from this analysis are for ring A of the monoacetate: $\tau_4 = 2.01$, $\tau_5 = 3.03$, $\tau_7 = 3.10$, $J_{45} = 8.9$ c.p.s., $J_{57} = 2.0$ c.p.s., $J_{47} \simeq 0.9$ c.p.s.; and for ring B: $\tau_2 = 2.43$, $\tau_5 = 2.45$, $\tau_6 = 2.76$, $J_{56} = 8.7$ c.p.s., and $J_{26} = 2.3$ c.p.s.

The direction of ring closure of both Ib and c suggests that the cyclization proceeds *via* intramolecular attack of an electrophilic nitrogen upon the most electron rich aryl ring available. Failure of Id to cyclize can be explained by reduction of the electron density of both aryl rings, thus preventing attack by electrophilic nitrogen. Alkylation of one urea nitrogen (Ie, f) could prevent the cyclization from taking place either by interference with the formation of the electrophilic nitrogen (*e.g.*, N-chlorination by hypochlorite) or by electronic interference with the ring closure.

Experimental

Melting points are uncorrected. All n.m.r. measurements were made on a Varian V-4300 B n.m.r. spectrometer operating at 60 Mc./sec. Spectra were calibrated by the audiofrequency side band technique,[11] a frequency counter being employed. Hypochlorite cyclizations were all run following the same general procedure described by Rosnati,[2] the preparation of 1-phenyl-6-chloro-2-benzimidazolinone serving as an example. The sodium hypochlorite employed was a commercially available 12% aqueous solution which was analyzed just prior to use.

Reaction of Carbanilide (Ia) with Three Moles of Hypochlorite.—To a slurry of 10.6 g. (0.05 mole) of carbanilide in 300 ml. of methanol was added a solution of 4.0 g. of sodium hydroxide in 15 ml. of water. After cooling in an ice bath, the mixture was treated with 110 ml. of 1.36 *M* (0.15 mole) sodium hypochlorite. The hypochlorite addition was conducted such that the solution temperature did not exceed 35°. As the addition proceeded, most of the carbanilide passed into solution, and the solution darkened in color. A half hour after the completion of the addition, a strong positive test for hypochlorite ion was noted with starch–iodide test paper. The reaction mixture was neutralized with dilute hydrochloric acid, the methanol removed by evaporation at reduced pressure, and the residue diluted with 500 ml. of water. The residue was collected by filtration, dissolved in 400 ml. of hot 10% aqueous sodium hydroxide, decolorized, and precipitated once more by acidification. The resultant residue (10 g.) was recrystallized from toluene to afford 6.0 g. (49%) of 1-phenyl-6-chloro-2-benzimidazolinone (IIb), m.p. 232–238°. Recrystallization once more from toluene afforded the pure material as white needles, m.p. 246–247°. Mixture melting point with carbanilide (m.p. 240–241°) showed 202–214°. The infrared spectrum had characteristic bands at 5.8 μ (C=O) and 3.15 μ (N—H).

Anal. Calcd. for $C_{13}H_9ClN_2O$: C, 63.8; H, 3.71; Cl, 14.5; N, 11.4. Found: C, 63.6; H, 3.97; Cl, 14.5; N, 11.3.

Acetylation of the above compound (1.0 g.) with acetic anhydride (10 ml.) and powdered, fused sodium acetate (0.5 g.) at steam bath temperatures provided the monoacetate, m.p. 160.0–160.5°, in 70% yield.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.8; H, 3.87. Found: C, 63.0; H, 3.98.

Reaction of Carbanilide (Ia) with One Mole of Hypochlorite.—Carbanilide (10.6 g., 0.05 mole), when treated with 45 ml. of 1.23 *M* (0.055 mole) of sodium hypochlorite, provided 1-phenyl-2-benzimidazolinone, (IIa), m.p. 203.5–204°, in 71% yield. Rosnati[2] reported m.p. 201–202° for his compound. The infrared spectrum shows absorption characteristic of the amide structure[5] with bands at 5.9 μ (C=O) and at 2.9, 3.2, and 3.5–3.7 μ (N—H). Acetylation and recrystallization from absolute ethanol afforded the monoacetate in 90% yield, m.p. 134–135°. Rosnati[2] reported m.p. 134–135° for his monoacetate derivative.

Reaction of 3,4,4′-Trichlorocarbanilide (Ib)[3] with Three Moles of Hypochlorite.—Treatment of the trichlorocarbanilide as described above provided 1-(3,4-dichlorophenyl)-6-chloro-2-benzimidazolinone (IIc) in 39% yield, m.p. 259–260°. Mixture melting point with 3,4,4′-trichlorocarbanilide (m.p. 254–256°) showed 219–228°.

Anal. Calcd. for $C_{13}H_7Cl_3N_2O$: C, 49.8; H, 2.25; Cl, 33.9; N, 8.93. Found: C, 50.0; H, 2.32; Cl, 34.1; N, 9.12.

Acetylation of IIc as described previously provided the monoacetate in 65% yield, m.p. 164–165°.

Anal. Calcd. for $C_{15}H_9Cl_3N_2O_2$: C, 50.6; H, 2.55; Cl, 29.9; N, 7.87. Found: C, 50.6; H, 2.62; Cl, 29.9; N, 8.00.

Reaction of 3,4-Dichlorocarbanilide (Ic)[3] with Three Moles of Hypochlorite.—Treatment of the dichlorocarbanilide as previously described, provided IIc in 13.7% yield. The sample was demonstrated as identical with the product obtained by cyclization of 3,4,4′-trichlorocarbanilide by m.p., mixture m.p., mp. and mixture m.p. of the monoacetate derivatives, and comparison of infrared spectra of the monoacetates, which were superimposeable.

Reaction of 3,3′,4,4′-Tetrachlorocarbanilide (Id),[3] 1-Ethyl-1-(4-chlorophenyl)-3-(3,4-dichlorophenyl)urea (Ie),[3] and 1-Methyl-1-(3,4-dichlorophenyl)-3-(4-chlorophenyl)urea (If) with Three Moles of Hypochlorite.—The N-methylated urea (If) was prepared by a standard reaction[3] of N-methyl-3,4-dichloroaniline with *p*-chlorophenyl isocyanate in ether to give the product, m.p. 159–160°.

Anal. Calcd. for $C_{14}H_{11}Cl_3N_2O$: C, 51.0; H, 3.36. Found: C, 51.0; H, 3.57.

The tetrachlorocarbanilide (Id), when treated as described earlier, was recovered unchanged in a yield of 75%. The N-alkylated ureas, treated similarly, were recovered unchanged in yields of 80% (Ie) and 86% (If) from the reaction mixtures.

Acknowledgment.—The authors gratefully acknowledge the assistance of Mr. O. E. Kinast in the infrared determinations.

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[11] J. T. Arnold and M. E. Packard, *J. Chem. Phys.*, **19**, 1608 (1951).

The Reaction of N,N-Bis(2-chloroethyl)amines with Hydrazine[1]

FRANK D. POPP[2]

Departments of Chemistry, University of Miami,
Coral Gables, Florida, and Clarkson College of Technology
Potsdam, New York

Received August 7, 1962

The reaction of a number of aromatic nitrogen mustards with hydrazine under mild conditions has been reported. For example, the reaction of *p*-[N,N-bis(2-chloroethyl)amino]benzaldehyde with hydrazine in ethanol gave the azine,[3] and the reaction of *p*-[N,N-bis(2-chloroethyl)amino]benzoyl chloride with hydrazine in dioxane–water gave the hydrazide.[4] In neither case did the mustard function react with the hydrazine. As indicated[4] his failure is noteworthy and it is also somewhat surprising in view of the ease in which certain bis(2-haloethyl)amines react with amines.[5]

We have now found that certain aromatic nitrogen mustards do react with hydrazine, *but under much more severe conditions*, to give 1-aminopiperazines. Thus refluxing ethyl *p*-[N,N-bis(2-chloroethyl)amino]benzoate in a large excess of 95% hydrazine gave the aminopiperazine hydrazide I. That the reaction led to an aminopiperazine and not a diazepine or bishydrazine

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[1] Supported in part by a research grant (CY 4814C2) from the National Institutes of Health.

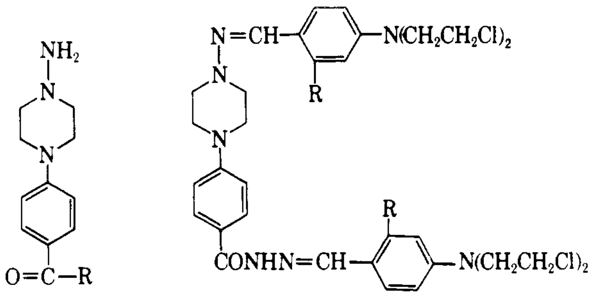
[2] Present address: Department of Chemistry, Clarkson College of Technology, Potsdam, N.Y.

[3] R. H. Wiley and G. Irick, *J. Org. Chem.*, **26**, 593 (1961).

[4] R. C. Elderfield and T.-K. Liao, *ibid.*, **26**, 4996 (1961).

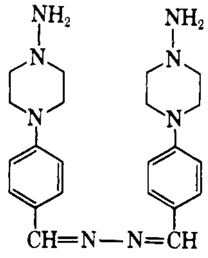
[5] See for example: W. Davis and W. C. J. Ross, *J. Chem. Soc.*, 2831 (1949).

was shown by the reaction of I with two moles of aldehydes to give compounds II and III.



I. R = NHNH$_2$
IV. R = OH

II. R = H
III. R = CH$_3$



V

In a similar manner p-[N,N-bis(2-chloroethyl)-amino]benzoic acid and 95% hydrazine gave compound IV which was also then reacted with an aldehyde. Both p-[N,N-bis(2-chloroethyl)amino]benzaldehyde and its azine[3] also reacted with hydrazine to give compound V.

These results are of interest in that they indicate that caution should be used in attempts to treat hydrazine with some function in a molecule which also contains the bis(2-chloroethyl)amino grouping. The sequence may also be a convenient route to 1-amino-4-substituted piperazines which have generally been prepared by nitrosation and reduction of an N-monosubstituted piperazine.[6]

Experimental[7]

Reaction of Ethyl p-[N,N-Bis(2-chloroethyl)amino]benzoate with Hydrazine.—A mixture of 9.1 g. (0.031 mole) of ethyl p-[N,N-bis(2-chloroethyl)amino]benzoate and 50 ml. of 95% hydrazine was heated for 2 hr. on a steam bath. After cooling, 6.75 g. (91%) of solid, m.p. 204–206°, was obtained. Recrystallization from a large volume of absolute ethanol[8] gave I, m.p. 203–205°.

Anal. Calcd. for $C_{11}H_{17}N_5O$: C, 56.15; H, 7.28; N, 29.77. Found: C, 56.54, 56.28; H, 7.48, 7.39; N, 29.46; Cl, 0.

Refluxing a suspension of I in absolute ethanol with an absolute ethanol solution of a slight excess of p-[N,N-bis(2-chloroethyl)-amino]benzaldehyde gave on cooling an 89% yield of II, m.p. 209–211°.[8]

Anal. Calcd. for $C_{33}H_{39}N_7Cl_4O$: C, 57.31; H, 5.68; N, 14.19; Cl, 20.51. Found: C, 57.45; H, 5.67; N, 13.78; Cl, 20.30.

Similarly I and 4-[N,N-bis(2-chloroethyl)amino]-2-methylbenzaldehyde gave a 97% yield of III, m.p. 188–189°.[8]

Anal. Calcd. for $C_{35}H_{43}N_7Cl_4O$: C, 58.42; H, 6.02; N, 13.63; Cl, 19.71. Found: C, 58.47; H, 5.91; N, 13.61; Cl, 20.12.

Reaction of p-[N,N-Bis(2-chloroethyl)amino]benzoic Acid with Hydrazine.—As described for the preparation of I, 4 g. (0.015 mole) of the acid and 25 ml. of 95% hydrazine on heating for 2 hr. gave 3.19 g. (96%) of IV, m.p. 262–266° dec.[8]

Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83. Found: C, 59.33; H, 6.87.

Refluxing IV with p-[N,N-bis(2-chloroethyl)amino]benzaldehyde gave an 81% yield of the hydrazone, m.p. 240–245°.[8]

Anal. Calcd. for $C_{22}H_{26}N_4Cl_2O_2$: C, 58.80; H, 5.83; N, 12.47; Cl, 15.78. Found: C, 58.65, 58.93; H, 6.02, 6.17; N, 12.37; Cl, 16.05.

Reaction of p-[N,N-Bis(2-chloroethyl)amino]benzaldehyde with Hydrazine.—As described for the preparation of I, 3 g. (0.012 mole) of the aldehyde and 25 ml. of 95% hydrazine on heating for 1.5 hr. gave 1.6 g. (33%) of V, m.p. >330°.[8]

Anal. Calcd. for $C_{22}H_{30}N_8$: C, 65.00; H, 7.44; N, 27.57. Found: C, 64.80, 64.79; H, 7.44, 7.45; N, 27.10.

The same material (V) was obtained in 73% yield from the azine[3] and hydrazine.

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[6] See for example: E. A. Conroy, U. S. Patent 2,663,706 (1953); *Chem. Abstr.*, **49**, 4730 (1955).

[7] All melting points are uncorrected. Analysis by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Drs. Weiler and Strauss, Oxford, England.

[8] All compounds described were purified in this manner.

The Reaction of Eneamines with Benzoyl Peroxide[1]

Robert L. Augustine

Department of Chemistry, Seton Hall University, South Orange, New Jersey

Received October 4, 1962

The versatility of the eneamine as an important intermediate in organic synthesis has been well established.[2] The reactions of this class of compounds have one thing in common—nucleophilic attack on the other reagent involved. It was therefore reasoned that such attack would also occur on the peroxy oxygen of benzoyl peroxide to give, after hydrolysis, 2-benzoyloxy ketones, thus providing a useful route to various types of 2-oxygenated ketones.

This postulate was shown to be correct by the reaction of 1-morpholinocyclohexene (Ia) with benzoyl peroxide at room temperature to give a 30% yield of 2-benzoyloxycyclohexanone (IIa). A 25% yield of 2-benzoyloxycyclopentanone (IIc) was also realized on reaction of the morpholine eneamine of cyclopentanone (Ic) with benzoyl peroxide. Use of the pyrrolidineeneamine (Ib) did not improve the yield, nor did running the reaction at 0° instead of at room temperature.

It was hoped that this reaction could be used on the eneamines of 1-methyl-2 (Id) or 1-benzoyl-4-piperidones[3] (Ie,f) to give products of possible psychotomimetic properties (IId,e).[4] Unfortunately, only intractible material could be obtained on reactions with either the morpholine or pyrrolidine eneamines of these ketones at room temperature or at 0°.

Experimental

2-Benzoyloxy Ketones.—To 0.07 mole of the eneamine[2,3] in 75 ml. of purified dioxane was added dropwise, with stirring, 17.0 g. (0.07 mole) of benzoyl peroxide in 125 ml. of purified dioxane over a period of 1 hr. The resulting solution became warm and turned a dark amber color. When addition was complete,

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[1] Support for this work by the National Institutes of Health through research grant 09696 from the Division of General Medical Sciences, U. S. Public Health Service, is gratefully acknowledged.

[2] See, for example, M. E. Kuehne, *J. Am. Chem. Soc.*, **84**, 837 (1962), and references cited therein.

[3] R. L. Augustine, *J. Org. Chem.*, **23**, 1853 (1958).

[4] A review of compounds with these properties has recently been published; D. F. Downing, *Quart. Rev.* (London), **XVI**, 133 (1962). See also S. B. Kadin and J. G. Cannon, *J. Org. Chem.*, **27**, 240 (1962).