

## Synthesis of ( $\pm$ )-Atractylon

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WE recently reported a new method<sup>1</sup> for synthesis of the furan moiety. In this paper this method is applied for the synthesis of a furanosesquiterpene, atractylon (I). Atractylon\* was isolated from *Atractylis ovata* Thunb.<sup>2</sup> and *Atractylodes japonica* Koizumi,<sup>3</sup> and its structure was established as (I) by Yoshioka and co-workers.<sup>4</sup> We have used as the starting material 2,3,4,6,7,8-hexahydronaphthalene-2-one (III) which was derived<sup>5</sup> from (II).

According to Nagata's method,<sup>6</sup> (III) was treated with hydrogen cyanide and triethylaluminum in dry tetrahydrofuran to give two monocyano-ketones, (IV), m.p. 105–106° [ $\nu_{\max}$  2225, 1680, and 1630  $\text{cm}^{-1}$ ,  $\lambda_{\max}$  235  $\text{m}\mu$  ( $\epsilon$  16,300)] and (V), m.p. 95–96° [ $\nu_{\max}$  2225, 1675, and 1630  $\text{cm}^{-1}$ ,  $\lambda_{\max}$  235  $\text{m}\mu$  ( $\epsilon$  16,250)] in 30%

yield. As the ratio of the optical density of a band at 2225  $\text{cm}^{-1}$  in the infrared spectrum due to the cyano-group in (IV) to that in (V) is about 1.6:1, (IV) has an equatorial cyano-group and (V) an axial cyano-group.<sup>7</sup>

Repetition of hydrocyanation of (IV) afforded only one dicyano-ketone (VI), m.p. 172–174° ( $\nu_{\max}$  2225 and 1725  $\text{cm}^{-1}$ ) in 85% yield. This fact indicates that compound (VI) is a *trans*-fused decanone derivative, according to Nagata's studies<sup>6</sup> on the stereochemistry of cyano-ketones.

The ethylene ketal (VII), m.p. 136–137°, of (VI) was hydrogenated with Raney nickel in ethanol-aqueous ammonia to give in a quantitative yield a monoaminomethyl derivative, which was further reduced with sodium borohydride in

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<sup>1</sup> H. Minato and T. Nagasaki, *Chem. and Ind.*, 1965, 899.

<sup>2</sup> S. Takagi and G. Hongo, *J. Pharm. Soc. Japan*, 1925, **44**, 539.

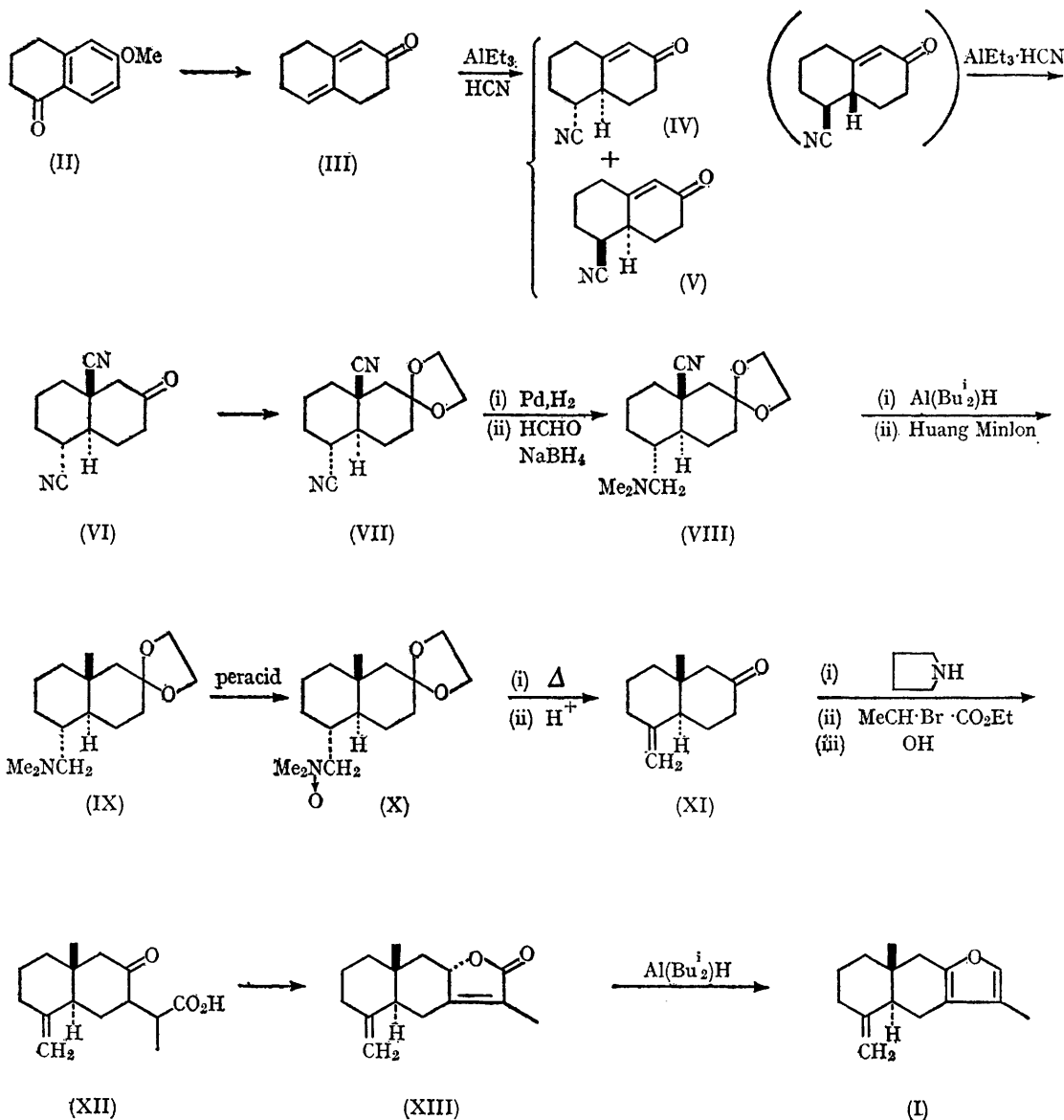
<sup>3</sup> I. Yoshioka, H. Hikino, and Y. Hikino, unpublished data.

<sup>4</sup> H. Hikino, Y. Hikino, and I. Yoshioka, *Chem. and Pharm. Bull. (Japan)*, 1962, **10**, 641; 1964, **12**, 755.

<sup>5</sup> N. N. Gaidamovich and I. V. Torgov, *Bull. Acad. Sci. U.S.S.R.*, 1961, 1682.

<sup>6</sup> W. Nagata, M. Yoshioka, and S. Hirai, *Tetrahedron Letters*, 1962, 461; W. Nagata, "Collection of Lectures Commemorating the Inauguration of the New Shionogi Research Laboratory Building," 1961–1962, p. 248; W. Nagata, I. Kikkawa, and M. Fujimoto, *Chem. and Pharm. Bull. (Japan)*, 1963, **11**, 226.

<sup>7</sup> W. Nagata, M. Yoshioka, N. Narisada, and H. Watanabe, *Tetrahedron Letters*, 1964, 3133.



formaldehyde and methanol to give a dimethyl-amino-compound (VIII), m.p.  $131\text{--}132^\circ$  ( $\nu_{\text{max}} 2225 \text{ cm.}^{-1}$ ) in 75% yield. Aluminium di-isobutyl hydride reduction<sup>8</sup> of (VIII), followed by modified Huang Minlon reduction<sup>9</sup> furnished (IX), m.p.  $42\text{--}43^\circ$ , in 70% yield. The *N*-oxide (X), m.p.  $97\text{--}98^\circ$ , which was obtained on treatment with

*m*-chloroperbenzoic acid, on heating at  $120\text{--}130^\circ$ , followed by treatment with 80% acetic acid gave compound (XI), b.p.  $90^\circ/5 \text{ mm.}$  ( $\nu_{\text{max}} 1710, 1640,$  and  $890 \text{ cm.}^{-1}$ ) in 55% yield.

The pyrrolidine enamine of (XI) was alkylated with ethyl  $\alpha$ -bromopropionate and hydrolyzed with 10% potassium carbonate in methanol to

<sup>8</sup> L. I. Zaharkin and I. M. Khorlina, *Doklady Akad. Nauk. S.S.S.R.*, 1957, **116**, 422.

<sup>9</sup> W. Nagata and H. Itazaki, *Chem. and Ind.*, 1964, 1194.

give an oily ketocarboxylic acid (XII) ( $\nu_{\max}$  1710, 1640, and 890  $\text{cm}^{-1}$ ). This compound (XII) was converted into the  $\alpha\beta$ -unsaturated  $\gamma$ -lactone† (XIII), m.p. 102—103° ( $\nu_{\max}$  1738, 1685, 1645 and 894  $\text{cm}^{-1}$ ) on heating with acetic anhydride and sodium acetate. The  $\gamma$ -lactone function of (XIII) was reduced to the furano-derivative by our new method, that is, on reduction with aluminium di-isobutyl hydride in tetrahydrofuran, (XIII) afforded racemic compound (I), b.p. 105—

110°/1.5 mm. (bath temp.) ( $\nu_{\max}$  3090, 1645, 1565, 1136, 890, and 848  $\text{cm}^{-1}$ ; maleic anhydride adduct, m.p. 93—95°), which was shown to be identical with atractylon by comparison of the infrared spectrum.

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† This compound was shown to be identical with the autoxidation product<sup>4</sup> of atractylon (I) by comparison of the i.r. spectrum. The authors wish to thank Prof. I. Yoshioka (Osaka University) for his courtesy of supplying the sample of the natural compound.