The Syntheses of 3, 5-Disubstituted 2-Oxopiperazines[*1]

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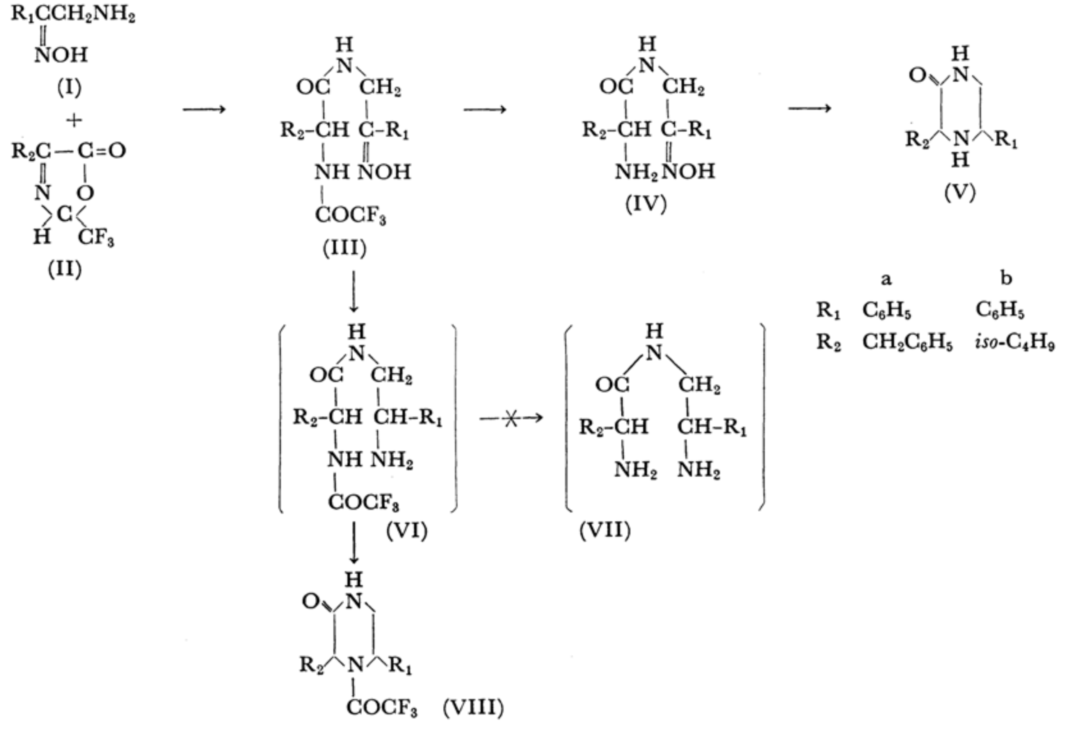
Although it has been known that many 3-substituted 2-oxopiperazines show some pharmacological activities[1] and can be prepared *via* the reaction of ethylenediamine with α-halo-,[2a] α-oxy acid ester,[2b] or cyanhydrine,[2c] only a few synthetic methods for 3, 5- or 3, 6-disubstituted 2-oxopiperazines have been reported.

Recently Masaki and Ohta[3] have synthesized some 3, 6-disubstituted 2-oxopiperazines by a new method, consisting of the reductive cyclization of the *N*-(2-oximinoalkyl) amino acid ester prepared by the reaction of α-halo oxime with the esters of amino acids, while Iwanami *et al.*[4] have described a synthesis of 3-ethoxycarbonylmethylene-6-methyl-2-oxopiperazine.

In our previous paper, it was shown that 3, 5-disubstituted 2-oxopiperazine could be synthesized by the reaction of α-halo nitrile with the ester of amino acid, followed by the reductive cyclization of the product.[5]

The present paper will describe the syntheses of 3, 5-disubstituted 2-oxopiperazines (V) by an alternative route, illustrated in Scheme 1.

Since 4-substituted 2-trifluoromethyl-5(2*H*)-oxazolone (II) has been shown to be useful as an aminoacetylating agent of amines,[6] the reaction



	a	b
R_1	C_6H_5	C_6H_5
R_2	$CH_2C_6H_5$	*iso*-C_4H_9

Scheme 1

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2) a) S. R. Aspinall, *J. Am. Chem. Soc.*, **62**, 1202 (1940). b) T. Kametani, This Bulletin, **31**, 860 (1958). c) J. S. Strong, W. E. Craigant and V. T. Elkind, U. S. Pat. 2649450 (1953); *Chem. Abstr.*, **48**, 8271 (1954).

3) M. Masaki and M. Ohta, This Bulletin, **36**, 922 (1963).

4) Y. Iwanami, Y. Kenjo, K. Nishibe, M. Kajiura and S. Isoyama, *ibid.*, **37**, 1740 (1964).

5) K. Masuzawa, M. Masaki and M. Ohta, *ibid.*, **38**, 2079 (1965).

6) F. Weygand, *Ann.*, **658**, 128 (1962).

of amino ketone oxime with II was expected to give readily the amino acid amide derivative (IV), the reductive cyclization of which would then result in 3, 5-disubstituted 2-oxopiperazine.

The treatment of 2-trifluoromethyl-4-benzyl-5(2*H*)-oxazolone (IIa) with phenacylamine oxime (I) in boiling benzene gave *N*-[(*N*′-trifluoroacetyl)-phenylalanyl]-2-oximinophenethylamine (IIIa), the structure of which was supported by elementary analysis and by its infrared spectrum. α-Halogen-substitution results in a shift in the carbonyl frequency to a higher value; the absorption bands at 1710 and 1660 cm^{-1} were ascribed to the trifluoroacetylamide carbonyl and the amide carbonyl group in IIIa. The trifluoroacetyl group of IIIa was removed by treatment with 1 N sodium hydroxide for 30 min, and the resultant *N*-phenylalanyl-2-oximinophenethylamine (IVa) was hydrogenated at 90°C in the presence of Raney nickel to give the expected 3-benzyl-5-phenyl-2-oxopiperazine (Va), which was identified by a mixed-melting-point determination with an authentic sample.5) The infrared spectrum of Va showed a band at 1660 cm^{-1} characteristic of an amide group, and there was no absorption band at 1600—1500 cm^{-1} in the region for the amide II, suggesting the presence of a cyclic amide.

In an analogous fashion, phenacylamine oxime (I) was treated with 2-trifluoromethyl-4-isobutyl-5(2*H*)-oxazolone (IIb) to give *N*-[(*N*′-trifluoroacetyl)leucyl] - 2 - oximinophenethylamine (IIIb), which after the removal of the trifluoroacetyl group, was hydrogenated to yield 3-isobutyl-5-phenyl-2-oxopiperazine (Vb). The product (Vb) was characterized as the crystalline hydrochloride.

In an attempt to obtain Va, the hydrogenation of IIIa was expected to yield *N*-[(*N*′-trifluoroacetyl)phenylalanyl]-2-aminophenethylamine (VI), 3-benzyl-4-trifluoroacetyl-5-phenyl-2-oxopiperazine (VIII) was obtained as the sole isolated product (17.2% yield).

Experimental*2

Phenacylamine Oxime (I). The starting material, phenacylamine oxime (I), was obtained in a good yield by the oximination of phenacylamine hydrochloride in the presence of acetic acid liberated from sodium acetate.5)*3

4 - Substituted 2 - Trifluoromethyl-5(2*H*)-oxazolones (IIa and IIb). These compounds were prepared according to the procedure of Weygand.6)

***N*-[(*N*′-Trifluoroacetyl)phenylalanyl] -2-oximinophenethylamine (IIIa).** A solution of IIa (7.3 g, 30 mmol) in benzene (40 m*l*) was added, drop by drop, to a suspension of I (4.5 g, 30 mmol) in benzene (200 m*l*), and the mixture was heated under reflux. The mixture became a clear solution after about 20 min; refluxing was continued for 5 hr. The crystalline product was collected by filtration and washed with benzene. Colorless needles (8.0 g, 66.6%) were thus obtained. A portion of the product was recrystallized from di-*n*-butyl ether - ethyl acetate and analyzed, mp 202—203.5°C. IR (KBr disk): 3370—3270 (broad, OH and NH), 1710 (trifluoroacetyl amide carbonyl), 1660 (amide carbonyl), 1550 (amide II) and 1220—1180 cm^{-1} (CF).

Found: C, 58.16; H, 4.92; N, 11.06%. Calcd for $C_{19}H_{18}O_3N_3F_3$: C, 58.01; H, 4.61; N, 10.68%.

***N*-Phenylalanyl-2-oximinophenethylamine (IVa).** The crude crystals (IIIa, 4.0 g, 10.2 mmol) were dissolved in 1 N sodium hydroxide (30 m*l*). After a few minutes, white crystals began to precipitate. The mixture was then allowed to stand at room temperature for 30 min, by which time the reaction was complete; carbon dioxide was then introduced to the suspension in order to complete the precipitation of IVa. The crystals were collected by filtration, washed repeatedly with water, and recrystallized from benzene as colorless needles, mp 114—115°C (2.7 g, 89.1%). IR (KBr disk): 3400—3300 (broad, OH and NH), 1660 (amide carbonyl) and 1550 cm^{-1} (amide II).

Found: C, 68.46; H, 6.74; N, 14.32%. Calcd for $C_{17}H_{19}O_2N_3$: C, 68.66; H, 6.44; N, 14.13%.

3-Benzyl-5-phenyl-2-oxopiperazine (Va). A solution of IVa (1.0 g, 3.4 mmol) in ethanol (30 m*l*) was shaken with Raney nickel (1.0 g) at an initial hydrogen pressure of 100 kg/cm^2 at 90°C for 5 hr. The catalyst was then removed by filtration, and the brown oil was obtained upon the concentration of the filtrate under reduced pressure. The oily product was crystallized on treatment with methanol, and the crystals were recrystallized twice from methanol to give colorless needles (0.43 g, 48.5%) (mp 148—150°C), which showed no depression in a mixing test with an authentic specimen.5) IR (KBr disk): 3300, 3180 (NH), 1660 cm^{-1} (amide carbonyl). (Found: C, 76.50; H, 6.70; N, 10.74%.)

***N*-[(*N*′-Trifluoroacetyl)leucyl] - 2 -oximinophenethylamine (IIIb)** IIb (6.5 g, 31 mmol) was treated with I (4.7 g, 31 mmol) in benzene (250 m*l*) in a manner analogous to the case of IIIa. After refluxing, the solution was concentrated under reduced pressure to give a viscous product which was recrystallized from benzene in the form of colorless crystals (5.6 g, 50.2%), mp 174—176°C.

IR (KBr disk): 3370 (OH), 3260 (NH), 1720 (trifluoroacetyl amide carbonyl), 1660 (amide carbonyl), 1540 (amide II) and 1220—1180 cm^{-1} (CF).

***N*-Leucyl - 2 - oximinophenethylamine (IVb).** A solution of IIIb (2.6g, 7.2mmol) in 1N sodium hydroxide (21 m*l*) was treated in the manner described above for IVa. The crystals were then collected by filtration and washed several times with water to yield colorless needles (1.5 g, 78.8%) (mp 126—127°C). These crystals were used for the next reduction step without further purification.

IR (KBr disk): 3370 (OH), 3300 (NH), 1660 (amide carbonyl) and 1540 cm^{-1} (amide II).

Found: N, 15.60%. Calcd. for $C_{14}H_{21}O_2N_3$: N, 15.96%.

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*2 The melting points were measured on a micro hot stage and are not corrected.

*3 In the course of the oximination, an unidentified compound, mp 181—182°C, was obtained. The elementary analysis and the molecular weight measurement of the product indicated the empirical formula $C_{24}H_{24}O_2N_4$.

3-Isobutyl-5-phenyl-2-oxopiperazine Hydrochloride (Vb HCl). IVb (1.5 g, 5.7 mmol) was hydrogenated according to a procedure analogous to that used in the case of IVa. The usual treatment of the reaction mixture gave an oily product, which was then dissolved in a mixture of ethanol (10 m*l*) and ether (50 m*l*); dry hydrogen chloride was introduced into the resultant solution to yield crystalline precipitates (0.62 g, 40.5%). The product was washed several times with the same solvent and recrystallized from isopropyl alcohol to give colorless needles, mp 222.5—227°C.

IR (KBr disk): 3180 (NH), 2800—2400 (NH_2^+), and 1660 cm^{-1} (amide carbonyl).

Found: C, 62.51; H, 7.85; N, 10.36%. Calcd for $C_{14}H_{20}ON_2 \cdot HCl$: C, 62.55; H, 7.88; N, 10.42%.

Reduction of IIIa. A solution of IIIa (1.56 g, 4 mmol) in ethanol (60 m*l*) was shaken with Raney nickel (1.0 g) at an initial hydrogen pressure of 97 kg/cm^2 at room temperature for 2 hr. The catalyst and the solvent were then removed by the usual procedure. When di-*n*-butyl ether was added to the residue, small needles slowly crystallized out. They were collected (0.25 g, 17.2%) and recrystallized twice from carbon tetrachloride to give 3-benzyl-4-trifluoroacetyl-5-phenyl-2-oxopiperazine (VIII) as colorless needles, mp 155—157°C.

IR (KBr disk): 3300, 3180 (NH), 1710 (trifluoroacetyl amide carbonyl), 1660 (amide carbonyl) and 1220—1180 cm^{-1} (CF).

Found: C, 62.72; H, 4.60; N, 7.71%. Calcd for $C_{19}H_{17}O_2N_2F_3$: C, 62.98; H, 4.73; N, 7.73%.

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