# The Reaction of *C*-Substituted Ethylenediamine with the Ester of α-Halo Acid

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In a previous report[1] it has been shown how 3,6-disubstituted 2-oxopiperazines were first synthesized by the reaction of α-chloro oximes with the esters of amino acids, followed by the reductive cyclization of the products. Recently Iwanami et al.[2] have described the synthesis of 3-ethoxycarbonylmethylene-6-methyl-2-oxopiperazine by the reaction of diethyl acetylenedicarboxylate with 1,2-propanediamine. 3-Substituted 2-oxopiperazines are usually synthesized by Aspinall's method,[3] which consists of the reaction of ethylenediamine with the ester of α-halo acid. The application of this method to the synthesis of disubstituted 2-oxopiperazine will involve the condensation of *C*-substituted ethylenediamine (III) with the ester of α-halo acid (IV). In such a case condensation may occur in one or both of two directions. Thus, the condensation of III with IV might give 3,6-disubstituted 2-oxopiperazine (V) or 3,5-disubstituted 2-oxopiperazine (VI), or a mixture of the two.

The present paper will describe the reaction of 1-phenylethylenediamine (IIIa) with ethyl α-bromo-β-phenylpropionate (IVa) and that of 1,2-propanediamine (IIIb) with ethyl α-bromopropionate (IVb), reactions yielding, as the main products, the corresponding 3,6-disubstituted 2-oxopiperazines (V). Although 1-phenylethylenediamine (IIIa) is usually prepared by reducing phenylaminoacetonitrile,[4] phenylglyoxime,[5] or phenylglycineamide,[6] these methods of preparation are troublesome or have defects in yield. The conversion of phenacylamine hydrochloride (I) to the oxime is usually in a low yield, because the former cyclizes rapidly to 2,5-diphenylpyrazine in the course of the reaction.[7] The oximination of α-halo and α-amino ketones have been known to be successfully carried out in the presence of acetic acid liberated from sodium acetate.[8] Phenacylamine hydrochloride (I) was converted to the oxime in a good yield by reaction with hydroxylamine hydrochloride and an excess of sodium acetate, and the resulting oxime was hydrogenated in the presence of Raney-nickel to IIIa. Ethyl α-bromo-β-phenylpropionate (IVa) was treated with an excess of IIIa in benzene to give, as the main product, crystals with a m. p. of 170—171.5°C

1) M. Masaki and M. Ohta, This Bulletin, **36**, 922 (1963).
2) Y. Iwanami, Y. Kenjo, K. Nishibe, M. Kajiura and S. Isoyama, This Bulletin, **37**, 1740 (1964).
3) S. R. Aspinall, *J. Am. Chem. Soc.*, **62**, 1202 (1940).
4) a) H. Reihlen, *Ann.*, **493**, 25 (1932); b) Z. Welvart, *Compt. rend.*, **239**, 1299 (1954).
5) Suzanne Ser, L. Piaux and P. Fréon, ibid., **229**, 376 (1949).
6) V. G. Yashunski, V. F. Vasil'eva, L. I. Tikhorova and M. N. Shchukina, *Zhur. Obshcheĭ. Khim.*, **29**, 2709 (1959).
7) a) S. Gabriel and G. Eschenbach, *Ber.*, **30**, 1126 (1897); b) S. Gabriel, ibid., **41**, 1127 (1908).
8) M. Masaki et al., unpublished work of this Laboratory.

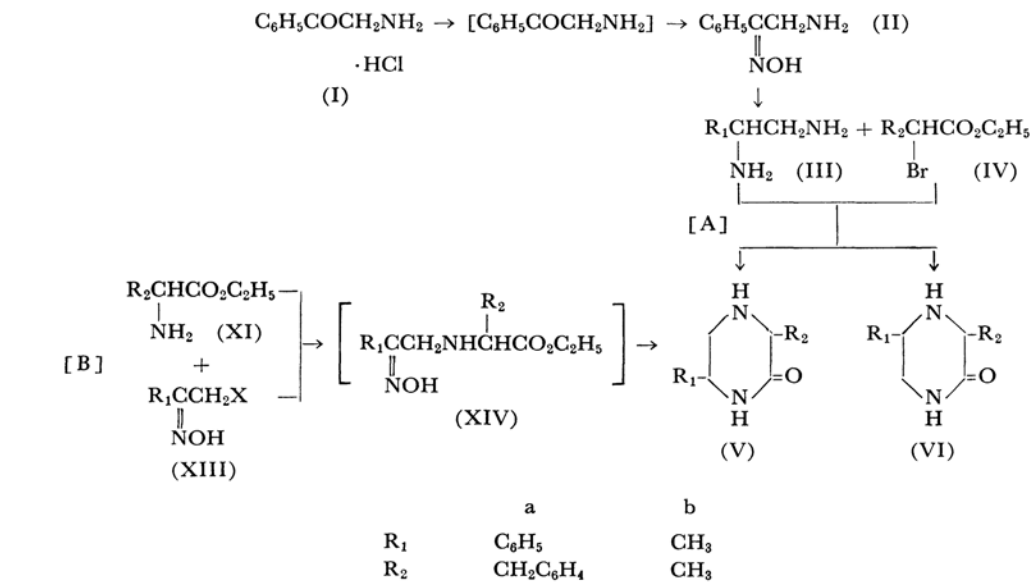


Fig. 1.

and a trace of a crystalline substance with an m. p. of 152—154°C, which was isolated from the mother liquor of the recrystallization of the former by means of column chromatography. The main product (m. p. 170—171.5°C) was easily identified as 3-benzyl-6-phenyl-2-oxopiperazine (Va) by a mixed melting point determination with an authentic sample.[1]

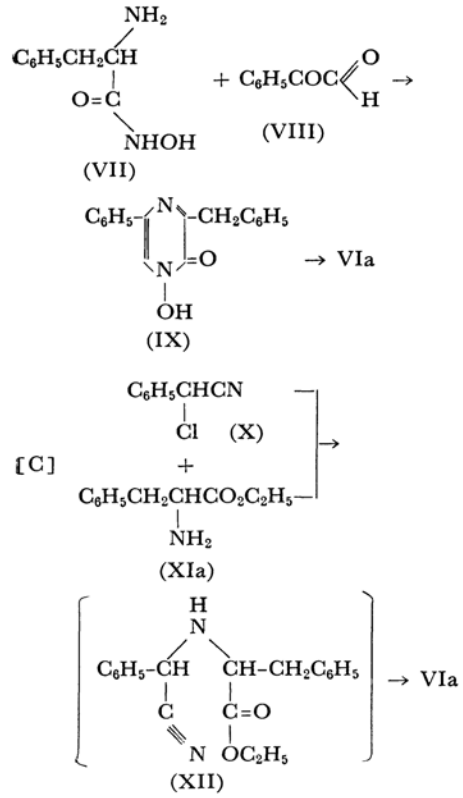


Fig. 2

The structure of the substance with an m. p. of 152—154°C was indicated as being the 3,5-isomer by an elementary analysis of it and by its infrared spectrum. In order to confirm this, 3-benzyl-5-phenyl-2-oxopiperazine (VIa) was then synthesized through other two routes. It has been shown by Dutcher[9] that Aspergillic acid (1-hydroxy-3-isobutyl-6-*s*-butyl-2-pyrazinone) can be reduced to the corresponding 3,6-disubstituted 2-oxopiperazine by zinc and acetic acid. In a similar manner, 1-hydroxy-3-benzyl-5-phenyl-2-pyrazinone (IX) which had been synthesized by the reaction of DL-phenylalanylhydroxylamine (VII) with phenylglyoxal (VIII) was reduced, yielding the required 3-benzyl-5-phenyl-2-oxopiperazine (VIa), which was also synthesized by alternative route. By the treatment of α-chlorophenylacetonitrile (X) with DL-phenylalanine ethyl ester (XIa) in the presence of equimolar triethylamine, the *N*-(α-cyanobenzyl)-phenylalanine ethyl ester was obtained as an oily product. The product, without purification, was hydrogenated at 80°C in the presence of Raney-nickel; a simultaneous cyclization then occurred, giving VIa. The crystalline by-product with an m. p. of 152—154°C, which was obtained in the reaction of IIIa with IVa, showed no depression in a mixing test with the 3-benzyl-5-phenyl-2-oxopiperazine (VIa) prepared above.

In a manner analogous to the above case, the reaction of 1,2-propanediamine (IIIb) with ethyl α-bromopropionate (IVb) in benzene gave an oily product; this was converted to crystalline hydrochloride and a phenylureido derivative, which were

9) J. D. Dutcher, *J. Biol. Chem.*, **171**, 321 (1947).

characterized as 2-oxopiperazine derivatives by an elementary analysis of them and on the basis of their infrared spectra. These derivatives showed no depression in a mixing test with the corresponding derivatives of the 3,6-dimethyl-2-oxopiperazine (Vb) synthesized by an alternative method, which consisted of the reaction of $\alpha$-chloroacetone oxime (XIIIb) with the DL-alanine ethyl ester in ether, followed by the reductive cyclization of the product. In the case of the reaction of IIIb with IVb, the formation of the 3,5-isomer was not observed.

It is of interest that 3,6-disubstituted 2-oxopiperazine is formed exclusively either in the reaction of *C*-substituted ethylenediamine with the ester of $\alpha$-halo acid or in the reaction of 1,2-propanediamine with diethyl acetylenedicarboxylate.

## Experimental

**Phenacylamine Oxime (II).** — A hot solution of sodium acetate (24.8 g., 300 mmol.) in water (50 ml.) was added with stirring to solution of hydroxylamine hydrochloride (7.0 g., 100 mmol.) and I[10] (8.6 g., 50 mmol.) in water (50 ml.). The temperature was then raised from 20°C to 55°C. After it had been stirred for several hours, the pale yellow solution was allowed to stand overnight. The solution was made alkaline with a saturated solution of sodium carbonate in water under cooling by ice water, and then the crystals which separated from the solution were collected by filtration, washed with cold water, and recrystallized from ethanol to give colorless plates (5.3 g., 70.6%), m. p. 142—144°C (lit.[7a] m. p. 138—140°C).

**DL-1-Phenylethylenediamine (IIIa).** — To a solution of II (3.2 g., 21 mmol.) in ethanol (100 ml.) Raney-nickel (2 g.) which had previously been rinsed with ethanol (25 ml.) was added. The mixture was then stirred with hydrogen at an initial pressure of 40 kg./cm$^2$ at 70°C. Hydrogen absorption ceased after 2 hr.; the catalyst and the solvent were thereafter removed by the usual procedures. The residue was distilled under a nitrogen stream, yielding DL-1-phenylethylenediamine (2.1 g., 72.7%), b. p. 101—103°C/5.5 mmHg. Dry hydrogen chloride was introduced to the solution of IIIa in ethanol in order to precipitate crystalline solids which, after recrystallization from methanol, afforded pure dihydrochloride, m. p. 295—300°C (decomp., lit.[6] 300—301°C).

Found: C, 45.89; H, 6.95; N, 13.11. Calcd. for $C_8H_{12}N_2 \cdot 2HCl$: C, 45.94; H, 6.75; N, 13.39%.

**The Reaction of IIIa with IVa.**—A solution of IVa (3.6 g., 14 mmol.) in benzene (5 ml.) was vigorously stirred, drop by drop, into a solution of IIIa (5.7 g., 42 mmol.) in benzene (11 ml.), and the mixture was heated at 80°C for 4 hr. To the reaction mixture, a solution of potassium hydroxide (0.79 g.) in ethanol (15 ml.) was added, and the separated potassium bromide was filtered off, when the filtrate was concentrated under reduced pressure and the residue was dissolved in benzene (25 ml.), the insoluble crystals in the benzene were removed completely. The filtrate was then dried over anhydrous sodium sulfate and evaporated to dryness at 100°C under diminished pressure in order to recover the original IIIa and IVa. Carbon tetrachloride (6 ml.) was added to the residue; thereupon small needles slowly crystallized out. They were collected (1.4 g., 37.6%) and recrystallized from methanol to give colorless needles, m. p. 170—171.5°C, which showed no depression in a mixing test with authentic Va. After Va had separated, the above carbon tetrachloride was evaporated to dryness. The residue was dissolved in benzene (10 ml.), and the solution was dried over anhydrous sodium sulfate and passed through a column of activated alumina. The column was then washed with additional benzene (20 ml.). The evaporation of the combined benzene eluate yielded pale yellow solids, which were recrystallized from methanol to give the isomer of Va (0.06 g.) as colorless needles, m. p. 152—154°C. IR (KBr disk): 3430, 3300, 3180, 3050, 1655 and 1454 cm$^{-1}$.

Found: C, 76.80; H, 6.89; N. 10.79. Calcd. for $C_{17}H_{18}ON_2$: C, 76.66; H, 6.81; N, 10.52%.

**1-Hydroxy-3-benzyl-5-phenyl-2-pyrazinone (IX).** —IX was prepared by the use of the procedure of Dunn et al.[11] A solution of phenylglyoxal (2.68 g., 20 mmol.) in methanol (30 ml.) was added drop by drop to a suspension of DL-phenylalanylhydroxylamine[12] (3.6 g., 20 mmol) in methanol (30 ml.) and water (20 ml.) at −30°C. A sodium hydroxide solution (12.5 ml.; 2 N) was added during a 5—10 min. period, and then mixture was stirred at −30°C for 15 min. The temperature was raised to 0°C during the next 10 min., at the end of which period dissolution was complete. Stirring was continued at 5°C for 3 hr. The solution was acidified with a dilute solution of acetic acid to give yellow solids. These were collected, washed with water, and recrystallized from a small amount of ethyl acetate to yield yellowish needles (2.8 g., 50.0%), m. p. 165—166°C. The product gives a wine red color with a methanolic ferric chloride solution.

Found: N, 10.23. Calcd. for $C_{17}H_{14}O_2N_2$: N, 10.23%.

**The Reductions of IX.** — 1-Hydroxy-3-benzyl-5-phenyl-2-pyrazinone (IX) (1.25 g., 4.5 mmol.) was added to a solution of acetic acid (12.5 ml.) and water (12.5 ml.); zinc dust was then added in three 0.5 g. portions during 4 hr. of refluxing. The solution was cooled, and diluted with 70 ml. of water, and hydrogen sulfide was introduced to the solution until no more zinc sulfide precipitated. After the filtration of the zinc sulfide, the solution was neutralized with sodium hydroxide and extracted with three 30 ml. portions of benzene. The benzene was washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure, yielding crystalline, pale yellow solids. Carbon tetrachloride (4 ml.) was added to the solids, and insoluble crystals in carbon tetrachloride were collected (0.8 g., 66.7%) and recrystallized from methanol to yield colorless needles, m. p. 152—153°C (unchanged by admixture with VIa obtained by the reaction of X with XIa).

**3-Benzyl-5-phenyl-2-oxopiperazine (VIa).** — Triethylamine (2.1 g., 21 mmol.) was added to a solution of X (3.1 g., 20.5 mmol.) and XIa (4.0 g., 20.5 mmol.) in benzene (30 ml.), and the mixture was

10) C. Mannich and F. L. Hahn, *Ber.*, **44**, 1542 (1911).

11) G. Dunn, J. A. Elvidge, G. T. Newbalt, D. W. C. Ramsey, F. S. Spring and W. Sweeny, *J. Chem. Soc.*, **1949**, 2707.

12) K. G. Cunningham, G. T. Newbalt, F. S. Spring and J. Stark, ibid., **1949**, 2091.

heated at 80°C for 16 hr. The clear solution gradually became dark brown. After the mixture had been kept overnight, the triethylamine hydrochloride which had separated was filtrated off. The filtrate was washed twice successively with water with 3% hydrochloric acid, and twice more with water, and then dried over anhydrous sodium sulfate. After the solution of benzene had been saturated with hydrogen chloride under cooling, the resultant solution was allowed to stand for several hours. The separated crystals were collected, and dissolved in water (10 ml.), and the solution was filtered to remove a small amount of an insoluble substance. The filtrate was then neutralized with potassium carbonate, and the oily free base (XII) separated and it was extracted twice with benzene; the combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give XII as an brown residue (2.0 g.). A solution of crude XII (2.0 g.) in ethanol (100 ml.) was shaken with a Raney-nickel catalyst (1.0 g.) at an initial pressure of 100 kg./cm² of hydrogen at 70—80°C. The product was separated from the catalyst, the filtrate was evaporated to dryness under reduced pressure, and ligroin (5 ml.) was added to the residue. After several hours, 3-benzyl-5-phenyl-2-oxopiperazine precipitated; they were collected and washed with ligroin. The yield was 0.48 g. An analytical sample was obtained by recrystallization from methanol as colorless needles, m. p. 152—154°C. No depression of the melting point was observed on admixture with VIa synthesized by the reaction of IIIa with IVa. IR (KBr disk): 3400, 3300, 3180, 3060, 1660 and 1457 $cm^{-1}$.

Found: C, 76.63; H, 7.20; N, 11.10. Calcd. for $C_{17}H_{18}ON_2$: C, 76.66; H, 6.81; N, 10.52%.

**The Reaction of IIIb with IVb.**—A mixture of IIIb (14.8 g., 200 mmol.) and IVb (6.0 g., 33.2 mmol.) in benzene (50 ml.) was heated at 80°C for 3 hr. while being stirred. The mixture was concentrated to a half of the initial volume, and then a solution of potassium hydroxide (2.1 g.) in ethanol (30 ml.) was added. After the precipitate had separated, the solution was distilled under reduced pressure to yield a viscous liquid (2.0 g., 47%), b. p. 115—118°C/1 mmHg. The oil solidified spontaneously upon standing.

*Hydrochloride:* Colorless needles, m. p. 285—287°C (decomp.). IR (KBr disk): 3270, 2950, 2780—2250, 1685, 1465 and 1348 $cm^{-1}$.

Found: C, 44.10; H, 7.87; N, 17.02%.

*Phenylureido Derivative:* Colorless prisms, m. p. 202—203°C (unchanged by admixture with the phenylureido derivative synthesized by the reaction of XIb with XIIIb).

Found: N, 17.06%.

**3, 6-Dimethyl-2-oxopiperazine (Vb).**—A solution of chloroacetone oxime (8.3 g., 77 mmol.) in absolute ether (40 ml.) was added drop by drop to a solution of XIb (18 g., 154 mmol.) in absolute ether (180 ml.), after a few minutes amino acid ester hydrochloride began to precipitate. The mixture was then allowed to stand for 3 days at room temperature until the reaction was complete. The precipitated salt (11.1 g., 93.8%) was filtered off and washed with absolute ether. The combined ethereal solution, concentrated to about 100 ml., was extracted with 20 ml. of 3 N hydrochloric acid three times. The extracts were washed with ether, and then potassium carbonate was added until a yellow oil had separated completely. This oil was repeatedly extracted with ether, and then all the extracts were washed with saturated solution of sodium chloride and dried over anhydrous sodium sulfate. After the ether had been removed, a crude brown oil (7.0 g., 48.5% of the theoretical amount) was obtained; it was used for the next reduction step without further purification. A solution of crude XIVb (6.0 g., 32 mmol.) in ethanol (60 ml.) was shaken with Raney-nickel (2.0 g.) at an initial pressure of 100 kg./cm² of hydrogen. The reaction was then allowed to proceed for 5 hr. at room temperature. The catalyst was removed by filtration, and the brown oil was obtained by the concentration of the filtrate under reduced pressure. The oily products were distilled under a nitrogen stream to give 3,6-dimethyl-2-oxopiperazine (2.5 g., 61.0%), b. p. 129 — 132°C/2 mmHg.

*Hydrochloride:* Colorless needles, m. p. 285—286.5°C (decomp.). Its infrared spectrum in a potassium bromide pellet was superimposable with that of the hydrochloride of Vb obtained above.

Found: C, 43.90; H, 7.96; N, 17.12. Calcd. for $C_6H_{12}ON_2 \cdot HCl$: C, 43.77; H, 7.95; N, 17.02%.

**3, 6-Dimethyl-4-phenylcarbamoyl-2-oxopiperazine.**—Vb was treated with phenyl isocyanate, yielding the phenylureido derivative. This was crystallized from dilute ethanol to give colorless prisms; m. p. 202—203°C.

Found: N, 17.06 Calcd. for $C_{13}H_{17}O_2N_3$: N, 16.99%.

**The Thin-Layer Chromatography of Disubstituted 2-Oxopiperazines.**

Table I. $R_f$ Values of disubstituted 2-oxopiperazines

| Compound | Va | Va | VIa | VIa | Vb | Vb |
|---|---|---|---|---|---|---|
| Method* | A | B | A | C | A | B |
| $R_f$ | 0.75 | 0.76 | 0.82 | 0.83 | 0.31 | 0.31 |

* For details of the method, see Fig. 1 and Fig. 2.
Solvent system (volume): *n*-Butylalcohol (4) - Acetic acid (1) - Water (2)
Adsorbent: Silica gel (Wakogel 10)
Sample: 2.5—5 μg. (0.01 ml. applied to plates)
Detection: $I_2$ vapor

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