Note

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Kuniyoshi Masuzawa,*1 Mitsuo Masaki, and Masaki Ohta*2 : Studies on Central Nervous System Depressants. II.*3 Synthesis of 2-Piperazinone Derivatives.

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In the previous paper, it has been shown that 5-aryloxymethyl-2-oxazolidinones obtained by the reaction of aryloxypropanediols with urea derivatives are pharmacologically interesting compounds.

This paper deals with the syntheses of ethyl 2-oxo-3-piperazine acetate derivatives and the reactions of those with urea. Ethyl 2-oxo-3-piperazine acetate (IIIa) has already been obtained by the reaction of ethylenediamine with diethyl fumarate (II).[1] The synthesis of ethyl 6 (or 5)-substituted 2-oxo-3-piperazine acetate by a similar method would require the condensation of C-substituted ethylenediamine with diethyl fumarate. Since in this case the product might be 3,6-disubstituted or 3,5-disubstituted 2-piperazinone, or a mixture of both, the reaction of 1,2-propanediamine (Ib) with II was investigated.

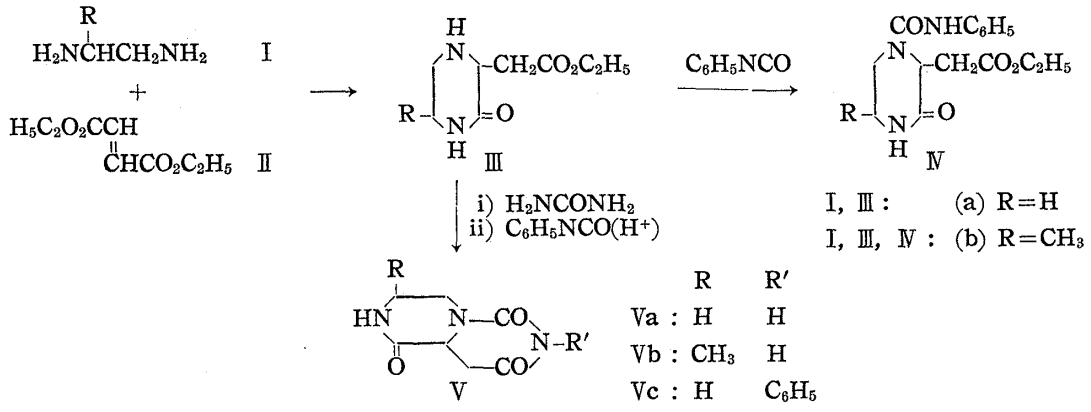

Chart 1.

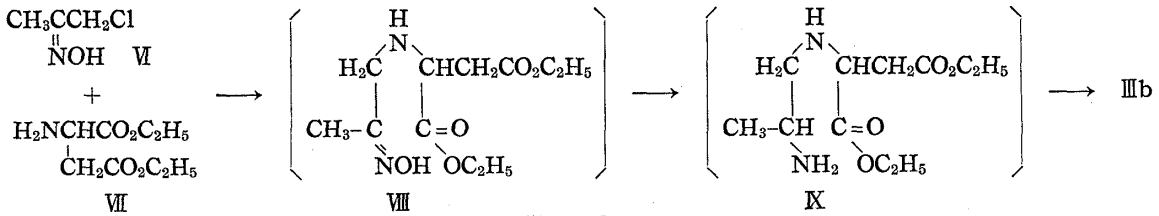

Chart 2.

Treatment of II with an excess amount of Ib in ether gave an oily product, infrared spectrum of which gave evidence for the presence of amide and ester groups. With phenyl isocyanate, the product gave crystalline phenylureido derivative, the elementary analysis of which indicated that the above oily product should be 3,6-disubstituted (or

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1) A. P. Phillips : U. S. Pat., 2,958,693 (1960). (C. A., 55, 9438a (1961)).

3,5-disubstituted) 2-piperazinone. In order to determine whether the product is 6-methyl derivative or 5-methyl derivative, ethyl 6-methyl-2-oxo-3-piperazine acetate was synthesized by another route which consisted in the reaction of 1-chloro-2-propanone oxime (Ⅵ) with DL-diethyl aspartate (Ⅶ) in ether followed by reductive cyclization of the product. The phenylureido compound derived from the product in the reaction of Ib with Ⅱ had the melting point identical with the phenylureido derivative of ethyl 6-methyl-2-oxo-3-piperazine acetate, and showed no depression in a mixing test with the latter. The mixture of these gave also one spot on a thin-layer chromatogram (TLC).*4 Thus, it is concluded that the reactions of C-substituted ethylenediamine with either α-halo ester[2] or diethyl fumarate yield mainly 3,6-disubstituted 2-piperazinone.

The reactions of methyl 2-piperidine acetate with carbonic acid derivatives have been studied by many workers[3] to give condensed piperidines which have some pharmacological utilities.[4] However, the analogous reaction in piperazine series has hitherto received little attention. Only Jucker and Rissi have described the reaction of piperazine derivatives with phenyl isocyanate.[5] In this paper the reaction of Ⅲa and Ⅲb with urea was also studied in order to test the pharmacological utilities of the product.

Fusion reaction of Ⅲa and Ⅲb with urea at 180~190° afforded crystalline products, Va and Vb, respectively. Infrared spectra of Va and Vb showed absorption bands at 1660~1680 cm^{-1} characteristic for amide groups and absence of absorption bands at 1180~1195 cm^{-1} in the region for ester. From the results of the infrared spectra and elementary analyses, Va and Vb are formulated as 1,3,8-triazabicyclo[4.4.0]decane-2,4,7-trione and 9-methyl-1,3,8-triazabicyclo[4.4.0]decane-2,4,7-trione. Treatment of Ⅲa with phenyl isocyanate in the presence of hydrochloric acid yielded phenyl derivative of V. The infrared spectrum of Vc showed three absorption bands at 1670, 1720 and 1775 cm^{-1} in the carbonyl region.

These reaction of the ethyl 2-piperazinone derivatives with urea could be performed without catalyst, while acid or base need to be generally used in the reaction of ethyl 2-piperidineacetate[3] or ethyl 1-methyl-3-piperazine carboxylate[5] with phenyl isocyanate or urethane.

Pharmacological studies will be reported at a later date.

Experimental*5

Reaction of 1,2-Propanediamine with Diethyl Fumarate——A solution of Ib (3.7 g.) in ether (30 ml.) was added, with stirring, to a solution of Ⅱ (8.6 g.) in ether (50 ml.). After the addition was completed, stirring was continued at room temperature for 3 hr. and then the yellow solution was allowed to stand overnight, after which it was concentrated *in vacuo* to afford a syrup. The syrup was distilled under reduced pressure. Colorless oil of $b.p_2$ 170~174° (7.6 g., 76%) was obtained. The oil solidified spontaneously on standing. TLC, Rf 0.43. IR $\lambda_{max}^{CHCl_3}$ cm^{-1} : 3390, 3280, 1720, 1180, 1670 and 1470.

The product was treated with phenyl isocyanate to give colorless prisms of m.p. 160~162° which showed no depression in a mixing test with phenylureido derivative of ethyl 6-methyl-2-oxo-3-piperazine acetate described below. IR λ_{max}^{KBr} cm^{-1} : 3325, 3215, 1710, 1670 and 1448. *Anal.* Calcd. for $C_{16}H_{21}O_4N_3$: C, 60.17; H, 6.63; N, 13.16. Found : C, 60.29; H, 6.62; N, 13.20.

*4 TLC : Silica gel plate, BuOH-AcOH-H_2O solvent, Detected by I_2 vapor.

*5 All melting points are uncorrected.

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Ethyl 6-Methyl-2-oxo-3-piperazine Acetate (IIIb)——A solution of 1-chloro-2-propanone oxime[6] (4.8 g.) in absolute ether (23 ml.) was added drop by drop to a solution of DL-diethyl aspartate[7] (17 g.) in absolute ether (110 ml.). The mixture was allowed to stand at room temperature for 5 days whereby the reaction was complete. The precipitated salt (10.0 g.) was filtered off and the filtrate was concentrated to about 50 ml. The solution was extracted three times with 15 ml. of 3*N* HCl. The combined extracts were washed with ether and then K_2CO_3 (10 g.) was added until the separation of yellow oil was completed. The oil was extracted repeatedly with ether and the combined extracts were washed with water and dried over anhydrous Na_2SO_4. The removal of the solvent gave diethyl N-(2-hydroxyiminopropyl)aspartate (VIII) as a crude oily product (8.5 g., 72.6% of theoretical amount) and it was used for the next reduction step without further purification. A solution of crude VIII (7.2 g.) in EtOH (120 ml.) was shaken with Raney Ni (2.0 g.) at an initial pressure of 100 kg./cm^2 of hydrogen. The reaction was allowed to proceed at room temperature for 4.5 hr. The catalyst was removed by filtration and the evaporation of the filtrate *in vacuo* afforded a syrup which was distilled under nitrogen stream to give ethyl 6-methyl-2-oxo-3-piperazine acetate (2.0 g., 36.3%), b.p$_2$ 172~174°, TLC, Rf 0.45. The infrared spectrum of this compound was identical with that of IIIb prepared by the reaction of Ib with II.

Ethyl 4-Phenylcarbamoyl-6-methyl-2-oxo-3-piperazine Acetate (IVb)——IIIb was treated with phenyl isocyanate in $CHCl_3$ yielding the phenylureido derivative. It was recrystallized from 10% aqueous EtOH to give colorless prisms (quantitative yield) m.p. 159~160.5°. IR λ_{max}^{KBr} cm^{-1} : 3325, 3210, 1710, 1670 and 1448. *Anal.* Calcd. for $C_{16}H_{21}O_4N_3$: C, 60.17; H, 6.63; N, 13.16. Found : C, 60.47; H, 6.84; N, 13.41.

1,3,8-Triazabicyclo[4.4.0]decane-2,4,7-trione (Va)——The mixture of IIIa (3 g.) and urea (1.9 g.) was heated at 180~190°. After about 10 min., the fused reaction mixture solidified. Heating at 180~190° was continued for 30 min. After cooling, the resultant solid was ground completely in 20 ml. of water. The crystalline substance was collected by filtration, washed with water and recrystallized from DMF to give colorless needles (1.28 g., 43.6%). The crystals became brown color at 280° and decompose at 300~305°. IR λ_{max}^{KBr} cm^{-1} : 3300, 3100, 1720, 1670 and 1458. *Anal.* Calcd. for $C_7H_9O_3N_3$: C, 45.90; H, 4.95; N, 22.94. Found : C, 45.97; H, 4.88; N, 23.51.

9-Methyl-1,3,8-triazabicyclo[4.4.0]decane-2,4,7-trione (Vb)——A mixture of IIIb (1.0 g.) and urea (0.6 g.) was treated in the same procedure as that described for Va to yield colorless needles (0.33 g., 35.4%), m.p. 270° (decomp.). IR λ_{max}^{KBr} cm^{-1} : 3200, 3050, 1720, 1665 and 1450. *Anal.* Calcd. for $C_8H_{11}O_3N_3$: C, 48.72; H, 5.62; N, 21.32. Found : C, 48.55; H, 5.83; N, 21.43.

3-Phenyl-1,3,8-triazabicyclo[4.4.0]decane-2,4,7-trione (Vc)——IIIa (3 g.) was slowly added to phenyl isocyanate (2.86 g.) at room temperature. After exothermic reaction ceased, the mixture was heated on a water-bath for 10 min. and 18% aqueous HCl (32 ml.) was added to the mixture. The product was, with stirring, heated at 110° for 1 hr., then made alkaline with an aqueous solution of NH_3 (25%). The reaction product was extracted several times with $CHCl_3$ and the combined extracts were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was recrystallized from EtOH to yield colorless needles (2.33 g., 56.1%), m.p. 255~256°. IR λ_{max}^{KBr} cm^{-1} : 3290, 3130, 1775, 1720, 1670, 1600, 1500, 1480 and 1440. *Anal.* Calcd. for $C_{13}H_{13}O_3N_3$: C, 60.22; H, 5.05; N, 16.21. Found : C, 60.45; H, 5.26; N, 16.47.

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