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Alkylation of Phthalimidines

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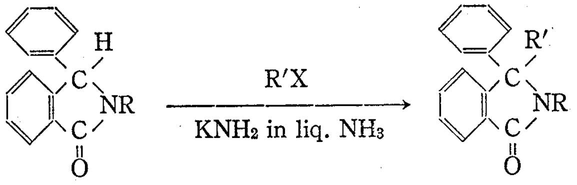
The present paper provides a new useful means of synthesis of 2,3,3-trisubstituted phthalimidines. Alkylation of phthalimidines at 3-position has been found to proceed with alkyl halide in liquid ammonia in the presence of potassium amide.

With the information about the carbanion-forming ability of C_3 of phthalimidines noted in the previous paper[2] we tried to carry out alkylation of phthalimidines at 3-position with alkyl halide in the presence of base. In chemical literature no report was found describing the alkylation of phthalimidines. Success was achieved in the alkylation by means of using potassium amide in liquid ammonia.

Examination on this alkylation was begun with 2-substituted phthalimidines to avoid N-alkylation. Control experiments were made with the substrates possessing varying N-alkyls and with varying alkyl halides. All the runs were processed under a uniformed condition in which to a liquid ammonia solution of potassium amide the substrate was dissolved and then ethereal solution of halide was added. The mixture was allowed to react at the refluxing temperature for 3 hr.

TABLE I. Alkylation[a] of 3-Phenyl-2-substituted Phthalimidines



Substrate (R)	Alkyl halide (R'X)	Yield[b] (%) of product
CH_3	$C_6H_5CH_2Cl$	69
$CH_3(CH_2)_2CH_2$	$C_6H_5CH_2Cl$	72
C_6H_5	$C_6H_5CH_2Cl$	45
CH_3	$CH_3(CH_2)_2CH_2I$	70
CH_3	CH_3I	81
CH_3	$CH_2=CHCH_2Cl$	19

a) molar ratio: substrate(0.02 mole): R'X: KNH_2=1: 1.1: 1.1, liq. NH_3: 50 ml
b) based on the product actually isolated

Table I shows results of the alkylation of 3-phenyl-2-substituted phthalimidines, giving fair yields of the desired alkylated products in most of the runs. Table II shows results of the alkylations of 2-methylphthalimidine with two molar equivalent of the alkyl halides. With such 2-substituted substrate only 3,3-dialkylated products were obtained. It was confirmed that even in the case of using one molar equivalent of benzyl chloride no monobenzylated product but the dibenzylated product was obtained.

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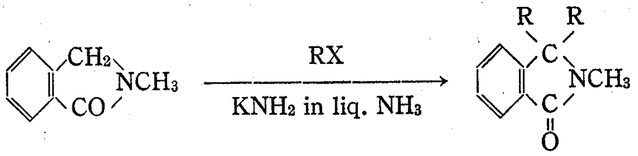
[1] Location: *2-2-1, Oshika, Shizuoka.*
[2] M. Sekiya and Y. Terao, *Chem. Pharm. Bull.* (Tokyo), 20, 2128 (1972).

Table II. Dialkylation[a] of 2-Methylphthalimidine



Alkyl halide (RX)	Yield[b] (%) of product	Alkyl halide (RX)	Yield[b] (%) of product
$C_6H_5CH_2Cl$	72	$CH_3(CH_2)_2CH_2I$	85
$CH_2{=}CHCH_2Cl$	31	CH_3I	80

a) molar ratio; substrate(0.02 mole): alkyl halide: KNH_2=1: 2.2: 2.2, liq. NH_3: 50 ml

b) based on the product actually isolated

Alkylation of 2-unsubstituted phthalimidines was begun with 3-phenylphthalimidine as a substrate, where both 2- and 3-benzylations were shown to proceed. Benzylation of phthalimidine was then examined by the use of varying amount of potassium amide. Results of these experiments are summarized in Table III. The above results in the use of 2-unsubstituted phthalimidines insist that electrophilic attack of alkyl halide at 3-position is favourable more than that at 2-position.

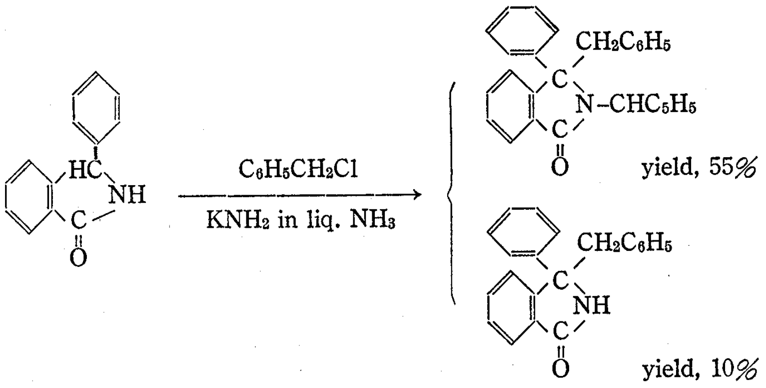
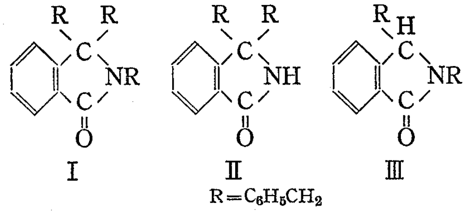


Table III. Benzylation[a] of Phthalimidine

Molar ratio			Yield[b] (%) of product			Recovered substrate (%)
Substrate (0.03 mole)	Benzyl-chloride	KNH_2	I	II	III	
1	3.3	1.1	0	20	0	53
1	3.3	2.2	17	20	3	43
1	3.3	3.3	51	12	26	0

a) 100 ml of liq. NH_3 was used.

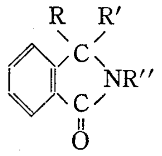
b) yield of the following products actually isolated



The structures for the products obtained were determined by infrared (IR) and nuclear magnetic resonance (NMR) spectral measurements (see Table IV). The presence of the lactam carbonyl characteristic of the phthalimidine derivatives was seen in their IR spectra as an absorption band at 1665—1700 cm^{-1}. The NMR spectra of the products exhibited their characteristic splitting patterns indicative of the assigned structures. The methylene protons of 2-benzyl in the products in which C_3 is asymmetric are non-quivalent displaying the AB pattern near AX (J=*ca.* 15 Hz). A similar splitting pattern[3] has been observed as to 2-benzyl-3-phenylphthalimidine. The methylene protons of 3-benzyl, in the 3-monobenzylated products, display the AB pattern because they are non-equivalent owing to the adjacent asymmetric C_3-carbon, and, in the 3,3-dibenzylated products, display the splitting patterns different upon the 2-substituents. In the products possessing the 2-substituent such as benzyl or methyl, the methylene protons of 3,3-dibenzyl appeared as the two doublets probably owing to the restricted rotation, while, in the 2-unsubstituted product appeared as the singlet, which was shown considerably to broaden at −60°.

The alkylation presented has opened a new method of synthesis of 2,3,3-trisubstituted phthalimidines which appeared more convenient than the earlier method.[4]

TABLE IV. Phthalimidine Derivatives



No.	R	R′	R″	Appearance (recryst. solvt.)	mp (°C)	IR ν_{max}^{KBr} cm^{-1} (C=O)
1	$C_6H_5CH_2$	C_6H_5	CH_3	prisms (EtOH)	170—171	1689
2	CH_2=$CHCH_2$	C_6H_5	CH_3	needles (ether)	148—150	1673
3	n-C_4H_9	C_6H_5	CH_3	prisms (ether)	48— 50	1673
4	CH_3	C_6H_5	CH_3	prisms (AcOEt)	109—110	1665
5	$C_6H_5CH_2$	C_6H_5	C_6H_5	needles (ether)	190—191	1686
6	$C_6H_5CH_2$	C_6H_5	n-C_4H_9	prisms (ether)	120—121	1682
7	$C_6H_5CH_2$	$C_6H_5CH_2$	CH_3	prisms (AcOEt)	147—148	1673
8	CH_2=$CHCH_2$	CH_2=$CHCH_2$	CH_3	needles (ether)	56— 59	1672
9	n-C_4H_9	n-C_4H_9	CH_3	prisms (ether)	66— 67	1672
10	CH_3	CH_3	CH_3	liquid	110—113[b)] (0.3 mmHg)	1666[c)]
11	C_6H_5	$C_6H_5CH_2$	$C_6H_5CH_2$	prisms (EtOH)	189—191	1682
12	C_6H_5	$C_6H_5CH_2$	H	prisms (EtOH)	198—200	3171 3091(NH) 1688
13	$C_6H_5CH_2$	$C_6H_5CH_2$	$C_6H_5CH_2$	needles (EtOH)	174—175	1678
14	$C_6H_5CH_2$	$C_6H_5CH_2$	H	needles (EtOH)	189—190	3183 3061(NH) 1698
15	$C_6H_5CH_2$	H	$C_6H_5CH_2$	prisms (AcOEt)	84— 86	1678

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3) A.H. Lewin, J. Lipowitz and T. Cohen, *Tetrahedron Letters*, **1965**, 1241.

4) C.-L. Mao, I.T. Barnish and C.R. Hauser, *J. Heterocyclic Chem.*, **6**, 475 (1969).

No.	NMR[a] τ (in $CDCl_3$) (J=Hz)	Formula	Analysis (%) Calcd. (Found) C	H	N
1	7.07 (3H, s, N-CH_3), 6.2 (1H, d), 6.3 (1H, d, J=13, -CH_2-)	$C_{22}H_{19}ON$	84.31 (83.96)	6.11 (6.05)	4.47 (4.56)
2	7.16 (3H, s, N-CH_3), 6.7—6.9 (2H, m, -CH_2-), 4.8—5.1 (3H, m, CH_2=CH-)	$C_{18}H_{17}ON$	82.10 (82.19)	6.51 (6.22)	5.32 (5.24)
3	7.3—7.7, 8.5—9.5 (9H, m, C_4H_9), 7.21 (3H, s, N-CH_3)	$C_{19}H_{21}ON$	81.68 (81.57)	7.58 (7.42)	5.01 (5.20)
4	8.13 (3H, s, CH_3), 7.15 (3H, s, N-CH_3)	$C_{16}H_{15}ON$	80.98 (81.31)	6.37 (6.47)	5.90 (5.80)
5	6.0 (1H, d), 6.1 (1H, d, J=13.6, -CH_2-)	$C_{27}H_{21}ON$	86.37 (86.12)	5.64 (5.64)	3.73 (3.88)
6	8.5—9.4, 6.5—7.0 (9H, m, C_4H_9), 6.1 (1H, d), 6.35 (1H, d, J=14.0, -CH_2-)	$C_{25}H_{25}ON$	84.47 (84.74)	7.09 (6.91)	3.94 (4.05)
7	6.83 (3H, s, N-CH_3), 6.65 (1H, d), 6.69 (1H, d, J=13.5, -CH_2-)	$C_{23}H_{21}ON$	84.37 (84.49)	6.47 (6.57)	4.28 (4.25)
8	7.1—7.5 (4H, m, -CH_2-), 6.99 (3H, s, N-CH_3), 4.7—5.3 (6H, m, CH_2=CH-)	$C_{15}H_{17}ON$	79.26 (78.87)	7.54 (7.29)	6.61 (6.26)
9	7.5—9.5 (18H, m, C_4H_9), 7.08 (3H, s, N-CH_3)	$C_{17}H_{25}ON$	78.71 (78.50)	9.72 (9.31)	5.40 (5.48)
10	8.56 (6H, s, CH_3), 6.97 (3H, s, N-CH_3)	$C_{11}H_{13}ON$	75.40 (75.01)	7.48 (7.62)	7.99 (8.35)
11	6.15 (1H, d), 6.25 (1H, d, J=13.5, -CH_2-), 5.2 (1H, d), 5.6 (1H, d, J=15.0, N-CH_2-)	$C_{28}H_{23}ON$	86.34 (86.33)	5.95 (5.88)	3.60 (4.06)
12	6.16 (2H, s, -CH_2-), −0.5—0.1 (1H, br, NH)[d]	$C_{21}H_{17}ON$	84.25 (83.75)	5.72 (5.74)	4.68 (4.73)
13	6.6 (2H, d), 6.95 (2H, d, J=12.5, -CH_2-) 5.34 (2H, s, N-CH_2-)	$C_{29}H_{25}ON$	86.32 (86.16)	6.25 (6.24)	3.47 (3.55)
14	6.75 (4H, s, -CH_2-), 8.2 (1H, br, NH)	$C_{22}H_{19}ON$	84.31 (84.32)	6.11 (6.14)	4.47 (4.75)
15	7.15 (1H, d.d, J=8.8 and 14.3), 6.6 (1H, d.d, J=4.8 and 14.3, -CH_2-), 5.25 (1H, d), 4.45 (1H, d. J=15.7, N-CH_2-), 5.4 (1H, d.d, J=4.8 and 8.8, -CH)	$C_{22}H_{19}ON \cdot 1/2H_2O$	81.96 (81.44)	6.25 (6.26)	4.34 (4.53)

a) The following abbreviations were used: s=singlet; d=doublet; m=multiplet; br=broad; d.d=doublet of doublets. b) boiling point c) liquid film d) CF_3CO_2H soln.

Experimental[5]

Alkylation of Phthalimidines——General Procedure: The alkylations were conducted by the use of the following substrates, 2-methyl-3-phenylphthalimidine[2] (mp 103—104°), 2-butyl-3-phenylphthalimidine[2] (mp 90—91°), 2,3-diphenylphthalimidine[2] (mp 215—216°), 3-phenylphthalimidine[2] (mp 192—193°), 2-methylphthalimidine (mp 113—114°) and phthalimidine (mp 149—150°).

To a colorless solution of potassium amide in liquid ammonia, which was prepared by dissolving potassium in the presence of catalytic amount of ferric nitrate, the phthalimidine substrate was added with stirring. After a while, to the resulting mixture a solution of alkyl halide in dry ether was dropwise added with stirring. Stirring with refluxing was continued for 3 hr. After addition of ammonium chloride the liquid ammonia was vaporized. The residue was extracted with chloroform and the solution was dried over $MgSO_4$. After removal of $CHCl_3$ the residue was recrystallized or, when not solidified, was distilled under reduced pressure to give the product. In the runs shown in Table III the products were isolated by silica gel column chromatography with $CHCl_3$ as an eluent.

Amount of the above staring matertials used are recorded in Table I, II and III. Identities of the products obtained were made by elemental analyses, IR and NMR spectral measurements, data of which are recorded in Table IV.

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5) All melting points were uncorrected. IR spectra were determined on a Hitachi EPI-G2 spectrophotometer. NMR spectra were taken at 60 MHz with a JEOL JNM-C-60H spectrometer using tetramethylsilane as the internal standard.