}^{hexane}$ mμ (log ε): 243 (4.07). NMR δ: 3.56—3.82 (4H, m, CH_2OCH_2), 3.10 (2H, s, $\trianglerighteq$CCH_2N$<$), 2.66—2.98 (4H, m, CH_2NCH_2), 1.96—2.56 (13H, m, 2×CH_2NCH_2, $\geqslant$CCH_2N$<$ and cyclohexene), 1.10—1.82 (16H, m, 2×C_3H_6 and cyclohexene). Mass Spectrum *m/e*: 361 (M^+). *Anal.* Calcd. for $C_{22}H_{39}ON_3$: C, 73.08; H, 10.87; N, 11.62. Found: C, 72.99; H, 10.80; N, 11.66. Hydrolysis of IX by refluxing with 10% HCl gave morpholine and 2,6-bis(piperidinomethyl)cyclohexanone, plates from ligroin, mp 79—80° (lit.[3] mp 83—84°). IR ν_{max}^{KBr} cm^{-1}: 1703 (CO). *Anal.* Calcd. for $C_{18}H_{32}ON_2$: C, 73.92; H, 11.03; N, 9.58. Found: C, 73.81; H, 11.09; N, 9.66. Refluxing toluene solution of IX (3.6 g in 30 ml) for 5 hr gave 1.0 g (37%) of VII in addition to 2.0 g (56%) of the recovered IX.

b) The reaction of 1,1′-methylenedipiperidine(22.8 g, 0.125 mole) with IV (8.4 g, 0.05 mole) was processed by the general procedure to give 6.2 g of a liquid fraction, bp 133—135° (1.5 mmHg), as a mixture composed of VIII and X. A thin-layer chromatogram of this liquid on silica gel exhibited two spots corresponding to VIII and X. Mass Spectrum *m/e*: 276 [M(VIII)$^+$], 274[M(X)$^+$]. A NMR spectrum and an analytical data nearly corresponded to a mixture in equimolar proportion. NMR δ: 5.08—5.25 and 4.64—4.85 (2H, m, $>$C=CH_2), 3.58—3.82 (2H, m, CH_2OCH_2), 3.07 (2H, s, $\trianglerighteq$CCH_2N$<$), 2.12—3.00 (4H, m, CH_2NCH_2), 2.09—2.54 (8H, m, CH_2NCH_2 and cyclohexene), 1.22—1.90 (11H, m, C_3H_6 and cyclohexene). *Anal.* Calcd. for $C_{35}H_{58}ON_4$[$C_{17}H_{28}ON_2$(VIII)+$C_{18}H_{30}N_2$(X)]: C, 76.31; H, 10.61; N, 10.71. Found: C, 76.75; H, 10.43; N, 9.94.

Reaction of N-(Morpholinomethyl)phthalimide (III) with 4-(1-Cyclohexene-1-yl)morpholine(IV)——A mixture of 30.8 g (0.125 mole) of III and 8.4 g (0.05 mole) of IV in 140 ml of toluene was refluxed for 5 hr with stirring. After filtration on cool, the filtrate was concentrated under reduced pressure. The oily residue was well

---

5) All melting and boiling points are uncorrected. IR spectra were determined with a Hitachi EPI-G2 spectrophotometer, and UV spectra were determined in hexane solution with a Hitachi EPS-3T spectrophotometer. Mass spectra were recorded with a Hitachi RMS-4 spectrometer. NMR spectra were taken at 60 MHz in $CDCl_3$ solution with a JEOL-C-60H spectrometer using tetramethylsilane as internal standard. The following abbreviations are used: s=singlet, m=multiplet.
6) M.O. Kolosova and V.I. Stavrovskaya, *Zhur. Obschei Khim.*, 33. 955 (1963) [*C. A.*, **59**, 8722 (1963)].
7) T.C. Simmons, F.W. Hoffmann, R.B. Beck, H.V. Holler, T. Katz, R.J. Koshar, E.R. Larsen, J.E. Mulvaney, K.E. Paulson, F.E. Rogers, B. Singleton, and R.E. Sparks, *J. Am. Chem. Soc.*, **79**, 3429(1955).
8) W. Reppe, *Ann*, **596**, 80 (1955).
9) H. Böhme and F. Eiden, *Chem. Ber.*, **89**, 2873 (1956).
10) A.F. Isbell and D.W. Hood, *J. Chem. Eng. Data*, **7**, **Pt 2**, 575 (1962) [*C. A.*, **58**, 10195 (1963)].
11) G.M. Robinson and R. Robinson, *J. Chem. Soc.*, **123**, 532 (1923).
12) J. Ficini and H. Normant, *Bull. Soc. Chim. France*, **1957**, 1454.
13) S. Hunig, E. Benzing and E. Lücke, *Chem. Ber.*, **90**, 2833 (1957).

mixed with 18.6 g of triethanolamine followed by extraction with petr. ether. Usual treatment of the petr. ether solution gave 4.2 g (30%) of 4-(6-methylene-2-morpholinomethyl-1-cyclohexen-1-yl)morpholine(V), physical, spectral and analytical data of which are recorded in Table II.

Acknowledgement The authors are indebted to Mr. K. Narita and the other members of the Analysis Center of this college for elemental analyses and spectral measurements.