[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Synthesis of 2-Chloro-10-(3-dimethylaminopropyl)phenoxazine: (a) The *o*-Phenoxyaniline Route; (b) a Modification of the Turpin Reaction

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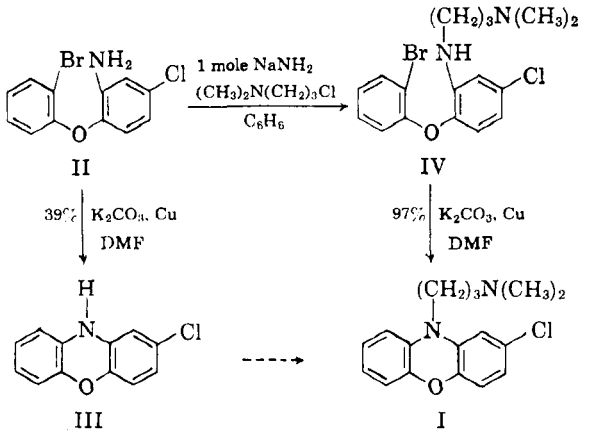
The synthesis of 2-chloro-10-(3-dimethylaminopropyl)phenoxazine (I) was accomplished by two independent routes. In the first synthesis the key intermediate was *N'*-[2-(*o*-bromophenoxy)-5-chlorophenyl]-*N*,*N*-dimethyl-1,3-propanediamine (IV) which on cyclization gave I. The second synthesis was accomplished by the cyclization of *o*-[5-chloro-*N*-(3-dimethylaminopropyl)-2-nitroanilino]phenol (IX). The chemistry of these critical intermediates and related compounds is presented.

The clinical effectiveness of chlorpromazine and related 2-substituted 10-dialkylaminoalkylphenothiazines[1] as tranquilizing agents prompted us to prepare 2-chloro-10-(3-dimethylaminopropyl)phenoxazine (I) for pharmacological screening. After this work was completed the preparations of I and several related analogs by other methods[2] was reported. However, as our work is substantially different from what has already been reported, we wish to present two new and independent syntheses of I.

2-Chlorophenoxazine, which appeared to be the key intermediate for the synthesis of I, was unknown at the time this investigation was undertaken. Although many multi-substituted phenoxazines have been reported,[3] relatively few preparative methods have been described.[4] Furthermore, the available methods were not applicable to the synthesis of 2-substituted phenoxazines. The three general methods for the preparation of phenoxazines that have been reported are: (a) The Turpin reaction,[4b] which is the nucleophilic displacement of the nitro group from a suitably substituted *o*-(2-nitroanilino)phenol by its phenoxide ion in alkaline medium.[4b,c] This reaction is perhaps the most widely used procedure. (b) The pyrolytic condensation of *o*-aminophenols and catechols, which is the method based on the first synthesis of phenoxazine itself reported by Bernthsen.[4a] (c) The condensation of activated (*e.g.*, nitro-groups) 1,2-dihalobenzenes with *o*-aminophenols in non-alkaline medium.[4d]

Our first method of synthesis may be regarded as being derived from method b and is analogous to the synthesis of chlorpromazine reported by Buisson, *et al.*[5] The pyrolytic condensation of sodium *o*-bromophenolate with 1,4-dichloro-2-nitrobenzene gave *o*-bromophenyl 4-chloro-2-nitrophenyl ether in 50–75% yield. Reduction of this product with stannous chloride and anhydrous hydrogen chloride in ether yielded 2-(*o*-bromophenoxy)-5-chloroaniline (II) in 80–90% yield. II was isolated and



purified as the hydrochloride salt. This salt hydrolyzed completely in water, and the free base was isolable without addition of alkali. Apparently, the free base was extremely insoluble in water. Furthermore, 1*N* hydrochloric acid did not extract the base from an ethereal solution. This property was utilized to separate II from the reaction product (IV) of a subsequent step.

An attempted cyclization of 2-(*o*-bromophenoxy)-5-chloroaniline (II) with sodium amide in boiling xylene for nineteen hours failed to give 2-chlorophenoxazine (III); only II was recovered in 69% yield. II was also recovered, almost quantitatively, when its cyclization was attempted with potassium carbonate in boiling butanol for twenty-four hours. However, the cyclization of II was effected when it was heated under reflux in *N*,*N*-dimethylformamide (DMF) with potassium

(1) J.-P. Bourquin, G. Schwarb, G. Gamboni, R. Fischer, L. Ruesch, S. Guldimann, V. Theus, E. Schenker, and J. Renz, *Helv. Chim. Acta*, **41**, 1061 (1958); **42**, 259 (1959).

(2) (a) British Patent 825,312 (Dec. 16, 1959) to Smith Kline & French Labs.; (b) P. N. Craig, U. S. Pat. 2,947,745; 2,947,747; (c) M. P. Olmsted, U. S. Pat. 2,947,746.

(3) (a) B. Boothroyd and E. R. Clark, *J. Chem. Soc.*, 1499, 1504 (1953); these authors also give earlier relevant references; (b) See ref. 4b, c, and d.

(4) (a) A. Bernthsen, *Ber.*, **20**, 942 (1887); (b) G. S. Turpin, *J. Chem. Soc.*, **59**, 714 (1891); (c) F. Ullmann, *Ann.*, **366**, 79 (1909); (d) F. Ullmann and S. M. Sané, *Ber.*, **44**, 3730 (1911); (e) S. Granick, L. Michaelis and M. P. Schubert, *J. Am. Chem. Soc.*, **62**, 1802 (1940).

(5) P. J. C. Buisson, P. Gailliot, and J. Gaudechon, U. S. Pat. 2,769,002 (1956).

carbonate and a trace of copper powder under dry nitrogen.[5] This material (III, 39% yield) was difficult to purify, although elemental analyses, infrared and ultraviolet spectral data indicated that ring closure had taken place. Recently, a modification of this cyclization has been accomplished through the *N*-formyl derivative of II.[2c,6] Because of the difficulties in preparing III from II, under the conditions described above, we chose an alternate route to I; namely, the *N*-alkylation of II with 3-chloro-*N*,*N*-dimethylpropylamine and one molar equivalent of sodium amide in anhydrous benzene. *N'*-[2-(*o*-Bromophenoxy)-5-chlorophenyl]-*N*,*N*-dimethyl-1,3-propanediamine (IV) was isolated in 48% yield as an oil. Distillation at reduced pressure resulted in extensive decomposition. However, partition chromatography showed that the crude reaction product was substantially pure. An excess of sodium amide did not effect the cyclization of IV, but gave anomalous products, the chemistry of which will be the subject of a future communication.

As the cyclization of II to III was apparently successful with potassium carbonate and a trace of copper powder in boiling *N*,*N*-dimethylformamide, these conditions were repeated successfully for the preparation of 2-chloro-10-(3-dimethylaminopropyl phenoxazine (I) from IV in 97% yield. I was an oil, which was converted to the hydrochloride salt in 81% yield.

A second independent synthesis of I was accomplished by an extension of the Turpin reaction.[4b] Several attempts from *o*-(5-chloro-2-nitroanilino)-phenol (VI) did not succeed. However, the elucidation of the chemistry involved in these unsuccessful trials materially aided the successful synthesis of I by this route.

VI was prepared in 20% yield from 2'-hydroxyacetanilide and 2,4-dichloronitrobenzene in ethanolic sodium methoxide under reflux. *o*-Anisidine, on the other hand, failed to react with 2,4-dichloronitrobenzene under the same conditions. These results indicated that the initial step in the formation of VI was a nucleophilic displacement of the 2-chlorine atom of 2,4-dichloronitrobenzene[7-9] by phenoxide ion. The immediate product of this reaction was, therefore, unisolated *o*-(5-chloro-2-nitrophenoxy)acetanilide (V), which then isomerized (Smiles rearrangement)[10] in the alkaline medium of the reaction. *o*-(2-Nitrophenoxy)anilines analogous to V have been reported to undergo the Smiles rearrangement[10,11] to give the isomeric *o*-(2-nitroanilino)phenols under similar conditions. Attempted cyclization of VI to give 2-chlorophenoxazine (III) by heating in alcoholic sodium hydroxide, sodium ethoxide or sodium methoxide was unsuccessful, in agreement with the conclusions of previous investigators[4c-d,11,12] regarding analogous compounds. VI was characterized as the *O*-acetate; *i.e.*, *o*-(5-chloro-2-nitroanilino)phenol acetate (X), prepared in 78% yield. The infrared spectrum of X showed the expected carbonyl absorption band at 5.70 μ.

4-Chloro-2-(*o*-nitroanilino)phenol (isomeric with VI) seemed to be another potential intermediate to III. This proposed synthesis was based on the work of Misslin and Bau,[13] who reported that x-halo-2-(*o*-nitroanilino)phenols were more susceptible to cyclization than the corresponding nonhalogenated intermediates in alkaline medium. This route was not attempted because a very similar intermediate—*i.e.*, 4-chloro-2-(2,4-dinitroanilino) phenol—did not undergo cyclization to give 2-chloro-7-nitrophenoxazine.[11c]

However, it has been shown,[3a,11a] that when the amino-hydrogen atom of *o*-(2-nitroanilino)phenols was substituted (*e.g.*, alkyl group), these compounds readily undergo cyclization in alcoholic alkaline medium.[14] For this reason, the preparation of I through intermediate IX, with the side chain already in place, seemed feasible. However, Farrington and Warburton,[8] in a paper on phenothiazines, were unable to prepare 2,8-dichlorophenothiazine by the Smiles rearrangement of 5'-chloro-2'-[(5-chloro-2-nitrophenyl)thio]acetanilide; in this case, rearrangement to *N*-(5-chloro-2-mercaptophenyl) - *N* - (5 - chloro - 2 - nitrophenyl)acetamide did take place, as evidenced by the isolation of its *S*-methyl derivative; ring closure, however, failed.

(6) M. P. Olmsted, P. N. Craig, and J. J. Lafferty, Abstracts of Papers, 138th Meeting Am. Chem. Soc., New York, N. Y., September 1960, p. 15P.

(7) Reaction at the 2-position is postulated since there is no known exception to the rule that "nucleophilic reagents react with 2,4-dihalonitrobenzenes to preferentially displace the 2-halogen atom.[6,9]"

(8) K. J. Farrington and W. K. Warburton, *Australian J. Chem.*, 9, 480 (1956).

(9) J. F. Bunnett and R. J. Morath, *J. Am. Chem. Soc.*, 77, 5051 (1955).

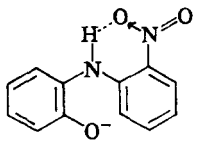
(10) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, 49, 362 (1951), (also see references therein).

(11) (a) K. C. Roberts and H. B. Clark, *J. Chem. Soc.*, 1312 (1935); (b) K. C. Roberts and C. G. M. deWorms, *J. Chem. Soc.*, 727 (1934); (c) K. C. Roberts, C. G. M. deWorms, and H. B. Clark, *J. Chem. Soc.*, 196 (1935); (d) K. C. Roberts and C. G. M. deWorms, *J. Chem. Soc.*, 1309 (1935); (e) K. C. Roberts and J. A. Rhys, *J. Chem. Soc.*, 39 (1937).

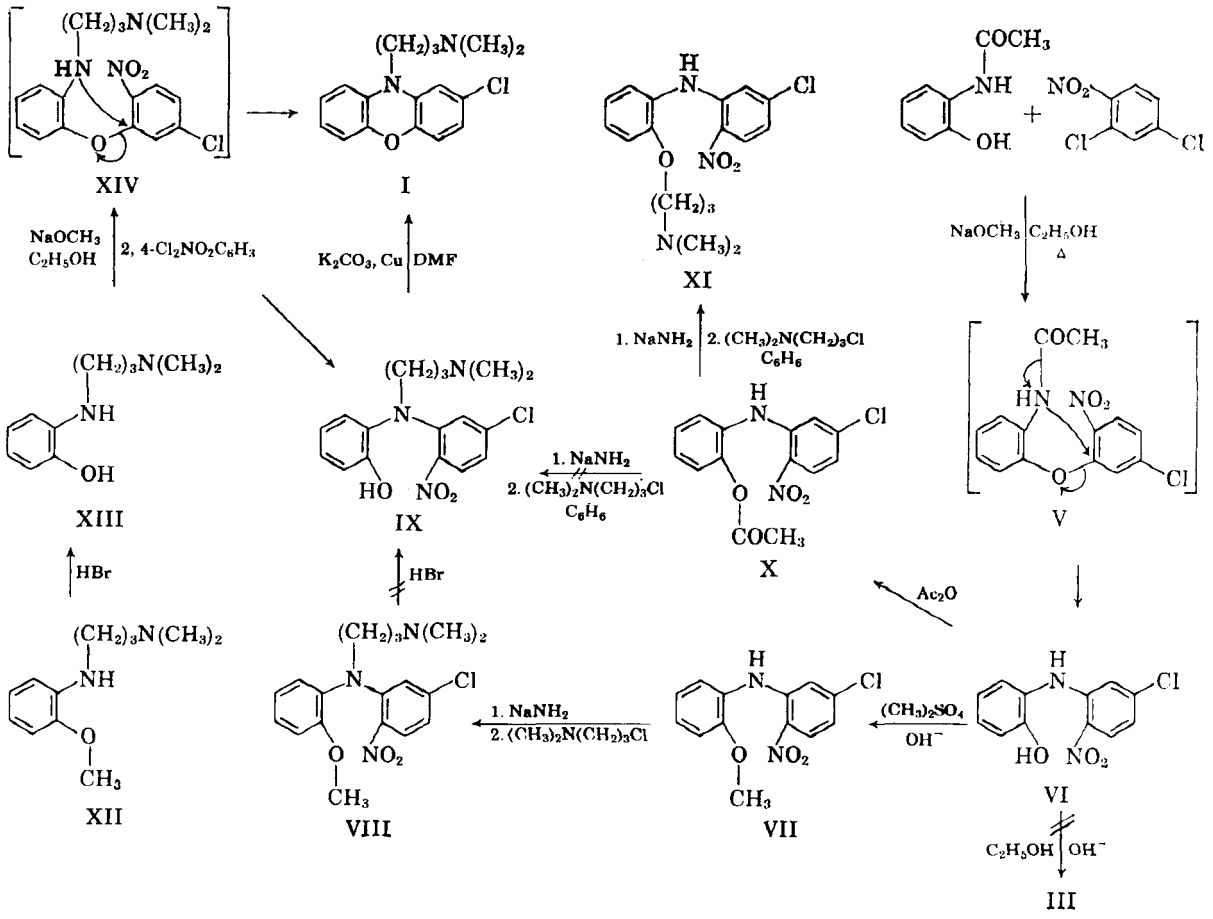
(12) O. L. Brady and C. Waller, *J. Chem. Soc.*, 1218 (1930).

(13) E. Misslin and A. Bau, *Helv. Chim. Acta*, 2, 285 (1919).

(14) The inability of *o*-(2-nitroanilino)phenols (*e.g.*, VI) to cyclize has been attributed[12] to hydrogen-bonding between the amino-hydrogen atom and the nitro group:



thus preventing the nucleophilic displacement of the nitro group by the phenoxide ion. Hydrogen-bonding of this type is not possible with the alkylated derivatives (*e.g.*, IX).



They attributed this failure to the electron-donating character of the chlorine atom *para*- to the nitro group, which decreases the electrophilicity of carbon-2 containing the nitro group. On the basis of these results it might have been expected that IX would not have yielded I. Nevertheless, Galbreath and Ingham[15] recently prepared 2-chlorophenothiazine from 2′-[(5-chloro-2-nitrophenyl)thio]acetanilide under similar conditions. Presumably this reaction involved a Smiles rearrangement in which *N*-(5-chloro-2-nitrophenyl)-*N*-(*o*-mercaptophenyl)-acetamide, analogous to IX, was the intermediate.

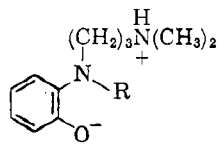
In view of these results we continued the synthesis of I from VI (VI→VII→VIII→IX→I). The phenolic function of *o*-(5-chloro-2-nitroanilino)-phenol (VI) was blocked by reaction with dimethyl sulfate in aqueous alkali, and *N*-(5-chloro-2-nitrophenyl)-*o*-anisidine (VII) was isolated in 52% yield. *N*-Alkylation of VII with 3-chloro-*N*,*N*-dimethylpropylamine and sodium amide gave the expected *N*-(5-chloro-2-nitrophenyl)-*N*-(*o*-methoxyphenyl)-*N*′,*N*′-dimethyl-1,3-propanediamine (VIII) in 30% yield. Attempts to remove the blocking group (OCH_3) from VIII with hydrobromic acid were unsuccessful, thereby ending this route to IX and I. The analogous route VI→X→IX also failed when the *O*-acetyl derivative of VI (X) was treated with 3-chloro-*N*,*N*-dimethylpropylamine and sodium amide in one case, and with sodium methoxide in another, in anhydrous benzene. Instead of the desired product (IX), 5-chloro-2′-(3-dimethylaminopropoxy)-2-nitrodiphenylamine (XI) hydrochloride was obtained in 57% yield. The structure of XI was established by its insolubility in alkali and its infrared spectrum, which did not show absorption bands in the 3.75–4.30 μ region (these absorption bands will be discussed later).

Due to these failures, the dimethylaminopropyl side chain was introduced early in the reaction sequence. The synthesis of IX and its subsequent cyclization to I was then successful. *o*-Anisidine was *N*-alkylated with 3-chloro-*N*,*N*-dimethylpropylamine under the conditions mentioned above to yield *N*′-(*o*-methoxyphenyl)-*N*,*N*-dimethyl-1,3-propanediamine (XII) in 49% yield. Hydrolysis of the methoxyl group in XII with 48% hydrobromic acid yielded *o*-(3-dimethylaminopropylamino)phenol (XIII) in 44% yield. The reaction of XIII with 2,4-dichloronitrobenzene and sodium methoxide in ethanol afforded *o*-[5-chloro-*N*-(3-dimethylaminopropyl)-2-nitroanilino]phenol (IX) in 40% yield. In addition to IX, a 26% yield of crude 2-chloro-10-(3-dimethylaminopropyl)phenoxazine (I) was isolated. It was purified by parti-

(15) R. J. Galbreath and R. K. Ingham, *J. Org. Chem.*, **23**, 1804 (1958).

tion chromatography, and its infrared spectrum was identical to that of the product prepared from IV. It was also obtained in 43% yield (purified base) by the cyclization of IX, under the conditions already described for the conversion of IV to I. This product (I from IX) was identical to the product prepared directly from IV or XIII as evidenced by identical infrared and ultraviolet spectra, as well as melting point, mixed melting point and elemental analyses of the hydrochloride salts. The key intermediate (IX) was presumably formed by a Smiles rearrangement of the unisolated *N'* - *o* - (5 - chloro - 2 - nitrophenoxy)anilino - *N,N*-dimethyl-1,3-propanediamine (XIV).

The infrared spectra of IX and XIII were similar and showed interesting properties. Each showed absorption bands at 3.75–4.30 μ (ammonium region), which indicated the probable existence of the dimethylamino and the phenolic groups in a zwitterionic structure:



IX. R = 5-Cl,2-$NO_2C_6H_3$
XIII. R = H

These absorption bands are not due to intermolecular hydrogen bonding since the infrared spectrum in solution did not change as the concentration was decreased.[16] The *O*-acetyl derivative as well as the *O*-methyl derivative (VIII) of IX, on the other hand, did not absorb in the 3.75–4.30 μ region. Furthermore, these bands were not present in the spectrum of *o*-(5-chloro-2-nitroanilino) phenol (VI), while *o*-aminophenol itself showed similar bands in the 3.5–3.9 μ region. These absorption bands, in the spectrum of *o*-aminophenol, may be attributed to intramolecular hydrogen bonding between the phenolic and amino groupings. On the other hand, the absence of these bands in VI may be explained on the basis of lower basicity of the amino group brought about by the presence of the second phenyl group and its electron-attracting substituents. Apparently absorption bands of this type have not been reported in the literature. However, Cromwell, *et al.*[17] have suggested that similar dipolar forms contribute appreciably to the ground state of some β-ketovinylamines.

Another possible route, analogous to the one just described, for the synthesis of I through *N'*-(5 - chloro - 2 - methoxyphenyl) - *N,N* - dimethyl-1,3,-propanediamine was also investigated. This intermediate was prepared in 45% yield by treating 2-amino-4-chloroanisole and 3-chloro-*N,N*-dimethylpropylamine. This approach was discontinued when several attempts to remove the blocking group with hydrobromic acid were unsuccessful.

Pharmacologically, when tested for tranquilizing properties, 2 - chloro - 10 - (3 - dimethylaminopropyl)phenoxazine (I) hydrochloride was approximately one-tenth as effective as chlorpromazine in reducing the motor activity of mice. Furthermore, it was approximately twice as toxic as chlorpromazine.[18,19] It is interesting to note that I can not be oxidized to the 5-oxide in the fashion that phenothiazine tranquilizers have been reported to be partially metabolized.[20,21]

EXPERIMENTAL[22]

Unless otherwise specified, the yields reported are those determined after purification of the products either by distillation and/or recrystallization to constant melting point.

Preparation of salts. The hydrochloride salts were prepared by treating a weighed quantity of the bases, in the minimum volume of absolute alcohol, with standardized alcoholic hydrogen chloride equivalent to the number of basic groups present.

o-Bromophenyl 4-chloro-2-nitrophenyl ether. A solution of 10.8 g. (0.20 mole) of sodium methoxide, 34.6 g. (0.20 mole) of *o*-bromophenol, and 38.8 g. (0.20 mole) of 1,4-dichloronitrobenzene in 100 ml. of anhydrous alcohol was evaporated to dryness *in vacuo* on a water bath, and the residue was heated for 2 hr. at 160–170° in an oil bath. The cooled fusion product was suspended in 200 ml. of 10% aqueous sodium hydroxide and extracted several times with ether. The combined ethereal extracts were washed with water until the washings were neutral to litmus paper, and dried over anhydrous magnesium sulfate. The ether was evaporated *in vacuo* and the residue extracted with boiling petroleum ether (b.p. 90–100°). Cooling of the combined petroleum ether extracts afforded the crude product, m.p. 71–73°. Recrystallization from ethyl acetate–petroleum ether (b.p. 90–100°) afforded 25.4 g. of crystalline product, m.p. 72–74°. Evaporation of the mother liquors yielded an additional 7.7 g. of product, m.p. 72–74°. The total yield was 33.1 g. (51%).

Anal. Calcd. for $C_{12}H_7BrClNO_3$ (328.57): C, 43.9; H, 2.15; Br, 24.3; Cl, 10.8; N, 4.26. Found: C, 44.2; H, 2.43; Br, 24.4; Cl, 10.7; N, 4.19.

A reaction employing one mole of reactants fused at 160–165° for 5 hr. afforded the above product in 75% yield.

2-(o-Bromophenoxy)-5-chloroaniline (II) *hydrochloride.* To a 500-ml. three neck flask equipped with condenser, stirrer and gas-inlet tube (in hood), was added 6.6 g. (0.02 mole) of *o*-bromophenyl-4-chloro-2-nitrophenyl ether, 18.1 g. (0.08 mole) of stannous chloride dihydrate and 200 ml. of

(16) R. C. Gore and E. S. Waight, *Determination of Organic Structures by Physical Methods*, Ch. 5, E. A. Braude and F. C. Nachod, ed., Academic Press, Inc., New York, 1955, p. 215.

(17) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *J. Am. Chem. Soc.*, 71, 3337 (1949).

(18) We wish to thank Dr. A. C. Osterberg and associates for the Experimental Therapeutic Research Section of these Laboratories for these test results.

(19) Thorazine is the trademark of Smith Kline & French Laboratories for chlorpromazine; 2-chloro-10-(3-dimethylaminopropyl)phenothiazine hydrochloride.

(20) N. P. Salzman, N. C. Moran, and B. B. Brodie, *Nature*, 176, 1122 (1955).

(21) L.-G. Allgén, B. Jönsson, A. Rappe, and R. Dahlbom, *Experientia*, 15, 318 (1959).

(22) All melting points are uncorrected and were taken in a Hershberg melting point apparatus.

ether. The mixture was stirred while a *slow* stream of anhydrous hydrogen chloride was passed through the mixture for 3 hr. The reaction was exothermic, and the hydrogen chloride addition was regulated to maintain a gentle reflux. The precipitated material, m.p. 205–235°, was collected by filtration (in the hood) and suspended in 150 ml. of water. The mixture was made alkaline with an excess of potassium carbonate and extracted with ether, and the ether extract (A) was saved. The reaction filtrate was evaporated to dryness and the residue treated with 150–200 g. of ice and water. This mixture was cooled in an ice bath and treated with a large excess of 40% sodium hydroxide solution (until the precipitated inorganic bases redissolved). The aqueous, strongly alkaline solution was extracted with ether several times and these ether extracts were combined with ether extract (A) above. The total ether extracts were washed thoroughly with water, dried over anhydrous magnesium sulfate, and evaporated to approximately 200 ml. This anhydrous ethereal solution, in an ice bath, on treatment with anhydrous hydrogen chloride, afforded the crystalline hydrochloride salt. Recrystallization from alcohol-ether afforded 5.7 g. (85%) of product, m.p. 167–170°.

Anal. Calcd. for $C_{12}H_9BrClNO.HCl$ (335.04): C, 43.0; H, 3.01; Br, 23.9; Cl, ionic, 10.6; N, 4.18. Found: C, 43.1; H, 3.27; Br, 24.0; Cl, ionic, 10.6; N, 4.46.

The free base, b.p. 162–164°/0.4 mm., n_D^{25} 1.641 was extracted with ether from an aqueous suspension of its hydrochloride salt. The ethereal solution was dried over anhydrous magnesium sulfate, evaporated to dryness, and distilled.

Anal. Calcd. for $C_{12}H_9BrClNO$ (298.58): C, 48.3; H, 3.05; Br, 26.8; Cl, 11.9; N, 4.69. Found: C, 48.0; H, 3.19; Br, 26.9; Cl, 11.6; N, 4.71.

N'-[2-(o-Bromophenoxy)-5-chlorophenyl]-N,N-dimethyl-1,3-propanediamine (IV) *and dihydrochloride.* A mixture of 29.9 g. (0.10 mole) of 2-(*o*-bromophenoxy)-5-chloroaniline (II) and 4.3 g. (0.10 mole) of sodium amide[23] in 200 ml. of anhydrous benzene was heated under reflux for 2.5 hr. with stirring. A solution of 13.4 g. (0.11 mole) of 3-chloro-*N,N*-dimethylpropylamine in 50 ml. of anhydrous benzene was added dropwise, and the reaction mixture was heated under reflux with stirring for another 18 hr. The cooled reaction mixture was filtered and the filtrate evaporated to dryness *in vacuo* on a water bath. The residue was dissolved in 100 ml. of ether and extracted with 1*N* hydrochloric acid. The aqueous acidic solution was made alkaline with an excess of potassium carbonate, and extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness. The residue was purified by partition chromatography as described below. Distillation of a sample of the crude residue gave the product, a viscous oil, in 48.4% yield, b.p. 184–187°/0.5 mm.; n_D^{25} 1.599.

Anal. Calcd. for $C_{17}H_{20}BrClN_2O$ (383.73): C, 53.2; H, 5.25; Br, 20.8; Cl, 9.24; N, 7.30. Found: C, 52.7; H, 5.24; Br, 20.4; Cl, 9.49; N, 7.12.

The dihydrochloride salt melted with decomposition at 181–183°.

Anal. Calcd. for $C_{17}H_{20}BrClN_2O.2HCl$ (456.66): C, 44.7; H, 4.85; Br, 17.5; Cl, 23.3; N, 6.13. Found: C, 44.3; H, 4.97; Br, 17.6; Cl, 23.3; N, 6.20.

The acid-extracted, ethereal mother liquor contained unreacted starting material (II), which was insoluble in 1*N* hydrochloric acid.

Purification of IV *by partition chromatography.* A *n*-heptane (2 l.) Methyl Cellosolve (350 ml.) system was used. The stationary phase, 250 ml. (Methyl Cellosolve) was thoroughly mixed with 500 g. of Celite "545"[24] and packed firmly into a 5.3 cm., i.d., × 90 cm. column in small uniform increments. A 5-g. sample of IV was dissolved in 25 ml. of each solvent phase, mixed with 50 g. of Celite "545" and packed on top of the above prepared column. The holdback volume was 710 ml. The mobile phase (*n*-heptane) was then run through the column and the effluent was run through a flow-cell[25] in a Beckman DU spectrophotometer, and the transmission at 240 mμ was recorded automatically on a Brown 0–50 mv. strip-chart. A small amount of impurity moved with the solvent front. The purified product was eluted completely in a narrow band near the end of the first holdback volume. Evaporation of this aliquot, *in vacuo* on a water bath, afforded 4.8 g of base, (IV) (96% recovery).

2-Chloro-10-(3-dimethylaminopropyl)phenoxazine (I) *and hydrochloride.* A mixture of 7.8 g. (0.02 mole) of *N'*-[2-(*o* - bromophenoxy) - 5 - chlorophenyl] - *N,N* - dimethyl-1,3-propanediamine (IV), 3.8 g. (0.03 mole) of potassium carbonate, and 0.6 g. of copper powder in 75 ml. of *N,N*-dimethylformamide was heated under reflux for 46 hr. The reaction mixture was cooled, filtered, and evaporated to dryness. The residue was dissolved in 250 ml. of ether, the mixture was filtered, and the filtrate was washed with water. The ethereal solution was dried over anhydrous magnesium sulfate and evaporated to dryness. The residue, 6.0 g. (97%), was a light amber oil. This material was chromatographically homogeneous. Distillation of the crude product gave a 55% recovery of the free base (I), b.p. 178–180°/0.5 mm. (lit.[2a] b.p. 178–180°/0.3 mm.). The hydrochloride, m.p. 220–222° dec. (lit.[2a] m.p. 223–224°) was prepared in 81% yield from the crude reaction product, and in 85% yield from the chromatographically purified material. A mixed melting point with a sample prepared by our alternate synthesis was not depressed. The ultraviolet absorption spectrum of I: $\lambda_{max}^{CH_3OH}$ 241 mμ, ε 48,000; 328 mμ, ε 8,000—was similar to that of the isosteric chlorpromazine.[19]

Anal. (HCl salt). Calcd. for $C_{17}H_{19}ClN_2O.HCl$ (339.26): C, 60.2; H, 5.94; Cl, 20.9; N, 8.25. Found: C, 59.8; H, 6.15; Cl, 21.2; N, 8.18.

Partition chromatography of 2-chloro-10-(3-dimethylaminopropyl)phenoxazine (I). A 4.5-g. sample of the crude base was chromatographed by the procedure described for the purification of IV. The purified free base moved very rapidly and was collected as a narrow band in the last half of the first holdback volume. Evaporation of the eluate *in vacuo* on a warm water bath afforded 4.0 g. (89% recovery) of purified I, n_D^{25} 1.614.

2-Chlorophenoxazine (III). A mixture of 5.0 g. (0.015 mole) of 2-(*o*-bromophenoxy)-5-chloroaniline (II) hydrochloride, 4.6 g. (0.033 mole) of potassium carbonate, and 0.4 g. of copper powder in 50 ml. of *N,N*-dimethylformamide was refluxed under dry nitrogen gas for 36 hr. The cooled reaction mixture was filtered and the filtrate evaporated to dryness *in vacuo* on a water bath; the residue was extracted with ether. The ethereal solution was washed successively with 6*N* hydrochloric acid, 5% sodium carbonate, and finally with water. It was then dried over anhydrous magnesium sulfate and evaporated to dryness. The residue, a pink solid, 1.3 g. (39%), m.p. 105–115° dec., was dissolved in 5 ml. of ethanol and precipitated with 25 ml. of water, m.p. 115–130°, (lit.,[2a] m.p. 144–145°). The yield was 0.5 g.

Anal. Calcd. for $C_{12}H_8ClNO$ (217.65): C, 66.2; H, 3.71; Cl, 16.3; N, 6.44. Found: C, 66.1 and 66.4; H, 3.49 and 4.10; Cl, 16.3; N, 6.46. $\lambda_{max}^{CH_3OH}$ 242 mμ, ε 41,360; 329 mμ, ε 6,760; $\lambda_{max}^{0.1\,N HCl}$ 247 mμ, ε 23,080; 335 mμ, ε 6,180; $\lambda_{max}^{0.1\,N NaOH}$ 243 mμ, ε 28,520; 332 mμ, ε 6,050.

o-(5-Chloro-2-nitroanilino)phenol (VI). A solution of 85.0 g. (0.563 mole) of 2'-hydroxyacetanilide, 108.0 g. (0.563 mole) of 2,4-dichloronitrobenzene, and 13.0 g. (0.563 g. atom) of metallic sodium in 1 l. of absolute alcohol was

(23) The sodium amide used was the 90%, technical grade under mineral oil; purchased from Matheson Coleman & Bell. Division of the Matheson Company, Inc.

(24) Celite "545," Product of Johns-Manville Corp.; before the commercial product was used it was washed successively with 6*N* hydrochloric acid, water, 95% alcohol, and finally was air-dried.

(25) The flow-cell was purchased from the Research and Industrial Instrument Co., Buxton, London S.W. 9, England.

heated under reflux for 18 hr. The mixture was cooled, filtered, and evaporated to dryness. The residue was dissolved in 500 ml. of benzene, washed well with water and evaporated to dryness *in vacuo* to yield 136 g. of a dark-red semisolid residue. Recrystallization from benzene afforded 29.1 g. (19.5%) of product, m.p. 148–149.5°.

Anal. Calcd. for $C_{12}H_9ClN_2O_3$ (264.65): C, 54.4; H, 3.43; Cl, 13.4; N, 10.6. Found: C, 54.5; H, 3.50; Cl, 13.4; N, 10.6.

N-(5-Chloro-2-nitrophenyl)-o-anisidine (VII). A solution of 40.0 g. (0.15 mole) of *o*-(5-chloro-2-nitroanilino)phenol (VI), 19.0 g. (0.15 mole) of dimethyl sulfate, and 6.0 g. (0.15 mole) of sodium hydroxide in 1500 ml. of water was heated on a steam bath for 30 min. The solution was cooled, the crystalline solid was filtered, and washed with water. Recrystallization from alcohol afforded 11.0 g. (52%) of product, m.p. 97–98°.

Anal. Calcd. for $C_{13}H_{11}ClN_2O_3$ (278.68): C, 56.0; H, 3.97; Cl, 12.7; N, 10.1. Found: C, 56.2; H, 4.13; Cl, 13.1; N, 10.1.

By diluting the alcoholic mother liquor with water 20 g. (50% recovery) of VI was isolated.

N-(5-Chloro-2-nitrophenyl)-N-(o-methoxyphenyl)-N',N'-dimethyl-1,3-propanediamine (VIII). A mixture of 21.4 g. (0.077 mole) of *N*-(5-chloro-2-nitrophenyl)-*o*-anisidine (VII) and 3.3 g. (0.077 mole) of sodium amide in 150 ml. of benzene was heated under reflux for 3 hr. A solution of 9.3 g. (0.077 mole) of 3-chloro-*N,N*-dimethylpropylamine in 25 ml. of benzene was added dropwise and the mixture heated under reflux 16 hr. longer. The cooled reaction mixture was filtered and the filtrate extracted with 500 ml. of 1*N* hydrochloric acid in three portions. The aqueous acidic phase was made alkaline with an excess of potassium carbonate and extracted several times with ether. The combined ether extract was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether yielded 16.2 g. of a red semisolid residue. Recrystallization from alcohol afforded 8.5 g. (30.4%) of product, m.p. 94–95.5°.

Anal. Calcd. for $C_{18}H_{22}ClN_3O_3$ (363.84): C, 59.4; H, 6.11; Cl, 9.75; N, 11.6. Found: C, 59.2; H, 6.21; Cl, 9.71; N, 11.4.

A 2.0-g. sample of VIII was heated under reflux for 4 hr. in 25 ml. of 48% hydrobromic acid. The black reaction mixture was diluted with 100 ml. of water and neutralized with potassium carbonate. Ether extraction afforded 0.7 g. of the ether-soluble, black, oily residue. The preparation of a hydrochloride was attempted without success. A dark gray amorphous solid separated which resisted several attempts at purification.

o-(5-Chloro-2-nitroanilino)phenol acetate (X). A solution of 24.0 g. (0.091 mole) of *o*-(5-chloro-2-nitroanilino)phenol (VI), in 100 ml. (1.05 moles) of acetic anhydride and 5 drops of pyridine was heated on a steam bath for 15 min. The solution was cooled and slowly treated with 150 ml. of water. The solid was filtered, washed with water, and dried. The crude product, 23.0 g., was recrystallized from alcohol to yield 21.8 g. (78%) of product, m.p. 117–118°.

Anal. Calcd. for $C_{14}H_{11}ClN_2O_4$ (306.71): C, 54.8; H, 3.61; Cl, 11.6; N, 9.14. Found: C, 54.8; H, 3.89; Cl, 11.6; N, 8.99.

5-Chloro-2'-(3-dimethylaminopropoxy)-2-nitrodiphenylamine (XI) *hydrochloride.* A mixture of 3.4 g. (0.01 mole) of *o*-(5-chloro-2-nitroanilino)phenol acetate (X) and 0.5 g. (0.013 mole) of sodium amide in 50 ml. of anhydrous benzene was heated under reflux for 2 hr. A solution of 1.6 g. (0.013 mole) of 3-chloro-*N,N*-dimethylpropylamine in 5 ml. of anhydrous benzene was added dropwise and the reaction mixture heated under reflux for 16 hr. The reaction mixture was worked up as described for the preparation of IV. The crude residue, 2.0 g. (57.2%), was converted to the hydrochloride in 5 ml. of absolute alcohol. The product, 0.6 g. (15.8%), melted at 134–135.5°.

Anal. Calcd. for $C_{17}H_{20}ClN_3O_3 \cdot HCl$ (386.27): C, 52.8; H, 5.84; Cl, 18.4; N, 10.9. Found: C, 52.6; H, 5.44; Cl, 18.6; N, 11.1.

N'-(o-Methoxyphenyl)-N,N-dimethyl-1,3-propanediamine (XII). This material was prepared by using the procedure described for the synthesis of IV. From 24.6 g. (0.20 mole) of *o*-anisidine, 8.0 g. (0.20 mole) of sodium amide in 200 ml. of anhydrous benzene and 24.3 g. (0.20 mole) of 3-chloro-*N,N*-dimethylpropylamine in 100 ml. of anhydrous benzene, was obtained 20.4 g. (49%) of product, b.p. 116–117°/1.0 mm., n_D^{25} 1.532. The dihydrochloride salt melted at 208–210°.

Anal. Calcd. for $C_{12}H_{20}N_2O \cdot 2HCl$ (281.20): C, 51.3; H, 7.88; Cl, 25.2; N, 9.96. Found: C, 51.5; H, 8.01; Cl, 25.1; N, 10.2.

o-(3-Dimethylaminopropylamino)phenol (XIII). A solution of 7.0 g. (0.034 mole) of *N'*-(*o*-methoxyphenyl)-*N,N*-dimethyl-1,3-propanediamine (XII) in 25 ml. of 48% hydrobromic acid was heated under reflux for 18 hr. The excess hydrobromic acid was distilled under reduced pressure and three 25 ml. portions of alcohol were added (distilling each portion under reduced pressure before the next portion was added). The residue was crystallized by the addition of ether. The dihydrobromide salt was recrystallized from alcohol to yield 5.4 g. (44.5%) of product, m.p. 195–198°.

Anal. Calcd. for $C_{11}H_{18}N_2O \cdot 2HBr$ (356.13): C, 37.1; H, 5.66; Br, 44.9; N, 7.86. Found: C, 37.4; H, 5.94; Br, 45.0; N, 7.73.

The free base from the above salt was recrystallized from alcohol–petroleum ether (b.p. 60–90°), m.p. 100–102.5°.

Anal. Calcd. for $C_{11}H_{18}N_2O$ (194.27): C, 68.0; H, 9.34; N, 14.4. Found: C, 67.7; H, 9.59; N, 14.7.

o-[5-Chloro-N-(3-dimethylaminopropyl)-2-nitroanilino]-phenol (IX). A mixture of 9.4 g. (0.048 mole) of *o*-(3-dimethylaminopropylamino)phenol (XIII), 2.8 g. (0.048 mole) of sodium methoxide and 9.3 g. (0.048 mole) of 2,4-dichloronitrobenzene in 500 ml. of anhydrous alcohol was refluxed for 20 hr. The cooled reaction mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in 100 ml. of ether and extracted with 1*N* hydrochloric acid. The aqueous acidic extract was made alkaline with an excess of potassium carbonate and extracted several times with ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate and evaporated to dryness *in vacuo*. The red semisolid residue was triturated with petroleum ether (b.p. 60–90°) and filtered. The petroleum ether filtrate (A) was saved and I was isolated from this fraction. The precipitate was recrystallized from 20 ml. of alcohol and afforded 6.7 g. (40%) of product, m.p. 143–145°.

Anal. Calcd. for $C_{17}H_{20}ClN_3O_3$ (349.81): C, 58.4; H, 5.76; Cl, 10.1; N, 12.0. Found: C, 58.6; H, 6.01; Cl, 9.97; N, 11.7.

2-Chloro-10-(3-dimethylaminopropyl)phenoxazine (I) *hydrochloride* [*from the petroleum ether filtrate* (A) of IX above]. The petroleum ether filtrate (A) was evaporated to dryness and the residue, 4.0 g. (26.2%) was chromatographed. The purest fraction contained 0.8 g. of I as an oil. It was converted to the hydrochloride, 0.4 g., m.p. 219–221°. Mixed melting point with a sample prepared from IX was not depressed. Infrared and ultraviolet spectra of the free base and hydrochloride salt were identical with those of I prepared from intermediate IX.

2-Chloro-10-(3-dimethylaminopropyl)phenoxazine (I) *hydrochloride* (*from* IX). A mixture of 8.0 g. (0.023 mole) of *o* - [5 - chloro - N - (3 - dimethylaminopropyl) - 2 - nitroanilino]phenol (IX), 5.0 g. (0.036 mole) of potassium carbonate, 1.7 g. of copper powder in 200 ml. of dimethylformamide was treated as described for the preparation of I from IV. Distillation of the residue afforded 3.0 g. (43%) of base (I), b.p. 166°/0.03 mm., n_D^{25} 1.614, from which 3.1 g. (91%) of hydrochloride salt, m.p. 221–222° dec., was prepared (lit.[2a], b.p. of base, 178–180°/0.3 mm.; m.p. of salt 223–224°). $\lambda_{max}^{CH_3OH}$ 241 mμ, ε 48,000; 328 mμ, ε 8,020.

Anal. Calcd. for $C_{17}H_{19}ClN_2O \cdot HCl$ (339.26); C, 60.2; H, 5.94; Cl, 20.9; N, 8.25. Found: C, 60.3; H, 6.24; Cl, 21.2; N, 8.37.

N'-(5-Chloro-2-methoxyphenyl)-N,N-dimethyl-1,3-propanediamine. A mixture of 40.8 g. (0.26 mole) of 2-amino-4-chloroanisole, 16.5 g. (0.38 mole) of sodium amide in 500 ml. anhydrous benzene was treated with a solution of 46.0 g.

(0.38 mole) of 3-chloro-*N*,*N*-dimethylpropylamine in 75 ml. of anhydrous benzene as described above for the preparation of IV and V. Distillation afforded 28.0 g. (44.7%) of product, b.p. 140–142°/1.4 mm., n_D^{25} 1.547.

Anal. Calcd. for $C_{12}H_{19}ClN_2O$ (242.75): C, 59.4; H, 7.89; Cl, 14.6; N, 11.5. Found: C, 59.8; H, 7.94; Cl, 14.8; N, 11.7.

Several attempts to hydrolyze the *O*-methyl ether linkage in this molecule with 48% hydrobromic acid or concentrated hydrochloric acid under gentle reflux resulted in decomposition products which could not be purified.

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The Reaction of Ketene with the 1-Phenyl-3-pyrazolidones

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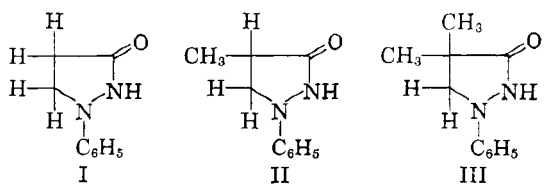
The reaction of ketene with 1-phenyl-3-pyrazolidone (I), 1-phenyl-4-methyl-3-pyrazolidone (II), and 1-phenyl-4,4-dimethyl-3-pyrazolidone (III) was studied. A mixture of the *N*-acetate (IV) and enol acetate (V) was formed in each case. The ratio of the two products formed was modified by acid and base catalysts. The structures of the products were determined by infrared and NMR spectra. Upon vacuum distillation, the enol acetates rearranged nearly quantitatively to the *N*-acetates.

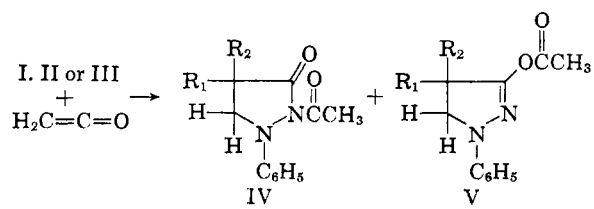
Reactions involving ketene have been studied extensively and the reactions with amines, alcohols, and amides are well known. Ketene also reacts with carbonyl compounds having an enolizable hydrogen to form enol acetates. These reactions are modified by acidic and basic catalysts, as has been pointed out in two reviews.[1,2]

No work, however, has been published on the reaction of ketene with 3-pyrazolidones such as 1-phenyl-3-pyrazolidone (I), 1-phenyl-4-methyl-3-pyrazolidone (II) or 1-phenyl-4,4-dimethyl-3-pyrazolidone (III), which may be regarded as amides or hydrazides in which the nitrogens are contained in a heterocyclic structure. Reaction of these compounds with ketene would involve the —NH, the enol OH, or the carbonyl group.



I II III

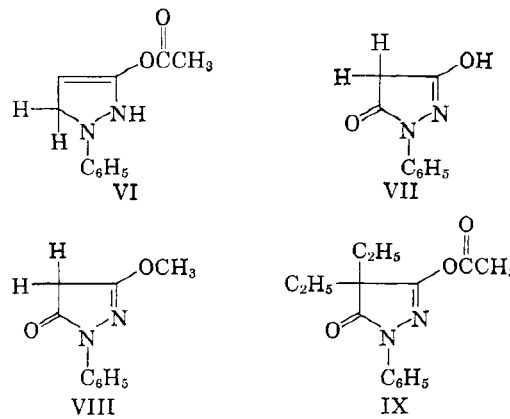
Ketene reacts with I, II, and III to yield mixtures of the *N*-acetyl derivatives, IV, and the enol acetates, V. The enol acetate (V) of III was not isolated but its presence in the reaction mixture was indicated by infrared spectra.



IV V

$R_1 = H$ or CH_3
$R_2 = H$
$R_1 = R_2 = CH_3$

As an enol acetate is formed by the reaction of ketene with I, II, and III, the 3-pyrazoline (VI) structure for an enol acetate must be ruled out. The infrared and NMR spectra confirm the 2-pyrazoline (V) structure as the correct one for the enol acetate. This structure is also consistent with the one reported by Conrad and Zart[3] for 1-phenyl-3-hydroxy-5-pyrazolone (VII). They proposed the enolized structure for this compound and prepared the monomethyl ether (VIII) and the monoacetate (IX) of the diethyl derivative.



VI VII VIII IX

The enol acetates and *N*-acetates were distinguishable by their infrared spectra. The *N*-acetates have two carbonyl groups and, therefore, have two carbonyl absorptions in the infrared region, one at

(1) H. J. Hagemeyer, *Ind. Eng. Chem.*, **41**, 765 (1949).
(2) G. Quadbeck, *Angew. Chem.*, **68**, 361 (1956).
(3) M. Conrad and A. Zart, *Ber.*, **39**, 2282 (1906).