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49. **Masao Shimizu and Fumihiko Uchimaru**: Studies on N-Substituted Nortropane Derivatives. IV. The Robinson-Schöpf Condensation Using α-Amino Acids.

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In Part I of this sereis,[1] Robinson-Schöpf condensation using the esters of α-amino acids was reported and the structure of resulting compounds was clarified by reducing them with complex metal hydride, as described in Parts II and III.[2] In the course of this reduction, 3α-hydroxy-8-nortropaneacetic acid was obtained as a by-product. Because a compound possessing carboxyalkyl group in the nitrogen of 3-nortropanone skeleton has not yet been reported, Robinson-Schöpf condensation using α-amino acid itself was attempted. Glycine, DL-α-alanine and DL-methionine were used as amino acids.

The condensation was carried out in the same way as reported in Part I.[1] For the separation of products, however, it was assumed that the extraction method with chloroform is almost ineffective because of the solubility of products. Accordingly the precipitation of sparingly soluble reineckate was adopted and it was found to be very effective for this purpose. After the reaction mixture was adjusted to pH 7 and concentrated, the solution was adjusted to pH 2 with conc. hydrochloric acid and a solution of ammonium reineckate was added. The resulting crude reineckate was converted via its sulfate to hydrochloride according to the usual method. Further, this hydrochloride was purified as a free base through a column of ion exchange resin, Amberlite IR-4B.

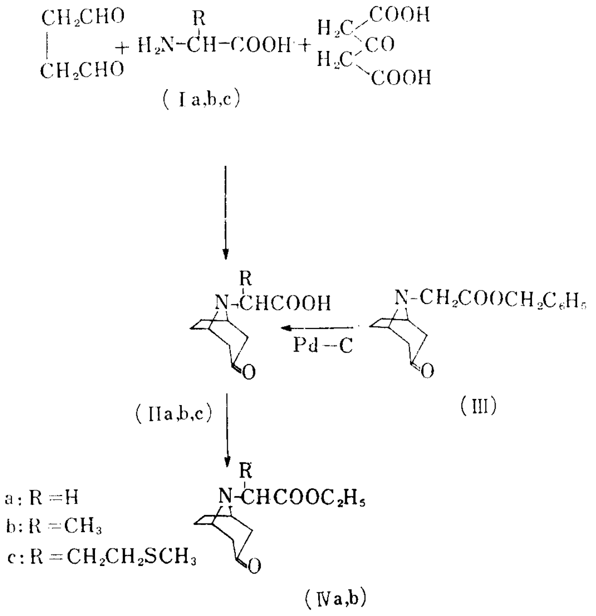

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Chart 1.

A condensation product of m.p. 159~161°, $C_9H_{13}O_3N$, was obtained from glycine. It showed absorptions at 1717 (six-membered ring ketone), 1631, and 1370 cm^{-1} (carboxylate ion) in its infrared spectrum. Consequently, this substance was considered to be the

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1) Part I. M. Shimizu, F. Uchimaru: This Bulletin, **9**, 300 (1961).

2) Part II. *Ibid.*, **9**, 304 (1961); Part III. *Ibid.*, **9**, 308 (1961).

desired keto-amino acid (Ⅱa). When this substance was esterified with ethanol and hydrochloric acid, and purified as its picrate, it was identical with the picrate of ethyl 3-oxo-8-nortropaneacetate (Ⅳa) reported in Part I, the structure of which was already determined. This compound was also obtained when benzyl 3-oxo-8-nortropaneacetate (Ⅲ) was debenzylated by reduction over palladium-charcoal. The identity of these two bases was confirmed by mixed fusion, infrared spectra, and Rf values in paper partition chromatography.

The foregoing facts proved that the structure of this condensation product is 3-oxo-8-nortropanecarboxylic acid (Ⅱa).

Entirely in the same way, the condensation with DL-α-alanine afforded colorless needles, m.p. 210~212°(decomp.), $C_{18}H_{22}O_{10}N_4$. From its infrared spectrum (Table I), the structure of this substance was presumed to be (Ⅱb) and this was confirmed by esterification to ethyl 3-oxo-α-methyl-8-nortropaneacetate (Ⅳb).

In the case of DL-methionine, a compound of m.p. 152~153°(decomp.) was obtained. Althogh the purification of this substance was somewhat difficult due to its unstability to heating, its structure was also presumed to be (Ⅱc) from its analytical and infrared spectral data (Table I).

Table I. Infrared Spectra of 3-Oxo-α-alkyl-8-nortropaneacetic acid (KBr tablet) (cm^{-1})

No.	Substituent at N N-R	Ketone	Active methylene	Methine			Carboxylate ion
		$\nu_{C=O}$	CO-CH_2-	$\nu_{HC\equiv}$	$\delta_{HC\equiv}$	C-N	ν_{C-O}
1	N-CH_2COOH	1715	1414	2890	(1326)	1004	1631 1370
2	$\text{N-CH}\langle{}^{\text{CH}_3}_{\text{COOH}}$	1726	1413	2895	1351	1001	1620 1374
3	$\text{N-CH}\langle{}^{\text{CH}_2\text{CH}_2\text{SCH}_3}_{\text{COOH}}$	1721	1402	2880	1358	996	1632 1373

Although the Robinson condensation has been regarded as a modification of Mannich reaction, very few cases using α-amino acid-type compounds have so far been reported concerning this reaction. Use of α-amino acid in Robinson-Schöpf condensation is considered to be an extension of this method.

Experimental*[2]

3-Oxo-8-nortropaneacetic Acid (IIa)——In accordance with 3-tropanone, a solution of 2.4 g. of succindialdehyde diethylacetal, 1.5 g. of glycine, 2.9 g. of acetonedicarboxylic acid, and 5.4 g. of AcONa in 100 cc. of distilled water (pH 4.6) was shaken at room temperature for 24 hr. (pH 7.8). After adjusting the pH to 7.0, the reaction mixture was extracted with $CHCl_3$-MeOH (extract 0.5 g., N, negative) and the aqueous layer was concentrated *in vacuo*. Separated inorganic salt was removed by filtration, the aqueous layer was acidified with conc. HCl (pH 2), and a solution of ammonium reineckate was added. The crude reineckate (1.76 g., 34%) was converted via its sulfate to the hydrochloride (m.p. 157~159°(decomp.)) by the usual method. Conversion of the hydrochloride to the free base by passage through a column of ion exchange resin (Amberlite IR-4B) afforded colorless needles (from iso-PrOH), m.p. 159~161°(decomp.). *Anal.* Calcd. for $C_9H_{13}O_3N$: C, 59.00; H, 7.15; N, 7.65. Found : C, 59.50; H, 6.86; N, 7.88.

Esterification of (IIa)——Dry HCl-gas was bubbled through a suspension of 70 mg. of (Ⅱa) in 10 cc. of EtOH and saturated with cooling for 20 min. The mixture was refluxed for 3 hr. in a water bath, allowed to stand overnight, and evaporated to dryness *in vacuo*, leaving 160 mg. of a crystalline residue. The crude base was converted to the picrate of m.p. ca. 130°(140 mg., 83%), purified by recrystallization from H_2O, yielding yellow plates, m.p. 145~146°. The melting point of the mixture with the picrate of ethyl 3-oxo-8-nortropaneacetate (Ⅳa) showed no depression. *Anal.* Calcd. for $C_{17}H_{20}O_{16}N_4$: C, 46.36; H, 4.58; N, 12.72. Found : C, 46.06; H, 4.21; N, 12.83.

Debenzylation of Benzyl 3-Oxo-8-nortropaneacetate (III)——Hydrogenation of 0.98 g. of (Ⅲ) in 20 cc. of EtOH was carried out in the presence of Pd-C (prepared from 30 cc. of 1% $PdCl_2$ and 0.4 g.

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*[2] All melting points are uncorrected.

of Norit). After absorption of 105 cc. of H_2 (1.15 moles), the catalyst was filtered off and the solution was evaporated *in vacuo* to give 0.5 g. (73%) of colorless plates, m.p. 150~153° (decomp.). Recrystallization from iso-PrOH yielded colorless needles, m.p. 162~163° (decomp.). *Anal.* Calcd. for $C_9H_{13}O_3N$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.99; H, 7.21; N, 7.78.

Infrared spectrum and mixed m.p. determination confirmed the identity of the product with (IIa) obtained as above. These two substances also showed the same Rf value (0.66, 0.67) in paper partition chromatography using a mixture of BuOH-AcOH-H_2O (4:1:5).

(±) **3-Oxo-α-methyl-8-nortropaneacetic Acid (IIb)**——In entirely the same way as in the case of (IIa), a solution of 4.8 g. of succindialdehyde diethylacetal, 3.6 g. of DL-alanine, 5.8 g. of acetonedicarboxylic acid, and 10.9 g. of AcONa in 200 cc. of distilled H_2O was shaken at room temperature for 26 hr. The reaction mixture was treated as above and yielded 3.6 g. (34%) of crude reineckate. Free base: Colorless prisms (from MeOH-iso-PrOH), m.p. 210~212° (decomp.). *Anal.* Calcd. for $C_{10}H_{15}O_3N$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.43; H, 7.25; N, 7.43.

Esterification of (IIb)——Dry HCl-gas was bubbled and saturated in a suspension of 100 mg. of (IIb) in 15 cc. of EtOH with ice-cooling for 20 min. The mixture was refluxed in a water bath for 3 hr. and evaporated *in vacuo* to dryness. The residue was converted to the picrate and yielded 190 mg. (82%) of yellow crystals, m.p. 124~126°. Repeated recrystallization from MeOH-Et_2O gave yellow needles of m.p. 131~133°, which was identical with the picrate of (IVb) in mixed fusion. *Anal.* Calcd. for $C_{18}H_{22}C_{10}N_4$: C, 47.58; H, 4.88; N, 12.33. Found: C, 48.28; H, 4.67; N, 12.33.

(±) **3-Oxo-α-(2-methylthioethyl)-8-nortropaneacetic Acid (IIc)**——A solution of 4.8 g. of succindialdehyde diethylacetal, 6.0 g. of DL-methionine, 5.8 g. of acetonedicarboxylic acid, and 10.9 g. of AcONa in 200 cc. of distilled H_2O was shaken at room temperature for 26 hr., the mixture, after being treated in a similar manner (recovery of unreacted DL-methionine, 33%), afforded 4.9 g. (41%) of crude reineckate. Free base: Gray crystals (from iso-PrOH), m.p. 152~153° (decomp.), S, positive. *Anal.* Calcd. for $C_{21}H_{19}O_3NS \cdot \frac{1}{2}H_2O$: C, 54.11; H, 7.57; N, 5.22. Found: C, 54.65; H, 7.16; N, 5.22.

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Summary

The Robinson-Schöpf condensation was corried out with α-amino acid itself. Structure of the products thereby obtained were established by identification with already obtained compounds and through their infrared spectra.

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