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47. Wataru Nagata and Ikuo Kikkawa : Angular Substituted Polycyclic Compounds. VIII.*1 Synthesis of *trans*-9-Methyl-2-decalone and *trans*-9-Aminomethyl-2-decalone from *trans*-2-Oxo-9-decalincarbonitrile.

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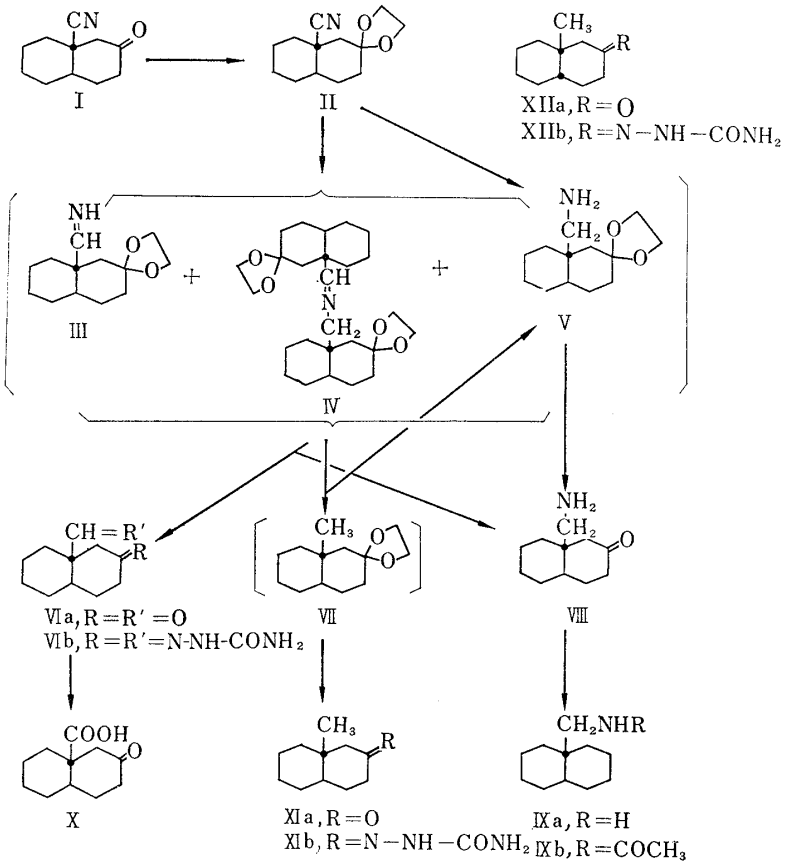
In a previous paper*1 we reported the highly stereospecific synthesis of *trans*-2-oxo-9-decalincarbonitrile (I) by cyanation of $\Delta^{1,9}$-2-octalone (4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone). The present paper describes the conversion of this angularly situated cyano group into other functional groups.

The smooth conversion of the angularly introduced cyano group into other groups is, in general, of special importance in synthesizing the natural products, such as terpenoids, steroids, and alkaloids. This conversion was already studied in the tetracyclic series,[1] and the stepwise reduction of *trans*-oxonitrile ethyleneketal to the imide with an excess of lithium aluminium hydride was found to be a convenient method for attaining this purpose, since the imide thus obtained could easily be converted into the desired aldo, carboxy or methyl groups. However, it was doubtful whether this method could also be applied to the bicyclic series, because the complete conversion of the cyano group



*1 Part VII : W. Nagate, I. Kikkawa, M. Fujimoto : This Bulletin, **11**, 226 (1963).

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1) *a*) W. Nagata, S. Hirai, H. Itazaki, K. Takeda : Ann., **641**, 196 (1961). *b*) W. Nagata : Tetrahedron, **13**, 287 (1961).

into the imide seemed to require special circumstances,[1] especially high rigidity*3 of the molecule.

With this in mind, we examined the reduction of *trans*-2-oxo-9-decalincarbonitrile ethyleneketal (II) with lithium aluminium hydride. II was prepared in the usual way in 75% yield and treated with an excess of lithium aluminium hydride in ether at 3~5° for 5 hours. The infrared spectrum of the crude product shows bands at 1650 (-CH=N-), 1628 (-CH=NH) and 1607 cm^{-1} (weak, $-NH_2$),[1a] indicating the existence of a mixture of imide III, anile IV, and amine V. Variation of the experimental conditions did not give the better results, and in this case, the stepwise reduction of II to III could not be achieved. This fact is consistent with the greater reactivity of the angular cyano group in I than in the tetracyclic series, which was already demonstrated in the alkaline hydrolysis.*1 This greater reactivity may be ascribed to lower rigidity*3,*4 of the bicyclic molecule.

Since the separation and isolation of these basic products were difficult, the crude reduction product was treated with diluted hydrochloric acid, and separated into the neutral and the basic fraction. The neutral fraction exhibits in the infrared spectrum a broad doublet at 2666~2720 cm^{-1} and 1733 cm^{-1} ascribable to the ketoaldehyde (VI) (46.4%) which could not, however, be crystallized and was characterized by conversion into its disemicarbazone, m.p. 230~232°. The crude VI was then oxidized with chromic acid in acetone[2] to the known *trans*-2-oxo-9-decalincarboxylic acid (X) which was identical with the authentic sample. The above basic fraction gave crystalline *trans*-9-aminomethyl-2-decalone (VIII), m.p. 145~149° in 33.6% yield, which was further characterized as its picrate, m.p. 160~164°. The infrared spectrum indicates that VIII exists in the bridged form (B) in the crystalline state, but in an equilibrium between (A) and (B) in chloroform, because a relatively weak but clear band appears at 1700 cm^{-1} in

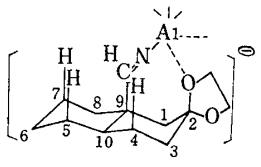
VIII

chloroform solution, while no band is observed in the carbonyl region in the solid state. VIII was then smoothly converted into the oily *trans*-9-aminomethyldecalin (IXa) in 81.5% yield as the picrate, m.p. 234~236°. Acetylation of IXa gave an acetate IXb, m.p. 150~151°. Since no epimerisation at C_9 occurs during the Huang-Minlon reduction,*1 IX must have a *trans*-fused ring juncture.

Next, the above mentioned crude product of the lithium aluminium hydride reduction of II was subjected to the Huang-Minlon reduction and the crude reduction product was cautiously separated into the neutral and the basic fraction with cold diluted tartaric acid. The neutral fraction which consisted mainly of VII was deketalized with diluted acetic acid and the crude *trans*-9-methyl-2-decalone (XIa) was purified by distillation (b.p_{15} 130°). Although XIa could not be crystallized, its infrared spectrum

*3 The word "rigidity" is used here to mean less ability of distortion and less mobility of conformations in a transition state.

*4 In the case of lithium aluminium hydride reduction, it can be assumed that the blocking effect of the axial hydrogen atoms at C_4, C_5, and C_7 is weakened owing to lower rigidity of the molecule in the above mentioned sense (cf. reference*3).



2) A. Bowers, T.G. Halsall, H.R.H. Jones, A.J. Lemin: J. Chem. Soc., **1953**, 2548.

in chloroform indicated clearly non-identity and non-contamination with *cis*-isomer XII*5 which had been prepared according to the literature[3] from $\Delta^{1,9}$-2-octalone with methyl magnesium iodide in the presence of cuprous bromide. XIa was further converted into its semicarbazone XIb, m.p. 209~211°, which was not identical with the semicarbazone XIIb[3] of the *cis*-isomer. Finally *trans*-2-oxo-9-decalincarbonitrile ethyleneketal (II) was treated with an excess of lithium aluminium hydride in boiling ether solution, and in this case the sole reduction product was 9-aminomethyl derivative V which was characterized as its picrate, m.p. 172~174° (70.7% yield). By deketalyzation with acetic acid, V was converted into *trans*-9-aminomethyl-2-decalone (VIII).

Experimental*6

***trans*-2, 2-Ethylenedioxy-9-decalincarbonitrile (II)**——A solution of *trans*-2-oxo-9-decalincarbonitrile (I) (2.2 g.), m.p. 56~58° and *p*-TsOH·H_2O (66 mg.) in 100 ml. of ethylene glycol was heated at 80~85° for 1 hr. and distilled slowly over a period of 2 hr. at about 7 mm. pressure.[4] The distillation temperature was 78~80°. The reaction mixture was made alkaline with a solution of KOH (300 mg.) in MeOH (3 ml.), poured into H_2O, and extracted with 50 ml. of $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and evaporated *in vacuo*. The crude product was crystallized from Et_2O and pentane to give 2.047 g. (75%) of *trans*-2,2-ethylenedioxy-9-decalincarbonitrile (II), m.p. 71~72°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2244 (C≡N), 1085 $\left(<\begin{matrix}O-\\O-\end{matrix}\right)$. *Anal.* Calcd. for $C_{13}H_{19}O_2N$: C, 70.55; H, 8.65; H, 6.33. Found: C, 70.85; H, 8.79; N, 6.16.

Reduction of *trans*-2,2-Ethylenedioxy-9-decalincarbonitrile (II) with $LiAlH_4$——i) To a solution of 500 mg. (2.355 mmoles) of II in 25 ml. of dry Et_2O was added dropwise with stirring at 3~5° a solution of 430 mg. (11.775 mmoles) of $LiAlH_4$ in 75 ml. of dry Et_2O and stirring was continued at the same temperature for 5 hr. The disappearance of the cyano group was checked by the IR spectrum. The excess of $LiAlH_4$ was destroyed with a solution[5] of 9 ml. of 1 *M*-aqueous Rochelle salt and 1.5 ml. of 0.25 *M*-aqueous tartaric acid, and then the organic layer was separated. The H_2O layer was extracted with Et_2O, and the combined Et_2O extracts were washed with H_2O, dried, and evaporated *in vacuo*. To a solution of the residue (450 mg.) (IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650 (-CH=N-), 1628 (=NH), 1607 (weak, NH_2)) in 40 ml. of MeOH was added 5 ml. of 2*N* NaOH, and the mixture was refluxed for 10 min. and evaporated *in vacuo*. The residue was mixed with 20 ml. of H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and evaporated *in vacuo*.

A mixture of the residue (440 mg.) and 80% $N_2H_4·H_2O$ (2.2 ml.), KOH (2.0 g.), and triethylene glycol (18 ml.) was heated to 140~145°, maintained at the same temperature for 1 hr., and heated further at 180~184° for 4 hr. The reaction mixture was added to 50 ml. of ice-water and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried, and evaporated to afford 414.5 mg. of a brown oil. The crude product (410 mg.) was mixed well with 20 ml. of ice-cooled 5%-tartaric acid solution, extracted with Et_2O, and the Et_2O layer was washed with H_2O, dried, and evaporated. The residue (228.5 mg.) was dissolved in 4 ml. of AcOH, diluted with 2 ml. of H_2O, and heated at 100° for 15 min. Then the reaction mixture was neutralized with 2*N* Na_2CO_3 and extracted with Et_2O. The extract was washed with H_2O, dried, and evaporated to give 165.5 mg. (44.0%) of a crude *trans*-9-methyl-2-decalone (XIa). The crude product was distilled at a reduced pressure to give the pure XIa; b.p_{15} 130°, n_D^{23} 1.4889, IR: $\nu_{max}^{CHCl_3}$ 1700 cm^{-1} (C=O). *Anal.* Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.29; H, 11.00. Semicarbazone XIb: m.p. 209~211° (recrystallized from $CHCl_3$ and MeOH), plates. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3474, 3384, 1684, 1605, 1565. *Anal.* Calcd. for $C_{12}H_{21}ON_3$: C, 64.54; H, 9.48; N, 18.82. Found: C, 64.32; H, 9.58; N, 18.80.

By the Birch-Robinson's method,[3] $\Delta^{1,9}$-2-octalone (I) was converted into oily *cis*-9-methyl-2-decalone (XIIa); b.p_{15} 126°, n_D^{25} 1.4895, IR: $\nu_{max}^{CHCl_3}$ 1700 cm^{-1} (C=O). *Anal.* Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.61; H, 10.91.

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*5 Gas chromatograhic analysis of XIa clearly showed its purity. However, the difference of the retention times between XIa and the *cis*-isomer XII was too small to demonstrate their non-identity.

*6 Melting points were measured on a Kofler-block "Monoscope" (Hans Bock Co., Frankfurt am Main, Germany) and are corrected. For elemental analyses, the samples having the melting points of below 120°, 120~180°, and over 180° were dried for 3 hr. over P_2O_5 *in vacuo* (1~2 mm.) at room temperature ~60°, 70~90°, and 100~120°, respectively.

3) A. J. Birch, R. Robinson: J. Chem. Soc., **1943**, 501.
4) W. S. Seymour, S. Bemstein, R. Littell: J. Am. Chem. Soc., **76**, 6116 (1954).
5) J. Schmidlin, G. Ann, J. R. Billeter, K. Heusler, H. Übermesser, P. Wieland, A. Wettstein: Helv. Chim. Acta, **40**, 2294 (1957).

Semicarbazone XIIb : m.p. 205～206°(from MeOH) (ref.[3] 212～213°). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3470, 3380, 1685, 1605, 1565. *Anal.* Calcd. for $C_{12}H_{21}ON_3$: C, 64.54; H, 9.48; N, 18.82. Found : C, 64.58; H, 9.60; N, 18.71.

On the other hand, the above tartaric acid solution was made alkaline with 2*N* NaOH at 5° and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried, and evaporated to give 169.5 mg. (33.5%) of a brown oil V. Picrate : m.p. 172～174°(from MeOH and Et_2O), yellow needles. IR ν_{max}^{Nujol} cm^{-1} : 3240, 1577(NH_2), 1615, 1500(phenyl), 1522(NO_2), 1080 $\left(\begin{matrix}O-\\O-\end{matrix}\right)$. *Anal.* Calcd. for $C_{19}H_{26}O_9N_4$: C, 50.21; H, 5.77; N, 12.33. Found : C, 50.14; H, 5.97; N, 12.67.

241 mg. of the picrate of V was shaken with 20 ml. of 2*N* NaOH and 20 ml. of $CHCl_3$ and the organic layer was separated. The H_2O layer was extracted with $CHCl_3$, and the combined organic layers were washed with H_2O, dried and evaporated *in vacuo* to afford 112 mg. of a crude oil V which could not be crystallized by various treatments. This crude oil V was dissolved in 2 ml. of 70% AcOH and heated at 100° for 30 min. After removal of the solvent *in vacuo*, the reaction mixture was treated with 10 ml. of 2*N* Na_2CO_3 and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried, and evaporated to dryness *in vacuo*. The residue (89.5 mg.) was crystallized from Et_2O and $CHCl_3$ to give 77.8 mg. (82.0%) of *trans*-9-aminomethyl-2-decalone (VIII), m.p. 145～149°, as a nearly colorless plates. IR : ν_{max}^{Nujol} 3316 cm^{-1}(>NH); IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3500(OH), 3325(>NH), 3080(broad, NH_2), 1700 (weak)(C=O). *Anal.* Calcd. for $C_{11}H_{19}ON$: C, 72.88; H, 10.57; N, 7.73. Found : C, 72.28; H, 10.51; N, 7.58,

Picrate : m.p. 160～164°, as yellow plates (from MeOH and Et_2O). IR ν_{max}^{Nujol} cm^{-1} : 3290(>NH), 1631, 1500(phenyl), 1560(NO_2)(no C=O band is present). *Anal.* Calcd. for $C_{17}H_{22}O_8N_4$: C, 49.75; H, 5.40; N, 13.65. Found : C, 49.89; H, 5.56; N, 13.82.

ii) To a solution of 1.5 g. (6.8 mmoles) of II in 50 ml. of anhyd. Et_2O was added dropwise with stirring at 3° a solution of 1.29 g. (34 mmoles) of $LiAlH_4$ in 250 ml. of anhyd. Et_2O and stirring was continued at the same temperature for 3 hr. The reaction mixture was worked up as above and the Et_2O extract was shaken well with 100 ml. of 5% tartaric acid solution. The Et_2O layer was washed twice with 20 ml. of H_2O, dried, and evaporated to give 209.5 mg. of an unknown product which, however, was not further examined.

A few drops of conc. HCl were added to adjust the pH of the tartaric acid layer to 1.0 and the mixture was heated on a steam bath for 15 min. The reaction mixture was extracted with Et_2O and the Et_2O extract was washed with H_2O, dried, and evaporated to afford 564.2 mg. (46.4%) of a crude *trans*-2-oxo-9-decalincarboxaldehyde (VIa) as a colorless oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2666～2720(CHO, broad doublet), 1733(C=O).

Disemicarbazone VIb : m.p. 230～232°(decomp.), plates (from MeOH and Et_2O). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3430, 3298, 3180, 3120, 1586, 1685, 1661. *Anal.* Calcd. for $C_{13}H_{22}O_2N_6$: C, 53.04; H, 7.53; N, 28.55. Found: C, 53.33; H, 7.66; N, 28.08.

The H_2O layer was made alkaline with 2*N* NaOH and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried, and evaporated to dryness *in vacuo*. The residual crystals were recrystallized from $CHCl_3$ and Et_2O to give 410.8 mg. (33.6%) of *trans*-9-aminomethyl-2-decalone (VIII), m.p. 145～149°, as plates.

iii) To a solution of 500 mg. (2.26 mmoles) of II in 25 ml. of dry Et_2O was added dropwise with stirring at room temperature a solution of 860 mg. (22.6 mmoles) of $LiAlH_4$ in 150 ml. of dry Et_2O and the mixture was refluxed for 5 hr. The excess of $LiAlH_4$ was destroyed carefully and the Et_2O extract was washed with H_2O and shaken with 40 ml. of 5% tartaric acid. The Et_2O solution was washed with H_2O, dried, and evaporated to afford 57.5 mg. of an oil which was not examined further.

The H_2O layer was made alkaline with 2*N* NaOH and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried, and evaporated to give 382 mg. of a crude oil V. Working up as above afforded 726.6 mg. (70.7%) of *trans*-9-aminomethyl-2,2-ethylenedioxydecalin (V) picrate, m.p. 174-176°, as yellow needles.

Huang-Minlon Reduction of *trans*-9-Aminomethyl-2-decalone (VIII)——A mixture of *trans*-9-aminomethyl-2-decalone (VIII) (100 mg.), 80% $N_2H_4 \cdot H_2O$ (1.0 ml.), KOH (250 mg.), and 5 ml. of triethylene glycol was worked up as above to give the crude product (90 mg.), which did not crystallize by various treatments.

The picrate was crystallized from MeOH and Et_2O to give 180 mg. (81.5%) of *trans*-9-aminomethyldecalin (IXa) picrate, m.p. 234～236°, as plates. *Anal.* Calcd. for $C_{17}H_{24}O_7N_4$: C, 51.51; H, 6.10; N, 14.14. Found : C, 51.28 ; H, 6.11 ; N, 13.86.

The free amine IXa (60 mg.) was treated with pyridine (1.0 ml.) and Ac_2O (0.5 ml.) and the mixture was allowed to stand overnight at room temperature. Working up as usual and crystallization from Me_2CO and Et_2O gave 71 mg. of *trans*-9-acetamidomethyldecalin (IXb), m.p. 150～151°, as plates. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3427(>NH), 1664(CO-NH). *Anal.* Calcd. for $C_{13}H_{23}ON$: C, 74.59; H, 11.08; N, 6.69. Found : C, 74.79; H, 11.18; N, 6.65.

Oxidation of *trans*-2-Oxo-9-decalincarboxaldehyde (VIa)——1.4 ml. of 8*N* chromic acid solution was rapidly added under stirring to a solution of 100 mg. of crude VIa in 20 ml. of Me_2CO (freshly distilled on $KMnO_4$) at room temperature and stirring was continued for 10 min. The reaction mixture was treated with 2 ml. of MeOH and 50 ml. of H_2O and the mixture was stirred for half an hour. The reaction mixture was extracted with $CHCl_3$ and the organic layer was washed with H_2O, dried, and evaporated *in vacuo*.

The residue (115.5 mg.) was dissolved in 10 ml. of 2*N* NaOH and extracted with $CHCl_3$. The H_2O layer was acidified with conc. HCl and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated *in vacuo*. The crystalline residue (92.2 mg.) was recrystallized from Et_2O to give 81.5 mg. (75%) of *trans*-2-oxo-9-decalincarboxylic acid (X), m.p. 118.5～120°, as plates.

We are very grateful to Dr. K. Takeda, Director of this laboratory for his constant encouragement. Our thanks are also due to the members of the analytical and the physicochemical department of this laboratory for analytical and optical data.

Summary

trans-9-Methyl- (XIa) and -9-aminomethyl-2-decalones (VIII) were prepared from the parent *trans*-2-oxo-9-decalincarbonitrile (I) by a series of reductions and were characterized.

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48. Yoshihisa Mizuno, Morio Ikehara, and Kyoichi A. Watanabe*1 : Potential Antimetabolites. VI.*2 An Improved Synthesis of 2-β-D-Ribofuranosyl-as-triazine-3,5(2*H*,4*H*)-dione (6-Azauridine).

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6-Azauridine (VI) is one of the most promising anticancer agents among a number of antimetabolites examined.[1] Chemical preparation of the nucleoside was already reported by Handschumacher,[2] Prystas *et al.*,[3] and authors.[4] Prystas' method which is the latest one consists in inhibition of ribosidation on nitrogen 4 of *as*-triazine-3,5-(2*H*,4*H*)-dione by introducing catalytically replaciable diphenylmethyl group on the nitrogen. Authors' method consists in protecting the same nitrogen from the ribosidation by introducing easily replaciable group, viz., methylmercapto group on position 5 of 1,2,4-triazine. The azauridine was prepared by us by way of azacytidine (V).[4]

Now, an alternative and more improved procedure to prepare the nucleoside was devised on the ground of the finding that methylmercapto group attached to position 5 of *as*-triazine-3(2*H*)-one quite easily replaced by nucleophilic reagent such as hydroxyl group,[5] leaving the rest of molecule intact. Thus, mild acid hydrolysis of 2-(2′,3′,5′-tri-O-benzoyl-β-D-ribofuranosyl)-5-methylmercapto-*as*-triazine-3(2*H*)-one (III) gave rise

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