A Convenient Synthesis of Condensed Cyclopentane System. Annelation by Intramolecular 1,3-Dipolar Addition of Nitrones

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Intramolecular 1,3-dipolar addition reactions of nitrones were investigated. Four alkenyl nitrones were studied: 2-allyl-, 2-(3-butenyl)-, 2-(4-pentenyl)-, and 2-(9-decenyl)-*N*-methylcyclohexanimine *N*-oxides. Among these, 2-(3-butenyl)-*N*-methylcyclohexanimine *N*-oxide was found to cyclize most smoothly, giving a perhydroindene derivative as a single regio- and stereoisomer. A perhydroazulene derivative was obtained by cyclization of 2-(3-butenyl)-*N*-methylcycloheptanimine *N*-oxide.

1,3-Dipolar addition reactions are currently of interest in the synthesis of natural products. The reaction between nitrones and olefins is frequently applied for the synthesis of alkaloids.[1] Both intra-[2] and intermolecular[3] 1,3-dipolar reactions are used, depending on the target molecules. Usually nitrones react with olefins stereo- and regiospecifically,[4] giving versatile 1,3-dipolar adducts. When a nitrone reacts intramolecularly with an olefin group as in the following system, a new carbocyclic ring is formed along with an isoxazolidine ring.

Fig. 1.

In order to develop a new annelation method, the authors studied the cyclization of the compounds **5**—**8**,[5] each of which has both a nitrone and an olefin group in the same molecule. These nitrones were easily prepared by treatment of the corresponding alkenylcyclohexanones **1**—**4** with *N*-methylhydroxylamine.

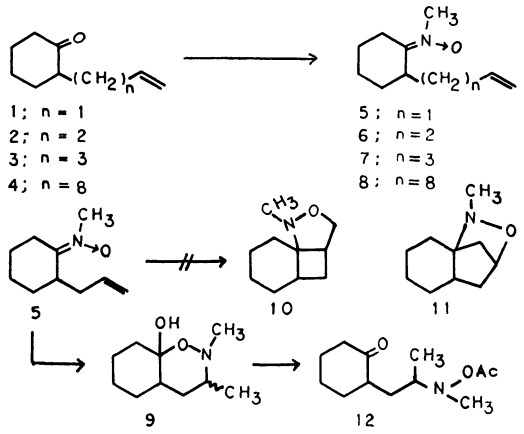

Fig. 2.

When the nitrone (**5**) having an allyl side chain was heated in refluxing benzene, it decomposed into a complex mixture, from which the expected cyclization products, **10** and **11**, could not be extracted. However, when **5** was allowed to stand at room temperature for one week, an unexpected oxazine (**9**) was obtained in 43% yield. The structure was assigned on the basis of spectroscopic data of **9** and its acetate (**12**), which was produced by the treatment of **9** with acetic anhydride in pyridine.

A possible mechanism for the formation of **9** is suggested by the equation in Fig. 3.

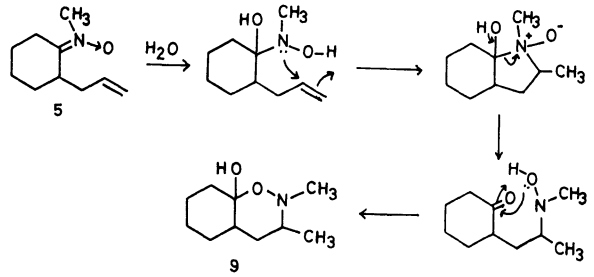

Fig. 3.

However, the nitrone (**6**), carrying a butenyl side chain, cyclized at room temperature to yield the expected cycloadduct (**13**) in a quantitative yield. In this case, neither the regioisomer (**16**) nor the oxazepine analog of **9** was formed; the reaction afforded a stereochemically single product.

Attempts to cleave the N–O bond with catalytic hydrogenation (on Pd/C or PtO_2) were unsucessful. Irradiation[6] of UV light (high pressure mercury lamp using a Pyrex filter) on a hexane solution of **18** in the presence of fluorenone gave rise to an oxazine (**21**) in 39% yield. The oxazine ring of **14** was cleaved with lithium aluminium hydride to give an amino alcohol (**15**). The N–O bond of **13** was cleaved more effectively with titanium(III) chloride, to yield the same compound (**15**).

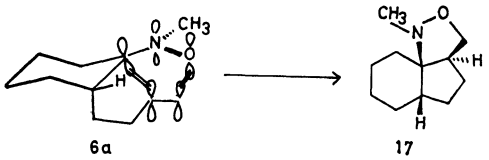

Fig. 4.

The stereochemistry of **13** was tentatively described as **17**; thus, the most favorable transition state leading to **13** seemed to be **6a**, because it permitted the maximum overlapping of the π orbitals of the nitrone and the side chain olefin groups.

Unlike **6**, the nitrone (**7**) resisted cyclization at room temperature for one week. However, when **6** was

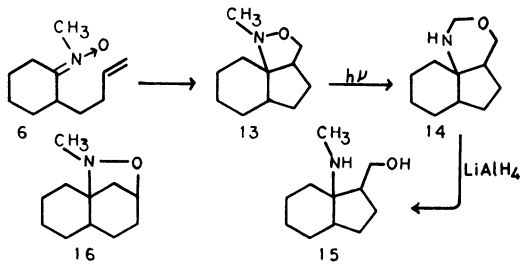

Fig. 5.

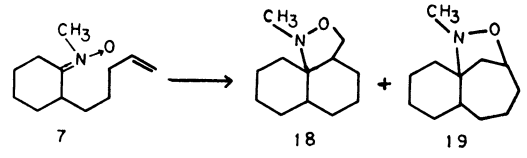

Fig. 6.

refluxed in benzene for 16 h, it gave rise to a 1 : 1 mixture of the intramolecular adducts, **18** and **19**. These adducts were separated by column chromatography.

The nitrone (**8**), which has a 9-decenyl side chain, gave no cyclized product. Thus, heating of **8** at 60 °C for 24 h resulted in the recovery of **8**, and heating at 120 °C for 1 h brought about decomposition.

From these results, a system bearing the 3-butenyl side chain such as in **6** was considered to be most suitable for annelation which would result in the formation of a cyclopentane ring. In order to confirm the utility of this annelation, we tried to synthesize a perhydroazulene system, which is a common skeleton of some sesquiterpenes.

A mixture of 2-(3-butenyl)cycloheptanone (**20**) and *N*-methylhydroxylamine in methanol was heated at reflux. The NMR of the reaction mixture showed a strong *N*-methyl signal (δ=3.67) due to the nitrone (**21**) after several hours. This signal gradually decreased, and it completely disappeared after 44 h; an intense *N*-methyl signal (δ=2.52) due to the cyclized product (**22**) remained. By simple purification, a perhydroazulene compound (**22**) was isolated in 84% yield as a single product.

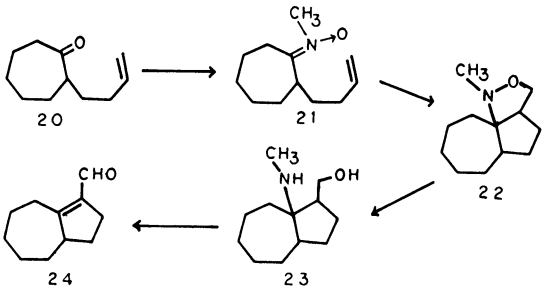

Fig. 7.

Although the N–O bond of substituted isoxazolidine or isoxazolidinium can be cleaved by reduction with zinc–acetic acid,[7] lithium aluminium hydride,[8] or catalytic hydrogenation,[9] these methods are not suitable for the compounds having easily reducible functions such as halogens, ketones, or esters. We found that the N–O bond of **22** can be cleaved by simple treatment with titanium(III) chloride in refluxing ethanol, affording an amino alcohol (**23**). Treatment of **23** with chromium trioxide–pyridine hydrochloride complex[10] effectively yielded **24**, Thus the nitrone-annelation would provide a new method for syntheses of hydroazulene derivatives.

Experimental

^{1}H-NMR spectra were recorded on a Hitachi H-60 instrument, TMS being used as an internal standard (ppm). IR spectra were taken on a Hitachi EPS-3T spectrometer. Mass spectra were obtained with a Hitachi RMU-6M spectrometer.

8a-Hydroxy-2,3-dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2H-1,2-benzoxazine(9). To a solution of *N*-methylhydroxylamine hydrochloride (889 mg, 10.6 mmol) in 5 ml of methanol was added a solution of potassium hydroxide (664 mg, 11.5 mmol) in 3 ml of methanol, followed by the addition of allylcylohexanone (865 mg, 6.27 mmol). The mixture was stirred overnight, and diluted with ether. The precipitate was removed by filtration, and the filtrate was concentrated to give crude **5** (830 mg) as an oil; IR($CHCl_3$) 3300 (H_2O), 1640, 990, and 910 (-CH=CH_2), 1590 (nitrone) cm^{-1}; NMR ($CDCl_3$) δ=5.75 (1H, m), 5.00 (2H, m), 3.75 (3H, s, CH_3–N(→O)=), 2.5—0.8 (11H, m). The crude nitrone **5** (830 mg) was allowed to stand at room temperature for 7 d. The resulting oil was chromatographed on silica gel, giving allylcyclohexane (650 mg), the unchanged nitrone **5** (298 mg), and a mixture of the oxazine stereoisomers **9** (316 mg, 43% from allylcyclohexanone): bp 59 °C/0.3 Torr†; IR(film) 3450 (OH), 1015 (C–O) cm^{-1}; NMR($CDCl_3$) δ=4.28 (1H, s, OH), 2.60 (3H, s, N–CH_3), 2.50 (1H, m, CH_3–C<u>H</u>–N), 1.05 (3H/2, d, J=6.5 Hz, C<u>H</u>$_3$–CH–N), 0.97 (3H/2, d, J=6.5 Hz, isomeric C<u>H</u>$_3$–CH–N), 2.0—1.0 (12H, m); ^{13}C-NMR($CDCl_3$) 98.14(s), 61.69(d), 61.54(d), 43.70(d), 43.55(d), 42.88(q), 35.62(t), 35.47(t), 35.31(t), 35.14(t), 28.97(t), 28.81(t), 25.83(t), 25.70(t), 23.19(t), 23.04(t), 22.84(q), 19.03(q). Found: C, 64.49; H, 10.15; N, 7.25%. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56%.

By repeated chromatography of the diastereomeric mixture **9** (500 mg) using benzene–ethyl acetate (10 : 1) as an eluting solvent, one isomer of **9** was obtained as a colorless oil (45 mg): NMR($CDCl_3$) δ=2.60 (3H, s), 2.50 (1H, m), 1.05 (3H, d, J=6.5 Hz); ^{13}C-NMR($CDCl_3$) 98.21(s), 61.54(d), 43.54(d), 43.88(q), 35.46(t), 35.13(t), 28.80(t), 25.79(t), 23.04(t), 19.03(q).

2-[2-(N-Acetoxymethylamino)propyl]cyclohexanone(12). A solution of diastereomers(**9**) (73 mg, 0.40 mmol) in 2 ml of pyridine was treated with acetic anhydride (2 ml), and the mixture was allowed to stand overnight. After the usual work-up, the resulting oil (91 mg) was chromatographed on silica gel, giving **12** (66 mg, 73%) as an oil: IR($CHCl_3$) 1750 (AcO), 1700 (C=O) cm^{-1}; NMR($CDCl_3$) δ=3.05 (1H, m, CH–N), 2.72 (3H, s, CH_3–N), 2.02 (3H, s, AcO), 1.08 (3H, d, J=6.5 Hz), 2.5—1.0 (11H, m).

Hydrolysis of **12** with potassium hydroxide in methanol afforded a diastereomeric mixture **9** in a quantitative yield.

Attempt at Cyclization of 5. The nitrone **5** exhibited a strong absorption band at 3300 cm^{-1} in its IR spectrum due to water. The nitrone in this state was labile to heat; thus, vaccum distillation at 65 °C/0.15 Torr produced a distillate, which showed at least six spots in TLC. The NMR spectrum

† 1 Torr=133.322 Pa.

of the distillate showed no singlet at 3.73 ppm due to the *N*-methyl group of **5**. Similarly, a complex mixture was obtained when **5** was heated in refluxing benzene. By chromatography of the product, minor amounts of **9** and 2-allylcyclohexanone were isolated. However, the expected cyclization product, **10** or **11**, was not detected.

12-Methyl-11-ox-12-azatricyclo[7.3.0.0^{1,6}]dodecane(13). Treatment of 2-(3-butenyl)cyclohexanone **2** with *N*-methylhydroxylamine afforded crude nitrone **6**: IR(film) 3300 (H_2O), 1635, 990, 910 (-CH=CH_2), 1590 (nitrone) cm^{-1}; NMR($CDCl_3$) δ=4.10 (1H, t, J=8.0 Hz), H_A of O-CH_AH_B-CH_X), 3.48 (1H, dd, J=3.5, 8.0 Hz, H_B of O-CH_AH_B-CH_X), 2.63 (3H, s, CH_3-N), 2.7—1.0 (14H, m); MS (70 eV), *m/e* (rel intensity), 181 (M^+, 100), 138 (72), 135 (84), 127 (77). An analytical sample was obtained by short-path distillation: bp 98—103 °C/17 Torr. Found: C, 72.79; H, 10.45; N, 7.65%. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.72%.

1-Methylamino-9-(hydroxymethyl)bicyclo[4.3.0]none (15). A solution of **13** (194 mg, 1.07 mmol) in 40 ml of hexane was irradiated for 18 h in the presence of fluorenone (23 mg, 0.13 mmol) with a high pressure mercury lamp (450 W) using a Pyrex filter. After removal of the hexane, the residue was chromatographed on silica gel. Elution with benzene gave fluorenone; further elution with benzene–ethyl acetate (3 : 1) gave **14** as an oil in a pure state (TLC). IR(film) 3300 (NH) cm^{-1}; NMR($CDCl_3$) δ=4.35 (2H, s, N-CH_2-O), 3.70 (2H, m, CH_2-O), 1.85 (1H, s, NH), 2.5—0.8 (14H, m). The oxazine **14** (49 mg, 0.27 mmol) was treated with lithium aluminium hydride (50 mg, 1.3 mmol) in 5 ml of tetrahydrofuran, and the mixture was stirred at room temperature overnight. The excess hydride was decomposed with water, 15% sodium hydroxide solution, and water, the precipitate being filtered. The filtrate was concentrated, and the residue was crystallized from ether, affording needles (33.8 mg, 68%): mp 188—190 °C; IR(KBr) 3325 (OH and NH); NMR($CDCl_3$) δ=3.78 (2H, br.s, NH and OH), 3.68 (2H, d, J=5.0 Hz, CH_2-O), 2.42 (3H, s, CH_3-N), 2.3—1.0 (14H, m). An analytical sample was obtained by bulb-to-bulb distillation: bp 130 °C/2 Torr. Found: C, 72.23; H, 11.69; N, 7.30%. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.54; N, 7.64%.

13-Methyl-12-ox-13-azatricyclo[8.3.0.0^{1,6}]tridecane (18) and 12-Methyl-11-ox-12-azatricyclo[8.2.1.0^{1,6}]tridecane (19). The nitrone **7** was prepared from the pentenylcyclohexanone **3** by a method similar to that described above. A solution of the nitrone **7** (2.2 g, 11.3 mmol) in benzene (100 ml) was heated under refluxing in a nitrogen atmosphere for 16 h. The solvent was evaporated, and the residue (2.51 g) was chromatographed on silica gel. Elution with benzene–ethyl acetate (10 : 1) produced **19** (260 mg, 11.8%), a mixture of **19** and **18** (820 mg, 37.3%), and **18** (162 mg, 7.4%). Analytical samples were prepared by short-path distillation: **18**: 60 °C/2 Torr; NMR(C_6D_6) δ=3.98 (1H, dd, J=10.0, 7.0 Hz, CH_2-O), 3.47 (1H, dd, J=9.0, 7.0 Hz, CH_2-O), 2.43 (3H, s, CH_3-N). Found: C, 73.92; H, 10.95; N, 7.48%. Calcd for $C_{11}H_{21}NO$: C, 73.79; H, 10.83; N, 7.17%. **19**: 80 °C/2 Torr: NMR(C_6D_6) δ=4.45 (1H, m, CH-O), 2.43 (3H, s, CH_3-N), 1.96 (1H, dd, J=12.5, 8.5 Hz, CH_AH_B-CH-O), 1.65 (1H, dd, J=12.5, 2.5 Hz, CH_AH_B-CH-O). Found: C, 73.91; H, 10.92; N, 7.43%. Calcd for $C_{12}H_{21}NO$: C, 73.79; H, 10.83; N, 7.17%.

Attempt at Cyclization of the Nitrone 8. 2-(9-Decenyl)-cyclohexanone **8**; bp 112—125 °C/13 Torr, was prepared in 78% yield by treating the pyrrolidine enamine of cyclohexanone with 10-iodo-1-decene. The decenylcyclohexanone **8** (213 mg, 0.9 mmol) was dissolved in methanol (6 ml), and *N*-methylhydroxylamine hydrochloride (178 mg, 2.1 mmol) was added. The solution was treated with a solution of potassium hydroxide (171 mg, 3.1 mmol) in methanol (1 ml), and the reaction mixture was heated at refluxing temperature for 18 h. The mixture was diluted with ether, the precipitate was filtered, and the filtrate was concentrated to a brown oil (202 mg). The formation of the nitrone **8** was confirmed by the absence of the carbonyl absorption in the IR spectrum, and the appearance of a singlet at δ 3.75 (3H) due to *N*-methyl of the nitrone group in the NMR. The oil was heated in benzene at 60 °C for 24 h. The NMR spectrum of the product exhibited no signal at δ 3.75. Although the product was cautiously chromatographed on silica gel, no cyclization product could be isolated.

13-Methyl-12-ox-13-azatricyclo[8.3.0.0^{1,7}]tridecane (22). A solution of 2-(3-butenyl)cycloheptanone **20** (520 mg, 3.13 mmol), *N*-methylhydroxylamine hydrochloride (449 mg, 3.74 mmol), and potassium hydroxide (238 mg, 4.24 mmol) in methanol (20 ml) was heated at refluxing. After 4 h, a small portion of the reaction mixture was taken out. The NMR spectrum exhibited a singlet at δ 3.67 due to the *N*-methyl group of the nitrone **21**, together with a singlet at δ 2.52 due to the *N*-methyl group of the cyclization product **22**. The reaction mixture was heated for an additional 44 h, and diluted with ether. The precipitate was filtered and the filtrate was concentrated. The residual oil was distilled with a Kuhgel-Rohr apparatus, affording **22** (514 mg, 84% from **20**): NMR ($CDCl_3$) δ=3.82 (1H, t, J=8.0 Hz, O-CH_AH_B-CH_X), 3.23 (1H, dd, J=4.5, 8.0 Hz, O-CH_AH_B-CH_X), 2.52 (3H, s, CH_3-N). An analytical sample was obtained by short-path distillation: 140 °C/17 Torr. Found: C, 73.65; H. 10.92; N, 7.00%. Calcd for $C_{12}H_{21}NO$: C, 73.79; H, 10.83; N, 7.17%.

10-Hydroxymethyl-1-(methylamino)bicyclo[5.3.0]decane (23). To a solution of **22** (435 mg, 2.2 mmol) in ethanol (80 ml) was added 20% aqueous titanium(III) chloride solution (22 ml), and the mixture was allowed to reflux under an argon atmosphere overnight. The solvent was removed on a rotary evaporator, and the pH of the residual mixture was brought to 14 with a potassium hydroxide solution. The alkaline mixture was continuously extracted with ether for 24 h, and the ethereal extract was concentrated. The resultant oil was distilled with a Kuhgel-Rohr apparatus, giving **23** (302 mg, 89%) as a colorless oil: bp 170 °C/4 Torr; IR(film) 3300 cm^{-1}; NMR($CDCl_3$) δ=3.73 (2H, m, CH_2O), 3.08 (2H, s, NH and OH), 2.34 (3H, s, CH_3-N). Found: C, 72.75; H, 11.69; N, 6.81%. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.74; N, 7.09%.

Bicyclo[5.3.0]dec-1(10)-ene-10-carbaldehyde (24). A solution of the alcohol **23** (30 mg, 0.15 mmol) in dichloromethane (1.5 ml) was treated with chromium trioxide–pyridine hydrochloride complex (41 mg, 0.34 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was diluted with ether, and water was added. The organic layer was separated, dried, and concentrated. After column chromatography of the residue on silica gel, a colorless oil **24** (12 mg, 52%) was obtained: IR(film) 2710, 1660 (CHO) cm^{-1}; NMR($CDCl_3$) δ=9.96 (HCO). High resolution mass spectrum: Found, M. W. 164.1185; Calcd for $C_{11}H_{16}O$, 164.1197.

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