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58. Bunji Shimizu, Akira Ogiso, and Issei Iwai*[1] : An Approach to Synthesis of Diterpenoid Alkaloids. I. Mannich Reaction of 2,6-Disubstituted Cyclohexanone.

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Recently, some 4-piperidone derivatives were synthesized from keto-compounds by Mannich reaction using two moles of formaldehyde and one mole of methylamine. While Anet *et al.*[1] prepared diethyl 3-methyl-8-oxo-3-azabicyclo[3.2.1]octane-1,5-dicarboxylate (I) from diethyl 2-oxo-cyclopentane-1,3-dicarboxylate, Blicke *et al.*[2] obtained 3-methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylic esters (II) from 2-oxo-cyclohexane-1,3-dicarboxylic esters by Mannich reaction. In these cases, it is seen that both α and α' carbon atoms of the keto-group are activated by carboxylic groups.

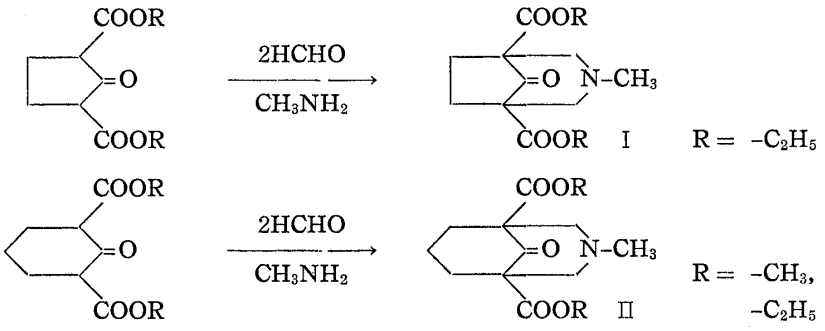

Chart 1.

In this paper we intend to report the preparation of new asymmetric methyl-azabicyclononanone compounds which are valuable starting materials for the synthesis of a diterpenoid alkaloid nucleus.[3] First of all, the ring formation of a cyclohexanone compound having only one carboxylic group at α-position of a keto group was investigated. Ethyl 2-oxo-cyclohexanecarboxylate (III) was condensed with two moles of formaldehyde and one mole of methylamine by Mannich reaction to give an oily basic product (IV) which showed absorptions at 2770 cm^{-1} ($N-CH_3$ piperidine type), 1730 cm^{-1} (COOEt) and 1718 cm^{-1} (C=O in a six-membered ring) in the infrared spectrum. IV was hydrolyzed to the corresponding free acid V, which was then decarboxylated with 50% sulfuric acid to give VI as colorless prisms, m.p. 14~15°. The infrared spectrum of VI did not exhibit any absorption of an ester group, but there were observed absorptions at 2770 cm^{-1} ($N-CH_3$ piperidine type) and 1724 cm^{-1} (C=O). Results of the elemental analysis of VI were in agreement with the calculated values for $C_9H_{15}ON$, and its structure was further confirmed by the following experimental facts. 3-Methyl-9-oxo-3-azabicyclo-[3.3.1]none-1,5-dicarboxylic acid (VII) (m.p. 134~136°) prepared by Blicke's method was decarboxylated to 3-methyl-3-azabicyclo[3.3.1]nonan-9-one (VI'), m.p. 14~15°, which formed a semicarbazone, m.p. 215~216°, undepressed by admixture with that of VI. The infrared spectra of both VI and VI' were also identical.

Next, a similar ring formation reaction was carried out on ethyl 2-oxo-3-methyl-cyclohexanecarboxylate (VIII) in which a methyl group was substituted at the position

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1) E.F.L.J. Anet, G.K. Hughes, D. Marmior, E. Ritchie : Australian J. Sci. Research, Ser. A., **3**, 330 (1950).
2) F.F. Blicke, F.J. McCarty : J. Org. Chem., **24**, 1379 (1959).
3) I. Iwai, A. Ogiso, B. Shimizu : Chem. & Ind. (London), **1962**, 1288.

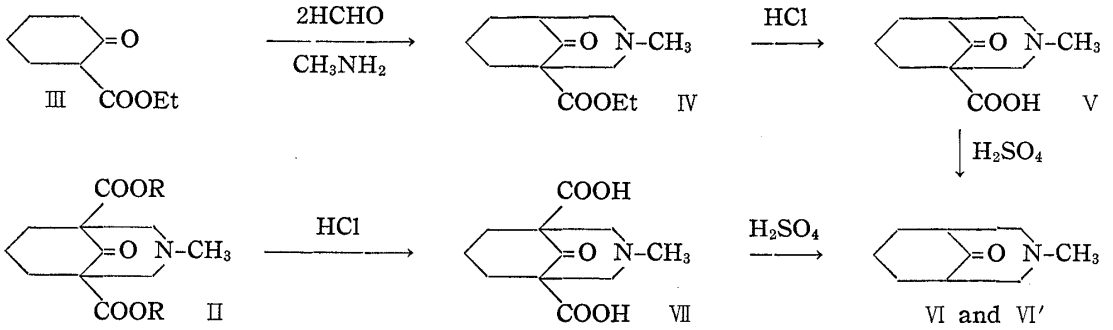

Chart 2.

adjacent to the keto-group. In this case, ethyl 1,3-dimethyl-9-oxo-3-azabicyclo[3.3.1]-nonane-5-carboxylate (IX) was obtained in a 78% yield. The infrared spectrum of IX showed absorptions at 2770 cm^{-1} ($N-CH_3$ piperidine type) and at 1715 cm^{-1} (C=O). IX gave a hydrochloride as colorless needles, m.p. 212~213° (decomp.), which was hydrolyzed with hydrochloric acid to give a hydrochloride of the corresponding free acid X (m.p. 206~208° (decomp.)).

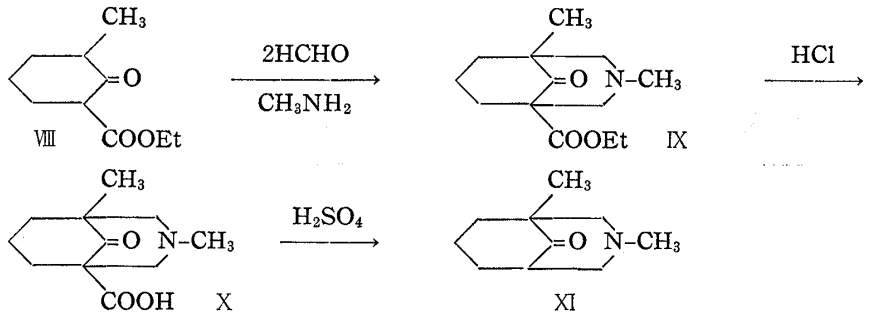

Chart 3.

When X was refluxed with 50% surfuric acid, an oily product of 1,3-dimethyl-3-azabicyclo[3.3.1]nonan-9-one (XI) was obtained, which did not show any absorption due to a carboxylic group but absorptions at 2770 cm^{-1} ($N-CH_3$ piperidine type) and at 1721 cm^{-1} (C=O) in the infrared spectrum. XI gave a hydriodide as colorless needles, m.p. 214~216° (decomp.). Guha obtained cyclohexanone[4] by carboethoxycyclohexanone with 50% sulfuric acid. Under this condition, however, IX afforded only a mixture of IX and XI without formation of an acidic substance X. It is evident that the carboxylic ester was not perfectly hydrolyzed but the resulted free acid was immediately decarboxylated.

Finally, we attempted to synthesize azabicyclononanone derivatives by the same condensation from keto compounds having no carboxylic group at the α-position. As the keto compounds, 2-methoxyphenyl-6-methylcyclohexanones (XIVa, b) were used, which were expected to furnish valuable azabicyclononanone derivatives for the synthesis of a diterpenoid alkaloid nucleus.

2-(*p*-Methoxyphenyl)cyclohexanone[5] (XIIIa) was treated with ethyl formate to give a 6-formyl derivative which was catalytically hydrogenated to XIVa, m.p. 74~75° in the presence of palladium-charcoal. A similar ring formation was carried out on the compound XIVa, whereby there was obtained an oily product of XVa which formed a hydrochloride (m.p. 230~231° (decomp.)) and a picrate (m.p. 188~189° (decomp.)).

4) P.C. Guha, N.K. Seshadrienger: Ber., **69**, 1207 (1936).
5) W.E. Bachmann, G.I. Fujimoto, L.B. Wick: J. Am. Chem. Soc., **72**, 1995 (1950).

Furthermore, a similar ring formation reaction was successfully carried out on 2-(*m*-methoxyphenyl)-6-methylcyclohexanone (XIVb) which was derived from 2-(*m*-methoxyphenyl)cyclohexanone (XIIb).[5] The azabicyclononanone derivative XVb thus obtained was an oil, but gave a hydrochloride (m.p. 224~226° (decomp.)) and a picrate (m.p. 173~175° (decomp.)). The elemental analyses of these derivatives were in good agreement with those calculated. The infrared spectrum of XVb showed absorptions at 2780 cm^{-1} ($N-CH_3$ piperidine type) and at 1718 cm^{-1} (C=O), but no absorptions in the NH region. The nuclear magnetic resonance spectrum of XVa exhibited a singlet at 9.10 τ, which indicated that the methyl group is present as $\geqslant C-CH_3$. The band due to the $\rangle N-CH_3$ group appeared at 7.07 τ, and its intensity corresponds to three protons.

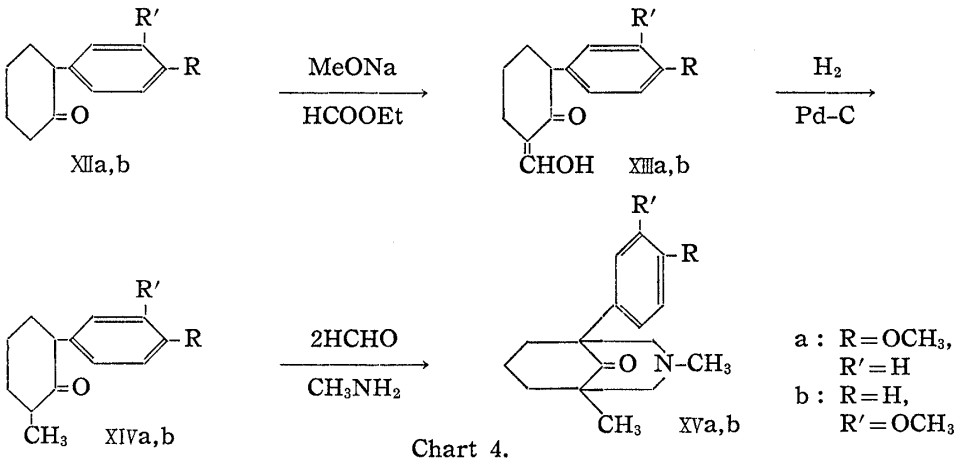

Chart 4.

Experimental

3-Methyl-3-azabicyclo[3.3.1]nonan-9-one (VI)——a) A solution of 0.3 g. of 3-methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylic acid hydrochloride (VII) in 2 cc. of 50% H_2SO_4 was refluxed on an oil bath for 6 hr. The bath temperature should be maintained at 140~150°. After cooling and washing with Et_2O, the acidic solution was made alkaline with 20% NaOH under ice cooling, and extracted three times with Et_2O. The combined extracts were washed with saturated NaCl-solution, dried over Na_2SO_4 and evaporated to dryness *in vacuo* (2 mm. Hg). After 0.16 g. of the oily residue were allowed to stand overnight in a refrigerator, pale yellow needles of VI' were obtained. An analytical sample was recrystallized from light petroleum to show m.p. 14~15°. IR in CCl_4 cm^{-1} : ν_{C-H} 2770; $\nu_{C=O}$ 1724. *Anal.* Calcd. for $C_9H_{15}ON$: C, 70.55; H, 9.87. Found : C, 70.21; H, 10.05.

b) A mixture of 6.0 g. (0.035 mole) of ethyl cyclohexanone-2-carboxylate (III), 5.7 g. (0.07 mole) of 37% HCHO, 4.3 g. (0.035 mole) of 25% CH_3NH_2 and 15 cc. of EtOH was stirred at 35° for 24 hr. After the EtOH was removed *in vacuo*, the reaction mixture was extracted with Et_2O. The Et_2O layer was shaken with dil. HCl. The acidic solution was made alkaline with 10% NaOH under ice cooling and extracted with Et_2O. The extracts were washed with H_2O, and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* gave 7.2 g. of ethyl 3-methyl-9-oxo-3-azabicyclo[3,3,1]nonane-1-carboxylate (IV). IR in CCl_4 cm^{-1} : ν_{C-H} 2770; ν_{COOR} 1730; $\nu_{C=O}$ 1718.

The ester IV was hydrolyzed with 25% HCl to the carboxylic acid V. V was then decarboxylated with 50% H_2SO_4 to give an oily product which was crystallized from light petroleum to give VI as pale yellow crystals, m.p. 14~15°. The IR spectrum of VI was identical with that of VI'.

Semicarbazone of VI; colorless needles, m.p. 215~216° (decomp.), from aq. EtOH. *Anal.* Calcd. for $C_{10}H_{18}ON_4$: C, 57.11; H, 8.63. Found : C, 57.18; H, 8.46. 2,4-Dinitrophenylhydrazone of VI; orange needles, m.p. 180~182° (decomp.), from EtOH. *Anal.* Calcd. for $C_{15}H_{19}O_4N_5$: C, 54.04; H, 5.75. Found : C, 53.81; H, 5.72. Thiosemicarbazone of VI; colorless prisms, m.p. 192~193° (decomp.), from aq. EtOH. *Anal.* Calcd. for $C_{10}H_{18}SN_4$: C, 53.08; H, 8.02. Found : C, 52.91; H, 8.14.

Ethyl 1,3-Dimethyl-9-oxo-3-azabicyclo[3.3.1]nonane-5-carboxylate Hydrochloride (IX)——A solution of 5.2 g. (0.028 mole) of ethyl 2-oxo-3-methylcyclohexanecarboxylate (VIII), 3.5 g. (0.028 mole) of 25% CH_3NH_2, 4.5 g. (0.056 mole) of 37% HCHO and 10 cc. of EtOH was worked up in the same way as described in the case of IV. Dry HCl gas was bubbled into the Me_2CO solution of the oily free base IX. After concentrating, the solution was allowed to stand in an ice bath. The precipitated HCl-salt weighed 7.4 g. (m.p. 202°) which was recrystallized from MeOH-Me_2CO to give colorless needles, m.p. 212~213° (decomp.). *Anal.* Calcd. for $C_{13}H_{22}O_3NCl$: C, 56.65; H, 7.98. Found : C, 56.18; H, 7.89.

1,3-Dimethyl-9-oxo-3-azabicyclo[3.3.1]nonane-5-carboxylic Acid Hydrochloride (X)——A solution of 1.2 g. of ethyl 9-oxo-1,3-dimethyl-3-azabicyclo[3.3.1]nonane-5-carboxylate (IX) in 6 cc. of 25% HCl was refluxed for 2 hr. After cooling and filtering, the reaction mixture was concentrated *in vacuo* to a half volume, and allowed to stand at room temperature. The resulting crystals were washed with EtOH and recrystallized from MeOH to obtain 0.81 g. of needles, m.p. 206~208° (decomp.). *Anal.* Calcd. for $C_{11}H_{18}O_3NCl$: C, 53.35; H, 7.27. Found: C, 53.26; H, 7.12.

1,3-Dimethyl-3-azabicyclo[3.3.1]nonan-9-one Hydriodide (XI)——A solution of 1.1 g. of 1,3-Dimethyl-9-oxo-3-azabicyclo[3.3.1]nonane-5-carboxylic acid hydrochloride (X) in 7 cc. of 50% H_2SO_4 was refluxed on an oil bath for 6 hr. (bath temperature should be maintained at 140~150°). After cooling, the solution was washed with Et_2O. The acidic solution was made alkaline with 20% NaOH under ice cooling and extracted with Et_2O. The ethereal extracts were washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. After 2 drops of 57% HI were added to the solution of the oily residue in dry Me_2CO, the solvent was removed to leave a viscous oil. The oil was treated with a small amount of Me_2CO-Et_2O and the solution allowed to stand overnight in a refrigerator. The precipitated hydriodide weighed 0.73 g. which was recrystallized from Me_2CO-MeOH to give white needles. (m.p. 214~216°). IR in $CHCl_3$ cm^{-1}: ν_{C-H} 2770; $\nu_{C=O}$ 1721. *Anal.* Calcd. for $C_{10}H_{18}ONI$: C, 40.70; H, 6.10. Found: C, 40.30; H, 5.80.

2-(*p*-Methoxyphenyl)-6-methylcyclohexanone (XIVa)——To a suspension of MeONa, freshly prepared from 6.9 g. of Na and MeOH, in 150 cc. of dry benzene was added dropwise a solution of 16 cc. of ethyl formate in 30 cc. of dry benzene with vigorous stirring in a nitrogen atmosphere. Stirring was continued for an additional 2 hr. at room temperature. A solution of 30 g. of 2-(*p*-methoxyphenyl)-cyclohexanone in 150 cc. of dry benzene was then slowly added at 0~5°. After addition of 200 cc. of benzene, stirring was continued for 14 hr. at room temperature. The reaction mixture was poured into 500 cc. of ice-water and the organic layer was removed. The aq. layer was washed with Et_2O, neutralized with HCl and extracted with Et_2O. The ethereal extracts were dried over Na_2SO_4 and evaporated to dryness *in vacuo*. 30 g. of 2-(*p*-methoxyphenyl)-6-hydroxymethylene-cyclohexanone (XIIIa) was obtained as a crude oil which was hydrogenated with 6 g. of 10% Pd-C in 300 cc. of EtOH. About 2 moles of H_2 were absorbed. After the catalyst was filtered, the solvent was removed. Recrystallization of the residue from hexane gave 26 g. of colorless needles (m.p. 74~75°). UV λ_{max}^{EtOH} mμ (ε): 224 (11,400), 275 (1,660), 281.5 (1,390). IR in CCl_4: $\nu_{C=O}$ 1724 cm^{-1}. *Anal.* Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.25; H, 8.19.

5-(*p*-Methoxyphenyl)-1,3-dimethyl-3-azabicyclo[3.3.1]nonan-9-one (XVa)——A mixture of 20 g. of 2-(*p*-methoxyphenyl)-6-methylcyclohexanone (XIVa), 10.2 cc. of 28% CH_3NH_2, 14.1 cc. of 39% HCHO and 50 cc. of EtOH was refluxed for 24 hr. After cooling, the mixture was poured into H_2O and extracted with Et_2O. Then the Et_2O solution was washed with H_2O, and shaken with dil. HCl. The separated acidic aqueous. layer was made alkaline with NH_4OH and extracted with Et_2O. The ethereal extracts were washed with H_2O, dried over Na_2SO_4 and evaporated, leaving 21 g. of a basic oil. By the usual method, the oil was converted into a crystalline hydrochloride which was recrystallized from MeOH to give 20 g. of colorless prisms, m.p. 230~231°. UV λ_{max}^{EtOH} mμ (ε): 223.5 (12,200), 272.5 (1,450), 279.5 (1,240). IR in $CHCl_3$ cm^{-1}: $\nu_{C=O}$ 1720; ν_{C-H} 2780. *Anal.* Calcd. for $C_{17}H_{24}O_2NCl$: C, 65.89; H, 7.81; N, 4.52. Found: C, 66.07; H, 7.61; N, 4.57. Picrate: m.p. 188~189° (decomp.). *Anal.* Calcd. for $C_{23}H_{26}O_9N_4$: C, 54.97; H, 5.22; N, 11.15. Found: C, 54.86; H, 4.92; N, 11.23.

2-(*m*-Methoxyphenyl)-6-methylcyclohexanone (XIVb)——From 30 g. of 2-(*m*-methoxyphenyl)-cyclohexanone and 16 cc. of ethyl formate, there was obtained 14 g. of crude 2-(*m*-methoxyphenyl)-6-hydroxymethylenecyclohexanone by the same procedure as described in XIIIa. The product XIIIb was pure enough for the next step. 14 g. of 2-(*m*-methoxyphenyl)-6-hydroxymethylenecyclohexanone was hydrogenated by the same method as XIVa to obtain a pale yellow oil. The yield of XIVb was 12 g. $b.p_{0.1}$ 120~126°. IR in $CHCl_3$: $\nu_{C=O}$ 1720 cm^{-1}.

5-(*m*-Methoxyphenyl)-1,3-dimethyl-3-azabicyclo[3.3.1]nonan-9-one (XVb)——The oily compound XVb was prepared from XIVb in the same manner as XVa. On treatment with HCl, it gave a crystalline hydrochloride, which was recrystallized from Me_2CO to give colorless needles, m.p. 224~226° (decomp.) IR in $CHCl_3$ cm^{-1}: $\nu_{C=O}$ 1718; ν_{C-H} 2780. *Anal.* Calcd. for $C_{17}H_{24}O_2NCl$: C, 65.89; H, 7.81. Found: C, 65.75; H, 7.89.

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Summary

Cyclohexanone derivatives, having one or no carboxylic group at α-position of the keto group, were allowed to react by Mannich reaction to give azabicyclononanone compounds. Of these compounds 5-(*m*- or *p*-methoxyphenyl)-1,3-dimethyl-3-azabicyclo-[3.3.1]nonan-9-one is a valuable starting material for the synthesis of a diterpenoid alkaloid nucleus.

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