Chem. Pharm. Bull. 18(10)2081—2086(1970)

UDC 547.233.3.04 : 547.551.04 : 542.951

C-Alkylation of α-N,N-Dialkylaminoketones

Minoru Sekiya and Jiro Kawarabata

Shizuoka College of Pharmacy[1]

(Received April 17, 1970)

C-Alkylations of α-N,N-dialkylaminoketones were effected with alkyl halides by means of potassium amide in liquid ammonia. The reaction scope and an application for preparation of (±)-ephedrine are described.

In continuing study of our previous work[2] on the C-alkylation of α-amidoketones, the further success was achieved in the C-alkylation of α-N,N-dialkylaminoketones with alkyl halides by means of using potassium amide in liquid ammonia. On survey of literature as for the analogous reaction, there was a paper of C-benzylation of 2-piperidinoacetophenone with benzyl chloride by means of using sodium powder in refluxing toluene.[3] Scattered papers have also reported on C-alkylation of the other types of aminoketones, such as α-anilinoacetophenone[4] and phenacylpyridinium salt,[5] by some other methods. Besides these available data, susceptibility of α-N,N-dialkylaminoketones toward C-alkylation by the above means had been found and investigated in some details for general application of this useful reaction.

Examinations of the alkylation with several alkyl halides were made with a variety of N,N-dialkylamino-2-propanones and of α-N,N-dialkylaminoacetophenones. Results of these experiments are summarized in Table I. All the runs were processed under uniform conditions, in which an ethereal solution of the substrate and succeedingly halide were added to a liquid ammonia solution of potassium amide and the mixture was allowed to react at a refluxing temperature for 8 hours.

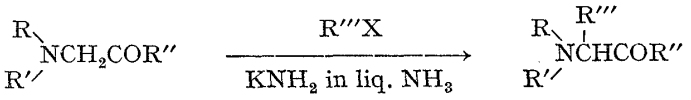
It can be seen from Table I that N-phenacyl compounds are more reactive than N-acetonyl compounds. Data of the alkylation products are described in Table II. Among these the known compounds showed well correspondence of physical data with those reported.

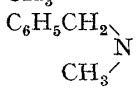
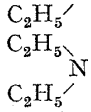
All the products obtained gave the corresponding compositions of the alkylation products and their picrates, and exhibited in their infrared spectra >C=O stretching vibration bands at 1667—1713 cm^{-1}. The nuclear magnetic resonance spectra of the representative methylation and benzylation products, shown in Table III, provided convincing evidence for the structural assignments, although the other alkylation products gave complex paterns of the spectra. As can be seen from the Table III, the methylation products would allow the assignments of the quartet at τ 5.94—5.71 to Cα-H and the doublet at τ 8.86—8.20 to Cβ-3H. The splitting paterns observed in the spectra of the benzylation products were well interpreted as ABX system, where Cβ-2H appeared as two sets of quartets at τ 7.38—7.06 and τ 6.95—6.17, and Cα-H appeared as quartet at τ 6.51—5.16.

By the benzylation process of N-methylanilino-2-propanone with benzyl chloride in liquid ammonia, 2-benzyl-1,3-dimethylindole was obtained in 27% yield, resulted in indole ringclosure with dehydration. The product showed well correspondence of melting point

1) Location: *160, Oshika, Shizuoka.*
2) M. Sekiya, J. Kawarabata and A. Hara. *Chem. Pharm. Bull.* (Tokyo), **18**, 2074 (1970).
3) R.V. Henley and E.E. Turner, *J. Chem. Soc.*, **1931**, 1182.
4) E. Wedekind and E. Bruch, *Ann.*, **471**, 73 (1929).
5) F. Kröhnke, H. Schmeiss and W. Gottstein, *Ber.*, **89**, 131 (1951).

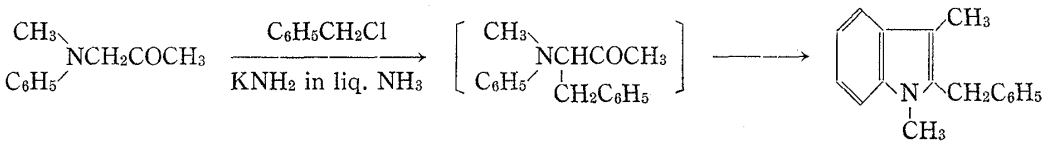
Table I. C-Alkylation[a] of α-N,N-Dialkylaminoketones



R, R'N	R''	R'''X	Yield (%)
	C_6H_5	$C_6H_5CH_2Cl$	71
	C_6H_5	CH_3I	69
	C_6H_5	$CH_2=CHCH_2Cl$	76
	C_6H_5	$CH_3CH_2CH_2I$	70
	C_6H_5	$C_6H_5CH_2Cl$	49
	C_6H_5	CH_3I	65
	C_6H_5	$C_6H_5CH_2Cl$	64
	C_6H_5	CH_3I	53
	C_6H_5	$C_6H_5CH_2Cl$	40
	C_6H_5	CH_3I	32
	C_6H_5	CH_3I	78
	CH_3	$C_6H_5CH_2Cl$	15
	CH_3	CH_3I	43
	CH_3	$C_6H_5CH_2Cl$	27
	CH_3	CH_3I	49
	CH_3	$C_6H_5CH_2Cl$	34
	CH_3	CH_3I	21

a) The standard conditions are written in Experimental.

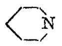
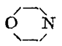
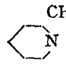
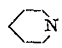
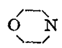
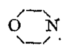
with that previously reported.[6] The observed nuclear magnetic resonance spectrum was interpreted to fit the structure by the following assignments: the three singlets at τ 7.17, 6.57 and 5.90, respectively, to CH_3–C⩽, CH_3–N< and >CH_2.



6) E.F.J. Janetzky and P.E. Verkade, *Rec. Trav. Chim.*, **64**, 129 (1945); *C.A.*, **40**, 4054 (1946).

As another reaction to form α-N,N-dialkylamino-ketones there has been well known Stevens rearrangement,[7] which involves migration of alkyl of trialkylphenacylammonium salt by action of base. Benzyldimethylphenacylammonium halide was known to undergo

TABLE II. Alkylation Products of Type $\begin{matrix} R \\ R' \end{matrix}\!\!>\!NCH(R''')COR''$

R, R' N	R''	R'''	Appearance (Recryst. solv.)	bp °C/mmHg	mp °C	IR ν_{max} cm^{-1} -CO-	Refractive index	Formula		Elemental analysis % C	H	N
	C_6H_5	$CH_2C_6H_5$	needles		79—80 (lit.[a]) 77—78.5)	1679		$C_{20}H_{23}ON$	Calcd.: Found:	81.87 81.83	7.90 7.83	4.77 4.89
	C_6H_5	CH_3	liquid	105—106/0.02 (lit.[b]) 154—156/4—6)		1680	n_D^{13} 1.5472	$C_{14}H_{19}ON$	Calcd.: Found:	77.38 77.10	8.81 8.59	6.45 6.63
	C_6H_5	$CH_2CH_2CH_3$	liquid	116—117/0.02 (lit.[c]) 134/1.4)		1672	n_D^{13} 1.5464	$C_{16}H_{23}ON$	Calcd.: Found:	78.32 78.07	9.45 9.36	5.71 5.40
	C_6H_5	$CH_2CH=CH_2$	liquid	103—104/0.03		1675	n_D^{13} 1.5408	$C_{16}H_{21}ON$	Calcd.: Found:	78.97 78.54	8.70 8.43	5.76 5.51
	C_6H_5	$CH_2C_6H_5$	needles (MeOH)		120—121	1679		$C_{19}H_{21}O_2N$	Calcd.: Found:	77.26 77.16	7.17 7.08	4.74 4.82
	C_6H_5	CH_3	liquid	110—111/0.01 (lit.[d]) 162—163/9)		1680	n_D^{17} 1.5466 (lit.[d]) n_D^{22} 1.5390)	$C_{13}H_{17}O_2N$	Calcd.: Found:	71.20 70.79	7.82 7.68	6.39 6.46
C_2H_5, C_2H_5 N	C_6H_5	$CH_2C_6H_5$	liquid	144—145/0.02		1679	n_D^{18} 1.5620	$C_{25}H_{26}O_8N$ (picrate)	Calcd.: Found:	58.82 59.00	5.13 5.22	10.98 11.08
C_2H_5, C_2H_5 N	C_6H_5	CH_3	liquid	84—85/0.02 (lit.[e]) 110—112/14)		1677	n_D^{16} 1.5208	$C_{13}H_{19}ON$	Calcd.: Found:	76.05 75.63	9.33 9.10	6.82 6.69
CH_3, CH_3 N	C_6H_5	$CH_2C_6H_5$	needles (MeOH)		76—77 (lit.[f]) 77—79)	1667		$C_{17}H_{19}ON$	Calcd.: Found:	80.57 80.46	7.56 7.55	5.53 5.63
CH_3, CH_3 N	C_6H_5	CH_3	liquid	82—83/0.04 (lit.[g]) 88.5—90/2)		1680	n_D^{16} 1.5289	$C_{11}H_{15}ON$	Calcd.: Found:	74.54 74.31	8.53 8.44	7.90 7.65
$C_6H_5CH_2$, CH_3 N	C_6H_5	CH_3	liquid	125—128/0.01 (lit.[h]) 157—164/2)		1685	n_D^{16} 1.5694	$C_{17}H_{19}ON$	Clacd.: Found:	80.57 80.70	7.56 7.57	5.53 5.39
	CH_3	$CH_2C_6H_5$	liquid	109—110/0.01		1710	n_D^{15} 1.5040	$C_{15}H_{21}ON$	Calcd.: Found:	77.88 77.76	9.15 8.94	6.05 6.33
	CH_3	CH_3	liquid	47—49/0.04		1710	n_D^{14} 1.4646	$C_9H_{17}ON$	Calcd.: Found:	69.93 69.49	11.04 10.93	9.02 9.30
	CH_3	$CH_2C_6H_5$	liquid	140—143/0.03		1705	n_D^{16} 1.5070	$C_{20}H_{22}O_9N_4$ (picrate)	Calcd.: Found:	51.95 51.73	4.80 4.85	12.12 11.86
	CH_3	CH_3	liquid	95—98/10		1705	n_D^{15} 1.4630	$C_8H_{15}O_2N$	Calcd.: Found:	61.12 61.14	9.62 9.62	8.91 8.77
C_2H_5, C_2H_5 N	CH_3	$CH_2C_6H_5$	liquid	108—109/0.4 (lit.[i]) 91—92/1)		1713	n_D^{13} 1.5018 (lit.[i]) n_D^{20} 1.5021)	$C_{14}H_{21}ON$	Calcd.: Found:	76.66 76.46	9.65 9.60	6.39 6.64
C_2H_5, C_2H_5 N	CH_3	CH_3	liquid	82—83/40 (lit.[j]) 168)		1710	n_D^{15} 1.4317	$C_{14}H_{20}O_8N_4$ (picrate)	Calcd.: Found:	45.16 45.13	5.41 5.54	15.05 14.80

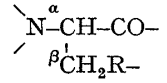
a) R.V. Henley and E.E.Turner, *J. Chem. Soc.*, **1931**, 1182.
b) A. Cattaneo, G. Gelmi, A. Jori and H. Zevio, *Farmaco (Pavia) Ed. Sci.*, **17**, 308 (1962); C.A., **58**, 4557.
c) Z. Welvart, *Compt. rend.*, **250**, 1870 (1960); C.A., **56**, 10174.
d) H.R. Henze, G.L. Sutherland and G.B. Roberts, *J. Am. Chem. Soc.*, **79**, 6230 (1957).
e) C. Mannich and G. Heilner, *Ber.*, **55**, 359 (1922).
f) G. Wittig, R. Mangold and G. Felletschin, *Ann.*, **560**, 116 (1948).
g) I.N. Nazarov, E.M. Cherkasova and G.S. Erkomaishvii, *Otdel. Khim.Nauk*, **1959**, 1605; C.A., **54**, 8699.
h) Y. Sawa, *Shionogi Kenkyujo Nenpo*, **2**, 25 (1952).
i) A.A. Durgaryan, *Izv. Akad. Nauk Arm. SSR, Khim, Nauki*, **15**, 535 (1962); C.A., **59**, 3812.
j) W. Reppe and B. Ritzenthaler, *Ger.* 897, 565, *Nov.* 23, 1953; *C.A.*, **1**, 16299.

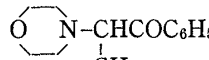
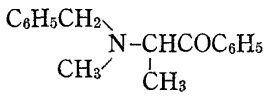
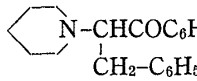
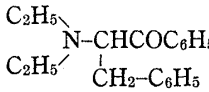
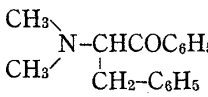
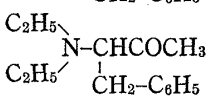
this reaction to result in the migration of N-benzyl to α-carbon. Compared with this reaction, α-benzylmethylaminoacetophenone was methylated with methyl iodide in liquid ammonia to give α-benzylmethylaminopropiophenone. From the above two reactions the alkylation in liquid ammonia means surely direct attack at α-carbon, not through the tertiary ammonium ion.

Previously, catalytic hydrogenolysis of the benzylmethylaminopropiophenone, prepared by another route, has been reported[3] to give (±)-ephedrine. Under condition of using palladium-on-charcoal in aqueous ethanolic medium containing 3% HCl, the same hydrogenolysis was confirmed to occur with the methylated product to give (±)-ephedrine in excellent yield.

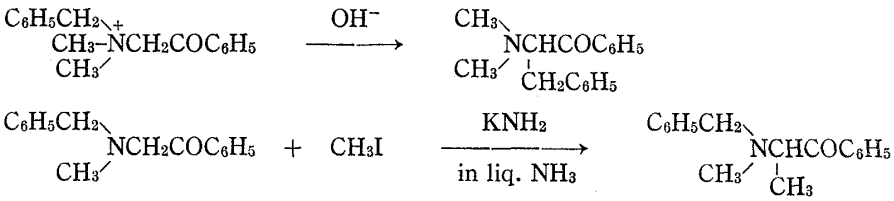
7) T.S. Stevens, E.M. Creighton, A.B. Gordon and M. MacNicol, *J. Chem. Soc.*, **1928**, 3193.

Table III. NMR Spectra of α-N,N-Dialkylaminoketones

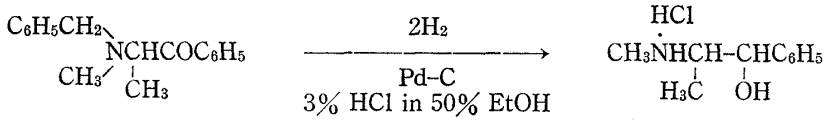


Compound	τ-Value (multiplicity) (J in cps)	
	C_α–H	C_β–3H
	5.94 (q) (6.6)	8.86 (d) (6.6)
	5.71 (q) (7.0)	8.20 (d) (7.0)
	5.16 (q) (4.5, 9.0)	7.06 (q) (4.5, 13.5) 6.17 (q) (9.0, 13.5)
	5.50 (q) (4.2, 9.0)	7.14 (q) (4.2, 13.5) 6.66 (q) (9.0, 13.5)
	5.70 (q) (4.5, 9.0)	7.12 (q) (4.5, 13.5) 6.72 (q) (9.0, 13.5)
	6.51 (q) (3.5, 8.2)	7.38 (q) (3.5, 12.0) 6.95 (q) (8.2, 12.0)

q=quartet, d=doublet



Consequently this preparative method through the alkylation process may be one of its useful application.



Experimental

Preparation of α-N,N-Dialkylaminoacetophenones——General Procedure: To a solution of 0.75 mole of secondary amine in 300 ml of benzene was added dropwise a solution of 0.3 mole of bromoacetophenone in 120 ml of benzene with stirring at room temperature. After stirring at room temperature for 4 hr the deposited hydrobromide of secondary amine was filtered off and the filtrate was washed with 20 ml of saturated aqueous K_2CO_3 solution and dried over K_2CO_3. The benzene was removed and the residue was distilled under reduced pressure to give α-N,N-dialkylaminoacetophenone. Yields and identities of the products are described in the following.

2-Piperidinoacetophenone: Obtained from piperidine, bp 106—109° (0.02 mmHg) (lit.[8] bp 124° (0.9 mmHg)). Yield, 67%. IR ν_{max}^{Liq} cm^{-1}: 1677 (>C=O), 753, 688 (Ph). NMR (25% in $CDCl_3$) τ: 8.7—8.1

8) F. Minisci and R. Galli, *Tetrahedron Letters*, **1964**, 3197.

(6H, multiplet, piperidine), 7.6—7.3 (4H, multiplet, piperidine), 6.23 (2H, singlet, $-CH_2-$), 2.7—1.8 (5H, multiplet, aromatic).

2-Morpholinoacetophenone: Obtained from morpholine as a solid distillate, bp 116—119°(0.017 mmHg), mp 57—59° (lit.[18] mp 52°). Yield, 57%. IR ν_{max}^{Liq} cm^{-1}: 1685 (>C=O), 1124 (-O-), 764, 697 (Ph).

2-(Diethylamino)acetophenone: Obtained from diethylamine, bp 142—145° (20 mmHg)(lit.[9] bp 148—152° (30 mmHg)). Yield, 67%. IR ν_{max}^{Liq} cm^{-1}: 1670 (>C=O), 759, 695 (Ph). NMR (20% in $CDCl_3$) τ: 8.92 (6H, triplet, $J=7.0$ cps, $2CH_3-$), 7.27 (4H, quartet, $J=7.0$ cps, $2-CH_2-CH_3$), 6.06 (2H, singlet, $>N-CH_2-CO-$), 2.7—1.8 (5H, multiplet, aromatic).

2-(Dimethylamino)acetophenone: Obtained from dimethylamine, bp 87—89° (2 mmHg) (lit.[20] bp 119—121° (9 mmHg)). Yield, 63%. IR ν_{max}^{Liq} cm^{-1}: 1684 (>C=O), 760, 694 (Ph).

2-(Benzylmethylamino)acetophenone: Obtained from benzylmethylamine, bp 127—129° (0.01 mmHg) (lit.[10] bp 195—205° (15 mmHg)). Yield, 70%. IR ν_{max}^{Liq} cm^{-1}: 1680 (>C=O), 745, 695 (Ph). NMR (30% in $CDCl_3$) τ: 7.63 (3H, singlet, CH_3-), 6.32 (2H, singlet, $-CH_2-$), 6.21 (2H, singlet, $-CH_2-$), 2.8—1.9 (10H, multiplet, aromatic).

Preparation of N,N-Dialkylamino-2-propanones——General Procedure: To a solution of 0.75 mole of secondary amine in 200 ml of benzene was added dropwise a solution of 0.3 mole of bromoacetone in 50 ml of benzene with stirring at room temperature. After stirring at room temperature for 4 hr (in the run with N-methylaniline stirring was held at 40° for 6 hr) the deposited hydrobromide of secondary amine was filtered off and the filtrate was extracted with three 30 ml portions of 10% HCl. To the aqueous solution was added potassium hydroxide and the separated oil was extracted with ether and the ether solution was dried over K_2CO_3. The ether was vented and the residue was distilled under reduced pressure to give N,N-dialkylamino-2-propanone, which gradually changed into brown on exposure to air. Yields and identities of the products are described in the following.

Piperidino-2-propanone: Obtained from piperidine, bp 83—86° (17 mmHg) (lit.[11] bp 98—99° (20 mmHg)). Yield, 54%. IR ν_{max}^{Liq} cm^{-1}: 1710 (>C=O), 1354, 1225, 1153, 1124. NMR (33% in $CDCl_3$) τ: 8.6—8.2 (6H, multiplet, piperidine), 7.87 (3H, singlet, CH_3-), 7.8—7.4 (4H, multiplet, piperidine), 6.88 (2H, singlet, $-CH_2-$).

Morpholino-2-propanone: Obtained from morpholine, bp 114—115° (32 mmHg) (lit.[12] bp 81° (2 mmHg)). Yield, 51%. IR ν_{max}^{Liq} cm^{-1}: 1708 (>C=O), 1134, 1103 (-O-), 862.

Diethylamino-2-propanone: Obtained from diethylamine, bp 57—58° (18 mmHg) (lit.[13] bp 61—63° (23 mmHg)). Yield, 75%. IR ν_{max}^{Liq} cm^{-1}: 2950, 2770, 1700 (>C=O), 1350, 1200.

N-Methylanilino-2-propanone: Obtained from N-methylaniline, bp 130—131° (8 mmHg) (lit.[14] bp 135—142° (18 mmHg)). Yield, 50%. IR ν_{max}^{Liq} cm^{-1}: 1726 (>C=O), 1598, 1501, 745, 688 (Ph). NMR (34% in $CDCl_3$) τ: 8.03 (3H, singlet, CH_3-C), 7.08 (3H, singlet, CH_3-N), 6.13 (2H, singlet, $-CH_2-$), 3.6—2.6 (5H, multiplet, aromatic).

C-Alkylation of α-N,N-Dialkylaminoketones——General Procedure: To a colorless solution of potassium amide in liquid ammonia, which was prepared from 1.7 g (0.044 gatom) of potassium, catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ and 80 ml of liquid ammonia, was added dropwise a solution of 0.04 mole of α-N,N-dialkylaminoketone in 16 ml of ether with stirring. After a while, to this 0.044 mole of the given alkyl halide was added dropwise and the mixture was refluxed with stirring for 8 hr. After addition of 1.1 g of ammonium chloride the liquid ammonia was vented. The residue was extracted with ether and the ether solution was dried over K_2CO_3. The ether was removed and the residue was distilled under reduced pressure to give C-alkylated α-N,N-dialkylaminoketone.

In the runs of the benzylation of 2-morpholinoacetophenone and 2-(dimethylamino)acetophenone the residue was solidified and the solid was purified by recrystallization.

Yields of the C-alkylation products obtained by the above procedures are listed in Table I and their properties and analytical data are recorded in Table II.

2-Benzyl-1,3-dimethylindole: Obtained by the above procedure from N-methylanilino-2-propanone and benzyl chloride as a solid distillate, bp 122—126° (0.03 mmHg). Yield, 27%. mp 93—94° (lit.[6] mp 92—93°). *Anal.* Calcd. for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.37; H, 7.20; N, 6.12. IR ν_{max}^{KBr} cm^{-1}: 732, 706, 688 (Ph). UV λ_{max}^{EtOH} mμ (log ε): 232 (4.60), 282s (3.85), 288 (3.89), 295s (3.86). NMR (10% in $CDCl_3$) τ: 7.17 (3H, singlet, CH_3-C), 6.57 (3H, singlet, CH_3-N), 5.90 (2H, singlet, $-CH_2-$), 3.0—2.3 (9H, multiplet, aromatic).

(±)-Ephedrine Hydrochloride: A solution of 5.5 g of 2-(benzylmethylamino)propiophenone dissolved in 30 ml of 50% ethanol containing 3% HCl was catalytically hydrogenated over palladium-on-charcoal

9) C.S. Marvel and v.du Vigneaud, *J. Am. Chem. Soc.*, **46**, 2098 (1924).
10) T.S. Stevens, *J. Chem. Soc.*, **1930**, 2107.
11) Z.N. Pazenko, *Ukrain. Khim. Zhur.*, **25**, 348 (1959); *C.A.*, **54**, 1499 (1960).
12) M. Kerfanto, *Bull. Soc. Chim. France*, **1965**, 3537; *C.A.*, **65**, 708 (1966).
13) W. Reppe, *Ann.*, **596**, 12 (1955).
14) H. Friedrich and K. Stange, *Ger.*, 945,844, July 19, 1956; *C.A.*, **53**, 2096 (1959).

(prepared from 0.15 g of $PdCl_2$ and 1.5 g of charcoal as usual) under ordinary pressure at room temperature. After uptake of hydrogen the mixture was filtered and the filtrate was concentrated to dryness. The solid residue was recrystallized from ethanol to give 3.8 g (89%) of (±)-ephedrine hydrochloride, mp 187—188° (lit.[13] mp 188°). The mixed melting point test with the authentic sample exhibited no depression and the infrared spectrum showed well correspondence with that of the authentic sample.

Acknowledgement The authers express their gratitudes to Dr. Y. Kawazoe of National Cancer Center for his kind help on NMR determination. They are indebted to Dr. H. Takamatsu of Dainippon Seiyaku Co. Ltd. for his kind gift of (±)-ephedrine hydrochloride and φ-(±)-ephedrine hydrochloride. Thanks are also due to the members of Analytical Center of this College for elemental analyses and NMR measurements.