Chemistry of Dichloromaleimides. II.[1] The Synthesis and Pharmacology of 1-(2-Arylamino-3-maleimidyl)pyridinium Salts

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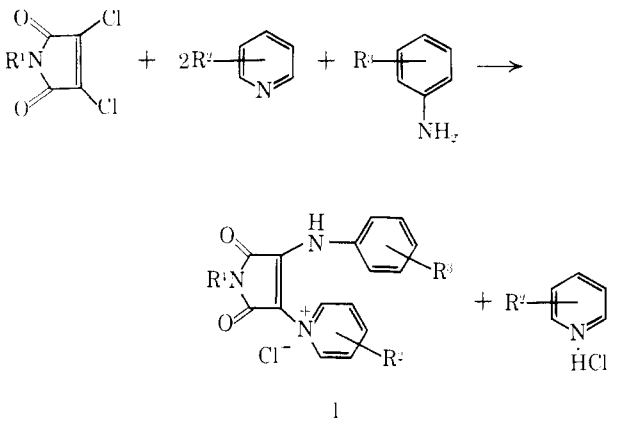
The reaction of N-substituted 2,3-dichloromaleimides with substituted pyridines and arylamines in inert solvents has been found to give novel 1-(2-arylamino-3-maleimidyl)pyridinium salts. A reaction path is postulated. The pharmacological activity of the salts is reported.

In the preceeding paper of this series,[1] the reaction of dichloromaleimides with tertiary amines in hydroxylic solvents was described. We now wish to report that dichloromaleimides react with substituted pyridines and arylamines in inert solvents to give the novel 1-(2-arylamino-3-maleimidyl)pyridinium salts (I) (see Chart I). The analogous reaction of 2,3-dichloro-1,4-naphthoquinone with substituted pyridines and anilines has been reported.[2]

CHART I



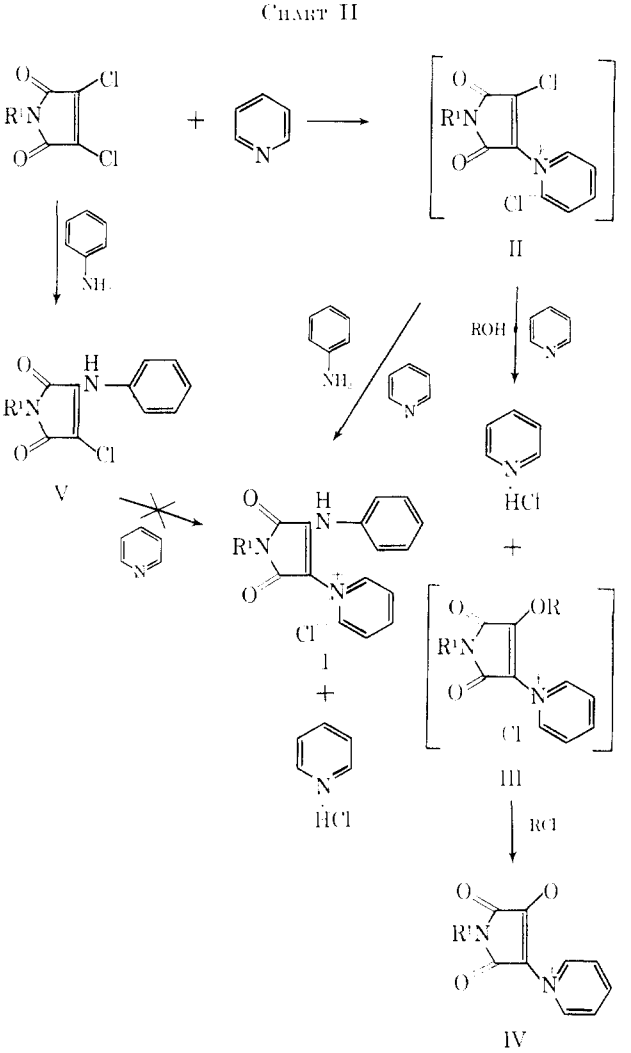
I

The reaction was generally carried out by mixing 1 equiv of the dichloromaleimide with 2 equiv of the pyridine compound in an inert solvent such as dichloroethane or benzene. To this solution 1 equiv of the arylamine was added and the reaction mixture was refluxed for 1–2 hr during which time the pyridinium salt crystallized. These results are summarized in Table I.

The course of the reaction of dichloromaleimides with pyridine and aniline, for example, is shown in Chart II. Presumably the intermediate in this reaction is II. In hydroxylic solvents,[1] II may be converted to IV *via* loss of alkyl chloride from III. Alternatively, in nonhydroxylic solvents, II may react with nucleophilic reagents such as arylamines to give I. The alternative intermediate V does not react with pyridine to give I. Refluxing equimolar quantities of V (R^1 = $C_6H_5CH_2CH_2$) and pyridine in dichloroethane for 1 hr resulted in a 95% recovery of V.

Pharmacology.—Most of the compounds exhibited a short hypotensive[3] effect by intravenous administration in dogs, decreasing the blood pressure 12–48 mm for 2–12 min in doses of 1–5 mg/kg. These substances also showed marked topical anesthetic[4] action on the cornea of rabbits (up to 65 min at a concentration of 0.1%).

CHART II



Experimental Section[5]

The N-substituted dichloromaleimides were prepared by treatment of dichloromaleic anhydride with the appropriate primary

(1) Paper I: M. J. Karten, S. L. Shapiro, E. S. Isaacs, and L. Freedman, *J. Org. Chem.*, **30**, 2657 (1955).

(2) G. A. Reynolds, R. E. Adel, and J. A. VanAllan, *ibid.*, **28**, 2687 (1963).

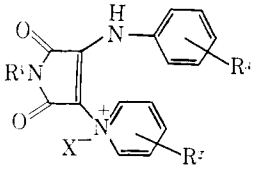
(3) R. P. Halliday, W. J. Kinnard, and J. P. Buckley, *J. Pharm. Sci.*, **53**, 19 (1964).

(4) J. Seifter, J. M. Glassman, and G. M. Hudyma, *Proc. Soc. Expl. Biol. Med.*, **109**, 664 (1962).

(5) Melting points were taken on a Fisher-Johns block and are corrected. Analyses are by Midwest Microlab, Inc., Indianapolis, Ind.

TABLE I

1-(2-ARYLAMINO-3-MALEIMIDYL)PYRIDINIUM SALTS[a]



No.	R^1	R^2	R^3	Mp, °C[b]	Recrystn solvent[c]	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	CH_3	H	H	284–286	A	33	$C_{16}H_{14}ClN_3O_2$	60.86	4.47	13.31	60.68	4.57	13.10
2	*i*-C_6H_{13}	H	H	250–252	B	42	$C_{21}H_{24}ClN_3O_2$	65.36	6.27	10.89	64.94	6.35	11.11
3	*n*-$C_{12}H_{25}$	H	H	235–237	C	38	$C_{27}H_{36}ClN_3O_2$	68.99	7.72	8.94	69.02	7.94	8.89
4	C_6H_{11}[d]	H	H	227–232	A	31	$C_{21}H_{22}ClN_3O_2$	65.70	5.78	10.95	65.36	5.89	11.09
5	$C_6H_5CH_2CH_2$	H	H	235–236	B	56	$C_{23}H_{20}ClN_3O_2$	68.06	4.97	10.35	68.32	5.21	10.49
6	2-$C_4H_3OCH_2$[e]	H	H	249–251	A	62	$C_{20}H_{16}ClN_3O_3$	62.91	4.22	11.00	63.14	4.42	10.83
7	1-$C_{10}H_7$[f]	H	H	244–246	A	41	$C_{25}H_{18}ClN_3O_2$	70.18	4.24	9.82	69.67	4.32	10.23
8	$C_6H_5CH_2CH_2$	4-CH_3	H	225–230	B	31	$C_{24}H_{22}ClN_3O_2$	68.64	5.28	10.01	68.48	5.42	9.83
9	$C_6H_5CH_2CH_2$	4-*n*-C_5H_{11}	H	215–216	B	28	$C_{28}H_{30}ClN_3O_2$	70.65	6.35	8.83	70.51	6.39	9.20
10	$C_6H_5CH_2CH_2$	H	4-CH_3	239–241	A	20	$C_{24}H_{22}ClN_3O_2$	68.64	5.28	10.01	68.42	5.30	10.24
11	$C_6H_5CH_2CH_2$	H	2-CH_3O	104–106	D	15	$C_{24}H_{22}N_4O_6$	62.33	4.80	12.12	62.16	5.05	12.18
12	$C_6H_5CH_2CH_2$	H	4-CH_3O	243–244	D	14	$C_{24}H_{22}N_4O_6$	62.33	4.80	12.12	62.55	5.14	12.45
13	$C_6H_5CH_2CH_2$	H	4-O_2N	210–211	D	15	$C_{23}H_{19}N_5O_7$	57.86	4.01	14.67	58.18	4.26	14.89

[a] Compounds 1–10 have X = Cl; 11–13 have X = NO_3. [b] With the exception of 11–13, the recorded melting points are decomposition points. [c] A = methanol–ether (1:5), B = acetonitrile, C = acetonitrile–methanol–ether (1:1:5), D = water. [d] C_6H_{11} = cyclohexyl. [e] C_4H_3O = furyl. [f] $C_{10}H_7$ = naphthyl.

amine in glacial acetic acid at 100–120°.[1,6] Dichloroethane was dried and distilled over P_2O_5 prior to use. Infrared spectra were obtained using a Beckman IR8 infrared spectrophotometer with filter-grating monochromator. The materials were examined as KBr pellets.

The infrared spectra of the compounds in Table I were examined. Three bands appeared consistently at 1755–1770, 1700–1715, and 1650–1665 cm^{-1}. The band at 1755–1770 cm^{-1} was sharp and of medium intensity. The band at 1700–1715 cm^{-1} was sharp and of strong intensity while the band at 1650–1665 cm^{-1} was somewhat broader and always the strongest band in the spectrum. These bands can be assigned to two carbonyl stretching frequencies (1755–1770 and 1700–1715 cm^{-1}) and a carbon–carbon double-bond stretching or ring vibration (1650–1665 cm^{-1}). These data are very similar to those obtained for compounds of the type IV and the assignments are virtually the same.[1] It may also be noted that V (R^1 = $C_6H_5CH_2CH_2$) shows three bands at 1760, 1700, and 1650 cm^{-1}.

The following procedures illustrate the method of preparation of the pyridinium salts.

A. 1-[N-(2-Furfuryl)-2-anilino-3-maleimidyl]pyridinium Chloride (6).—Pyridine (6.3 g, 0.08 mole) was added, all at once, to a suspension of N-(2-furfuryl)dichloromaleimide (10.0 g, 0.04 mole) in 50 ml of dichloroethane to give a purple solution. Aniline (3.3 g, 0.04 mole) was then added, all at once, and the solution was refluxed for 1 hr during which time a large quantity of yellow solid precipitated. The mixture was filtered while hot and washed with acetonitrile. The crude solid was recrystallized twice from a minimum amount of hot methanol and ether and dried to give 9.5 g (62%) of product, mp 249–251° dec.

B. 1-[N-Phenethyl-2-(4-nitroanilino)-3-maleimidyl]pyridinium Nitrate (13).—Pyridine (15.8 g, 0.2 mole) was added, all at once, to a suspension of N-(phenethyl)dichloromaleimide (27.0 g, 0.1 mole) in 100 ml of dichloroethane to give a purple solution. 4-Nitroaniline (13.8 g, 0.1 mole) was added, all at once, and the solution was refluxed for 1 hr during which time a yellow solid precipitated. The mixture was filtered while hot, washed with dichloroethane, and dried. The crude product (12.4 g, 34%) was dissolved in 150 ml of hot water and filtered into 20 ml of 5 *N* HNO_3. The yellow solid which crystallized was filtered, washed with water, recrystallized twice from hot water, washed with water, ethanol, and ether, and dried to give 7.0 g (15%) of product, mp 210–211°.

N-Phenethyl-2-anilino-3-chloromaleimide (V, R^1 = $C_6H_5CH_2CH_2$).—A mixture of N-(phenethyl)dichloromaleimide (2.7 g, 0.01 mole), aniline (2.8 g, 0.03 mole), and 20 ml of ethanol was heated for 5 min until solution occurred. The yellow solid that crystallized from the solution was filtered, washed with ethanol, and recrystallized from a minimum amount of hot ethanol to give 2.0 g (61%) of product, mp 172–173°.

Anal. Calcd for $C_{18}H_{15}ClN_2O_2$: C, 66.16; H, 4.63; N, 8.57. Found: C, 66.33; H, 4.92; N, 8.54.

Acknowledgment.—The authors are grateful to Dr. J. M. Glassman and his staff for determination of biological activities and to Mrs. O. Kitrey for the infrared spectra.

(6) S. L. Shapiro, L. Freeman, and M. J. Karten, U. S. Patent 3,129,225 (1964).