THE REACTION OF DICHLOROMALEIMIDES WITH AMINES

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Abstract—Aliphatic primary amines react exothermally with dichloromaleimide or N-phenyldichloromaleimide yielding N-alkyl-2-alkylamino-3-chloromaleimides. The main factors which determine the remarkable ease of exchange of imide nitrogen are the nucleophilicity of amide nitrogens and inductive effect of chlorine of the chloromaleimides.

INTRODUCTION

THE reaction of dihalomaleimides has received considerable attention. Dichloromaleimide(I) reacts with aniline to give 2-anilino-3-chloromaleimide(II) and with ammonia to give 2-amino-3-chloromaleimide.¹ Dichloromaleimides react with tertiary arylamines in the presence of sodium cyanide to give 4-(2-cyano-3-maleimidyl) arylamines,² while with tertiary amines in methanol or acetic acid to give N-(Nsubstituted 2-oxy-3-maleimidyl)ammonium betaines (III).³ Dichloromaleimides react with hydrogen sulfide to give 1,4-dithiins(IV).⁴



The reaction of I with aliphatic primary amines have not been reported, so it was of interest to know whether I would react with the amines in a fashion analogous to the reaction of I with hydrogen sulfide. Some interesting transformations were observed in this investigation.

RESULTS AND DISCUSSION

Treatment of I (1 mole) with laurylamine (3 moles) in ethanol at room temperature gave a reaction product quantitatively which was not the anticipated 1,4-diazine but 2-chloro-N-lauryl-3-laurylaminomaleimide(V).

$$I + n - C_{12}H_{23}NH_2 - C_{12}H_{23}NH$$

The reaction of I with the amine (molar ratio, 1:2) gave 73% of V and an equimolecular mixture of these also gave V in 67% yield (based on the amine). These results suggest that the rate of substitution of chlorine and that of the transimidation are comparable.

Similar results were obtained from other aliphatic primary amines (Table 1), while aromatic amines and piperidine gave 2-amino-3-chloromaleimides (Table 2).

The reaction of II with aliphatic primary amines also gave transimidation products (Table 3), although the reaction was slow at room temperature.

The remarkable ease of conversion of 2-chloromaleimides into N-alkyl-2-chloromaleimides has not been reported, but similar results were observed in the reaction of phthalimides,⁵⁻⁸ and the following scheme of reaction between N-substituted phthalimides and amines was considered.



Barker and Wragy⁶ suggest that the main factors which determine the end products are the electronic characteristics of R and R' and such relevant properties as solubility of their derivatives in the reagent used or volatility at the reaction temperature.

N-Carboethoxyphthalimide has excellent properties for the phthaloylation of amino acids under mild conditions and the reaction mechanism is discussed in detail.⁹

$$\underbrace{ \begin{pmatrix} c_0 \\ N-COOR + NH_2-CH_2-COO^{\theta} \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-CH_2-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \end{pmatrix}}_{CO} \xrightarrow{CO} \underbrace{ \begin{pmatrix} c_0 \\ N-COO^{\theta} + NH_2COOR \\ c_0 \\ COO^{\theta} + NH_2COOR \\ COO^{\theta} + NH_2COOR \\ COO^$$

The reaction is facilitated by electron-attracting properties of the carbamate residue and the sterically favoured position of the reacting groups.⁹

The scope and limitations of the reaction of dichloromaleimides with amines were studied. Equimolecular mixture of succinimide and n-butylamine gave N-butyl-succinamide (m.p. 191–193°, yield, 83%). Treatment of N-phenylmaleimide with one equivalent of cyclohexylamine gave N-cyclohexyl-N'-phenylmaleamide (yield, 64%) under the conditions used in the reaction of I with amines. N-Phenyldichloromale-imide reacted with some aliphatic primary amines to give the same compounds as those shown in Table 1 (yield, 87–93%).

The reaction of N-benzyldichloromaleimide with laurylamine gave V (yield, 75%), while the reaction with cyclohexylamine gave N-benzyl-2-chloro-3-cyclohexylaminomaleimide and the reaction of N-lauryldichloromaleimide with cyclohexylamine gave 2-chloro-3-cyclohexylamino-N-laurylmaleimide. These results suggest that steric effects may be important in the first step (A) of the transimidation, because TABLE 1. N-ALKYLMALEIMIDE



		Carbon, %		Hydrogen, %		Nitrogen, %		Chlorine, %			
R	М.р.	%	Formula	Found	Calc.	Found	Calc.	Found	Calc.	Found	Calc.
Мс	167-169°	73	C ₆ H ₇ ClN ₂ O ₂	41.42	41-26	4.17	4.02	15.84	16-00	20-42	20-34
Et	626 4 °	75	C ₁ H ₁₁ ClN ₂ O ₂	47-34	47-44	5-51	5-48	13.83	13.83	17-45	17.50
n-Bu	35–36°	95	$C_{12}H_{10}CIN_2O_2$	56-05	55.70	7-49	7-40	10-82	10-83	13-68	13·70
n-C ₁₂ H ₂₅	6263°	96	C28H51CIN2O2	69-49	69.60	10-77	10-64	5.68	5.80	7·50	7-34
cyclo-C ₆ H ₁₁	152-154°	88	C16H21CIN2O2	62-07	61.82	7.73	7.46	9-01	9-01	11-47	11-41
Ph-CH ₂	97– 9 8°	98	$C_{12}H_{13}CIN_2O_2$	66.36	66-15	4.71	4.63	8-56	8·57	10-81	10-85
Pb-CH ₂ CH ₂	124–125°	94	C20H19CIN2O2	68-07	67·69	5.34	5-04	8-05	7-90	10-09	9-99

TABLE 2. 2-AMINO-3-CHLOROMALEIMIDE



	Carbon, %		Hydrogen, %		Nitrogen, %		Chlorine, %				
RNH ₂	М.р.	%	Formula	Found	Calc.	Found	Calc.	Found	Calc.	Found	Calc.
Aniline	196–197 [∞]	91	C ₁₀ H ₇ ClN ₂ O ₂	54.28	54-00	3.24	3.17	12.63	12.58	15.75	15-93
p-Toluidine	180-182°	64	C ₁₁ H ₂ CIN ₂ O ₂	55· 4 0	55·81	3-45	3-81	11-54	11-84	14-91	15-05
p-Anisidine	231–233°	88	C ₁₁ H ₉ ClN ₂ O ₃	52-42	52-36	3.79	3.59	11-02	11-09	14-01	14-05
β-Naphthylamine	219-220°	98	C1.H.CIN2O2	61-40	61.66	3.30	3.33	10-03	10-28	13-12	13-00
Piperidine	128-129°	93	C ₉ H ₁₁ ClN ₂ O ₂	50-50	50-35	5.28	5.13	12.59	13-05	16-41	16-52

^e Lit.¹ m.p. 196–197°

TABLE 3. N-ALKYL-2-ANILINO-3-CHLOROMALEIMIDE

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	Yield,			Carbon, %		Hydrogen, %		Nitrogen, %		Chlorine, %	
R	М.р.	%	Formula	Found	Calc.	Found	Calc.	Found	Calc.	Found	Calc
Ме	152–153°	57	C11HoCIN2O2	55-66	55.82	3.85	3.83	12-06	11.84	14.98	14-98
Et	12 4 –126°	51	$C_{12}H_{11}CIN_2O_2$	57-64	57·48	4.34	4.42	10-88	1 1·18	14-18	14-14
n-Bu	88–89°	80	$C_{14}H_{15}CIN_2O_2$	60-05	60-32	5-54	5.42	9-95	10-05	12.70	12.72
iso-Bu	126-127°	19	$C_{14}H_{13}CIN_2O_2$	60-10	60-32	5.50	5.42	10-02	10-05	12.67	12.72
p-C12H21	69–70°	97	$C_{22}H_{31}CIN_2O_2$	67·44	67.58	8.13	7·99	7.12	7.17	9·18	9.07
cyclo-C ₆ H ₁₁	147–148°	38	$C_{16}H_{17}CIN_{2}O_{2}$	63-05	63-04	5.59	5.62	9.22	9-91	11.63	11-63
Ph-CH ₂	130-131°	90	$C_{17}H_{13}CIN_2O_2$	65·15	65·29	4·21	4.19	8.93	8-96	11.40	11.34

basicity of the two amines is the same (Pka, 10.6) and even more basic piperidine also failed to do so.



In the second step (B), inductive effect of chlorine facilitate the attack of more nucleophilic amide nitrogen at the amide carbon and resonance effect of vinylic chlorine may be important for the stabilization of the intermediate. It seems reasonable to assume that the transimidations of phthalimides are also effected by an electron withdrawing phenyl group.



C1

	RNH	N-R'
		τ value
R	R'	
Ph	Н	2.94(m), 0.60, -0.68; 5:1:1
p-MeOC ₆ H₄	н	6.72(s), 3.18(q), 0.82, -0.53; 3:4:1:1ª
p-MeC ₆ H₄	н	$7.75(s)$, $3.09(s)$, 0.75 , -0.59 ; $3.4:1:1^{a}$
Ph	C ₂ H,	8-81(t), 6-48(q), 2-9(m); 3:2:6
Ме	CH ₃	7-04(s), 6-77(d), 4-65; 3:3:1
Et	C ₂ H,	8-86(t), 8-75(t), 6-5(m), 4-7; 3:3:4:1
cyclo-C ₆ H ₁₁	cyclo-C ₆ H ₁₁	9·0-7·7(m), 4·85; 22:1
cyclo-C ₆ H ₁₁	C ₆ H ₄ -CH ₂	9·1-8·85(m), 5·50(s), 4·9, 2·92(s); 11:2:1:
Ph	C ₆ H ₅ -CH ₂	5.46(s), 3.2-2.65(m), 2.86(s); 2:6:5
Ph-CH ₂	C,H,-CH,	5.60(s), 5.46(d), 4.26(t), 2.97(s); 2:2:1:10

^a in DMSO

The NMR spectra of some compounds obtained are shown in Table 4. The IR spectra of the compounds in Tables 1, 2, 3 indicate characteristic bands of maleimide ring.³

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were obtained in Nujol. NMR spectra were determined in CDCl₃, unless otherwise stated, containing TMS as internal standard.

N-Alkyl-2-alkylamino-3-chloromaleimides and 2-amino-3-chloromaleimides

A soln of 1.66 g (0.01 mole) dichloromaleimide in 30 ml EtOH was treated with a soln of 0.03 mole of an amine in 10 ml EtOH at 60° for 2 hr, the soln was cooled to precipitate the product. Sometimes, it was necessary to dilute the cooled reaction mixture with water to obtain the product. The yellow ppt was filtered off, and recrystallized from EtOH. The results are shown in Tables 1 and 2. The reactions of N-substituted dichloromaleimides with amines were also carried out as described above.

N-benzyl-2-chloro-3-cyclohexylaminomaleimide: m.p. 97-99°, yield, 76%. (Found: C, 63.47; H, 6.15; N, 8.49; Cl, 11.42. C₁, H₁₀ClN₂O₂ requires: C, 64.04; H, 601; N, 8.79; Cl, 11.42%).

2-Chloro-3-cyclohexylamino-N-laurylmaleimide: m.p. 51-53°, yield, 81%. (Found: C, 66·35; H, 9·61; N, 7·04; Cl, 8·93. C₂₂H₃₇ClN₂O₂ requires: C, 66·57; H, 9·40; N, 7·06; Cl, 8·87%).

N-Alkyl-2-anilino-3-chloromaleimide (Table 3)

A mixture of 2.23 g (0-01 mole) 2-anilino-3-chloromaleimide, 0-01 mole of an amine and 50 ml EtOH was heated to 60-65° for 2 hr, poured into 50 ml water, and refrigerated. The yellow solid which precipitated was filtered off, and recrystallized from EtOH.

N-Cyclohexyl-N'-phenylmaleamide

A mixture of 1.73 g (0.01 mole) N-phenylmaleimide, 0.97 g (0.01 mole) cyclohexylamine, and 30 ml EtOH was heated to 65-70° for 2 hr, cooled to precipitate the product, and filtered. Recrystallization of the product from EtOH yielded 1.8 g as colourless crystals, m.p. 149-151°. (Found: C, 70.58; H, 7.50; N, 10-20. $C_{16}H_{20}N_2O_2$ requires: C, 70.56; H, 7.40; N, 10.29%).

REFERENCES

¹ G. Ciamician and P. Silber, Chem. Ber. 22, 2490 (1889).

² E. L. Martin, C. L. Dickinson and J. R. Roland, J. Org. Chem. 26, 2032 (1961).

- ³ M. J. Karten, S. L. Shapiro, E. S. Isaacs and L. Freedman, J. Org. Chem. 30, 2657 (1965).
- 4 W. Draber, Chem. Ber. 100, 1559 (1967).
- ⁵ F. S. Spring and J. C. Woods, J. Chem. Soc. 625 (1945).
- ⁶ H. J. Barker and W. R. Wragy, Nature, Lond. 158, 514 (1946).
- ⁷ F. S. Spring and J. C. Woods, Ibid. 158, 754 (1946).
- ⁸ A. K. Bose, F. Greer, J. S. Gots and C. C. Price, J. Org. Chem. 24, 1309 (1959).
- ⁹ G. H. L. Nefkens, G. I. Tesser and R. J. F. Nivard, Rec. Trav. Chim. 79, 688 (1960).