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46. Masao Shimizu and Fumihiko Uchimaru: Studies on N-Substituted Nortropane Derivatives. I. Synthesis of N-Substituted 3-Nortropanones by the Robinson-Schöpf Condensation.

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3-Tropanone (tropinone[*2]), the starting material for synthesis of tropane alkaloids was synthesized by Robinson[1] by a one-step process in 1917, and later Schöpf[2] modified this method under biological condition. These works were the first of the hypotheses in the field of alkaloid biogenesis. After that, this condensation method was applied to the syntheses of various alkaloids, e.g. meteloidine,[3] valeroidine,[4] etc. The authors have attempted to synthesize various N-substituted nortoropane derivatives in order to compare their pharmacological action with that of natural tropane alkaloids. In this paper, the Robinson-Schöpf condensation using the esters of α-amino acids is mainly described.

The Robinson-Schöpf condensation consists in preparing 3-tropanone with succindialdehyde, acetonedicarboxylic acid, and methylamine in a comparatively good yield under biological conditions of temperature, dilution, and pH. It has been reported that alkyl,[5] hydroxyalkyl,[5] benzyl,[5] and aromatic and heterocyclic amines[6] are used as the basic component in this condensation, but no case has been known to use the esters of α-amino acids. For the conditions of condensation referring to the descriptions of Keagle and Hartung,[5] and Stoll, *et al.*,[6] syntheses of 3-tropanone with methylamine hydrochloride, 3-nortropanone[7] with ammonium chloride, and 8-(2-hydroxyethyl)-3-nortropanone with ethanolamine were examined. Among the other components, acetonedicarboxylic acid was prepared from citric acid by the usual method.[8] For preparation of succindialdehyde, the method from pyrrole[9] and furan[6] has been reported but the synthesis of its acetal from acetylene was effectively adopted according to the method of Preobrashenski[10] or Wibaut.[11] The method is effected in a fairly good yield although the intermediate, acetylenedicarboxaldehyde bis(diethylacetal), is somewhat unstable (Tables I and II). While reduction in the last step was made at 20°

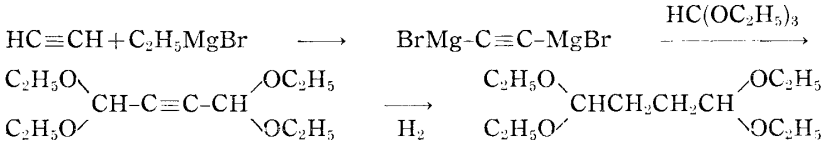

Chart 1.

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*2 For traditional nomenclature see G. Fodor, K. Nádor: J. Chem. Soc., **1953**, 721. The present one follows the I.U.P.A.C. rules.

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11) J.P. Wibaut, A.L. van Hulsenbeck, C.M. Siegmann: Proc. Koninkl. Ned. Akad. Wetenschap., **53**, 989 (1950) (C.A., **45**, 5167 (1951)).

Table I. Syntheses of Acetylenedicarboxaldehyde Bis(diethylacetal)

Expt. No.	EtMgBr (mole)	Reaction period with Acetylene (hr.)	Reaction period with $HC(OEt)_3$ (hr.)	Yield* (%)
1	0.58	11	7.5	34.6
2	1.75	11	6.0	69.7
3	1.76	10	7.0	74.3
4	2.95	10	8.0	83.4
5	2.95	10	8.0	82.8
6	2.95	9	8.5	79.6

* The yield was calculated on the amount of reacted ethyl orthoformate.

Table II. Syntheses of Succindialdehyde Bis(diethylacetal)

Expt. No.	Starting material (g.)	H_2 mole	H_2 time (hr.)	Raney nickel (cc.)	Raney nickel (days)*	Product n_D (°C)	Product Yield (%)
1	12.6	2.15	8	2	1	1.4180 (26)	84.3
2	13.0	2.08	17	2+2	9	1.4216 (26)	77.9
3	20.7	2.05	19	4+2	2	1.4226 (21)	91.6
4	60.0	2.17	11	12+4	9	1.4230 (16)	91.7
5	111.0	2.25	18	10+4	1	1.4214 (16)	90.2
6	49.1	2.55	10	10	9	1.4224 (16)	88.3

* Number of days after preparation of the catalyst. The speed of hydrogen absorption differs markedly between 1 and 2 moles while the catalyst is fresh.

and 100 atm. pressure by Wibaut[11] the desired product was obtained in about 90% yield using Raney Nickel W-5 as a catalyst at room temperature and normal pressure. The acetal is a stable compound and can be preserved for a long time without any appreciable change.

The condensation reaction was carried out as follows : To a succindialdehyde solution, prepared from the bis-diethylacetal by shaking with 0.5% sulfuric acid solution, acetonedicarboxylic acid and amine hydrochloride were added, and buffered with sodium acetate to pH 4.6~5.2. After dilution with water, the mixture was shaken at room temperature for several days. The longer the shaking time, the better was the yield. The reaction mixture was basified with potassium hydroxide and extracted exhaustively with chloroform. The yield was calculated on the amount of eluate from alumina chromatography. All the products of attempted condensation showed strong infrared absorptions ascribed to a six-membered ring ketone.*3 Examples of condensation carried out are shown in Table III.

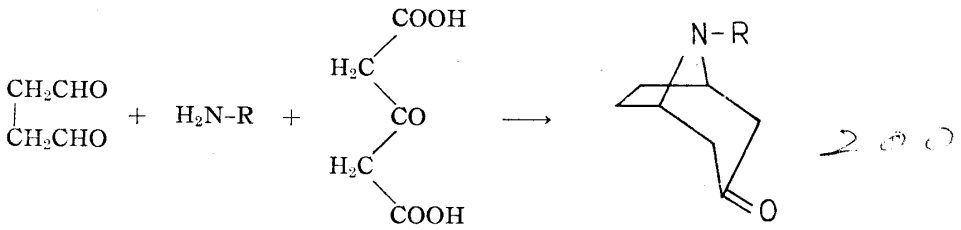

Chart 2.

The structures of 8-(1-alkoxycarbonylalkyl)-3-nortropanones obtained in this work were further confirmed by identification with the known compounds derived from 3-tropanone (tropinone). These will be reported in a subsequent paper.

*3 More detailed results will be shown in a subsequent paper.

Table III. Robinson-Schöpf Condensation

Expt. No.	Amine R-NH_2	Acetal (g.)	Shaking time (hr.)	Reaction time (days)	Eluted product (g.)	Eluted product (%)
1	NH_4·Cl	2.4	10	7	0.58	45.2
2	Methylamine hydrochloride	4.8	11	3	1.84	64.6
3		9.6	33	5	4.17	73.2
4		28.8	40	11	11.0	64.3
5		19.2	40	6	8.00	70.2
6		28.8	32	6	14.2	83.2
7	Ethanolamine	2.4	2	3	0.62	36.2
8		4.8	1.5	4	0.87	25.4
9		9.6	19	4	4.74	69.3
10	Glycine methyl ester hydrochloride	9.6	33	6	6.16	76.3
11	Glycine ethyl ester hydrochloride	2.4	0	3	0.64	29.6
12		6.0	14	4	2.25	41.6
13		9.6	22	4	6.00	69.3
14		4.8	22	5	2.73	63.2
15	Glycine benzyl ester hydrochloride	2.4	27	4	1.12	42.2
16	DL-Alanine ethyl ester hydrochloride	2.4	25	4	1.51	65.5
17	DL-Methionine ethyl ester hydrochloride	2.4	19	4	2.70	92.4

Experimental*4

Succindialdehyde Bis(diethylacetal)——EtMgBr, prepared from 42 g. of Mg and 192 g. of EtBr in Et_2O, was bubbled with purified acetylene for 11 hr. and 270 g. of ethyl orthoformate was added. The resulting mixture was reacted in benzene for 6 hr. at 55~60° (inner temp.). The reaction product was decomposed by adding cold, satd. solution of $AcONH_4$, extracted with Et_2O, and the extract was dried over Na_2SO_4 and evaporated. The residue was distilled *in vacuo* and yielded 67 g. (24.8% recovery) of ethyl orthoformate and 110 g. (69.7%) of colorless liquid, b.p_4 109~111°. This liquid was immediately hydrogenated over Raney Ni W-5 (14 cc.) in EtOH at room temperature and 2.25 mol. equiv. of H_2 was taken up in 18 hr. After filtration of the catalyst and evaporation of the solvent, the residue was distilled *in vacuo* to leave 101.2 g. of colorless liquid, b.p_6 97~101° (90.2%). n_D^{16} 1.4214. IR $\nu_{max}^{liq.}$ cm^{-1} : 1125, 1063 (ν_{C-O}).

3-Tropanone——To a solution of succindialdehyde, prepared by shaking 9.6 g. of bis-diethylacetal with 0.5% H_2SO_4 for 2 hr., methylamine hydrochloride (5.4 g.), acetonedicarboxylic acid (11.7 g.), and AcONa (21.8 g.) were added, the volume of the mixture was made up to 400 cc. (pH 4.0) by dilution with distilled water, and the mixture was allowed to stand at room temperature for 5 days with occasional shaking (total, 33 hr.) (pH 4.4). The resulting solution was made alkaline with KOH while cooling, saturated with NaCl, and extracted thoroughly with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residue (13.0 g.) was chromatographed on alumina (100 g.) and the fraction (5.75 g.) eluted with Et_2O crystallized to plates (73.2%), m.p. 40~43°, b.p_9 97~100°.
Picrate : Yellow needles (from H_2O), m.p. 217~219°. *Anal.* Calcd. for $C_{14}H_{16}O_8N_4$: C, 45.65; H, 4.38; N, 15.21. Found : C, 46.17; H, 4.61; N, 15.39.
Methiodide : Colorless prisms (from MeOH-Me_2CO), m.p. 273~274° (decomp.). *Anal.* Calcd. for $C_9H_{16}ONI$: C, 38.45; H, 5.74; N, 4.98. Found : C, 38.53; H, 5.61; N, 4.48.

N-Substituted 3-Nortropanones——The 3-tropanones listed in Table III were prepared in accordance with 3-tropanone.

3-Nortropanone——Picrate : Yellow plates (from H_2O), m.p. 167~169°. *Anal.* Calcd. for $C_{13}H_{14}O_8N_4$: C, 44.07; H, 3.98; N, 15.82. Found : C, 44.28; H, 4.04; N, 15.89.

8-(2-Hydroxyethyl)-3-nortropanone——Faintly yellow oil, b.p_4 150~153°.
Picrate : Yellow prisms (from H_2O), m.p. 172~174°. *Anal.* Calcd. for $C_{15}H_{18}O_9N_4$: C, 45.23; H, 4.55; N, 14.07. Found : C, 45.07; H, 4.44; N, 14.14.
Methiodide : Colorless plates (from MeOH-Me_2CO), m.p. 215~217°. *Anal.* Calcd. for $C_{10}H_{18}O_2NI$: C, 38.60; H, 5.84; N, 4.50. Found : C, 38.48; H, 5.70; N, 4.66.

*4 All m.p.s are uncorrected.

Methyl 3-Oxo-8-nortropaneacetate——Picrate : Yellow prisms (from H_2O), m.p. 159~160°(decomp.). *Anal.* Calcd. for $C_{16}H_{18}O_{10}N_4$: C, 45.07; H, 4.26; N, 13.14. Found : C, 44.78; H, 4.29; N, 13.52.

Ethyl 3-Oxo-8-nortropaneacetate——Picrate : Yellow prisms (from H_2O), m.p. 146~147°. *Anal.* Calcd. for $C_{17}H_{20}O_{10}N_4$: C, 46.36; H, 4.58; N, 12.72. Found : C, 46.52; H, 4.59; N, 12.71.

Benzyl 3-Oxo-8-nortropaneacetate——Picrate : Yellow plates (from iso-PrOH), m.p. 162~163°. *Anal.* Calcd. for $C_{22}H_{22}O_{10}N_4$: C, 52.59; H, 4.41; N, 11.15. Found : C, 52.41; H, 4.23; N, 11.34.

Ethyl (±) 3-Oxo-α-methyl-8-nortropaneacetate——Picrate : Yellow needles (from MeOH-Et_2O), m.p. 133~135°. *Anal.* Calcd. for $C_{18}H_{22}O_{10}N_4$: C, 47.58; H, 4.80; N, 12.33. Found : C, 47.53; H, 5.07; N, 12.31.

Ethyl (±) 3-Oxo-α-(2-methylthioethyl)-8-nortropanone—Free base : Yellow oil, S, positive, somewhat unstable, and colors on exposure to air. Picrate and methiodide did not crystallize. IR $\nu_{max}^{liq.}$ cm^{-1}: 1725 (six-membered ring ketone), 1739 (ester).

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Summary

Several new N-substituted 3-nortropanones were prepared by the Robinson-Schöpf condensation using the esters of α-amino acids. The compounds obtained were characterized as their picrates after purification by alumina chromatography and their structure confirmed through their infrared spectra.

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