

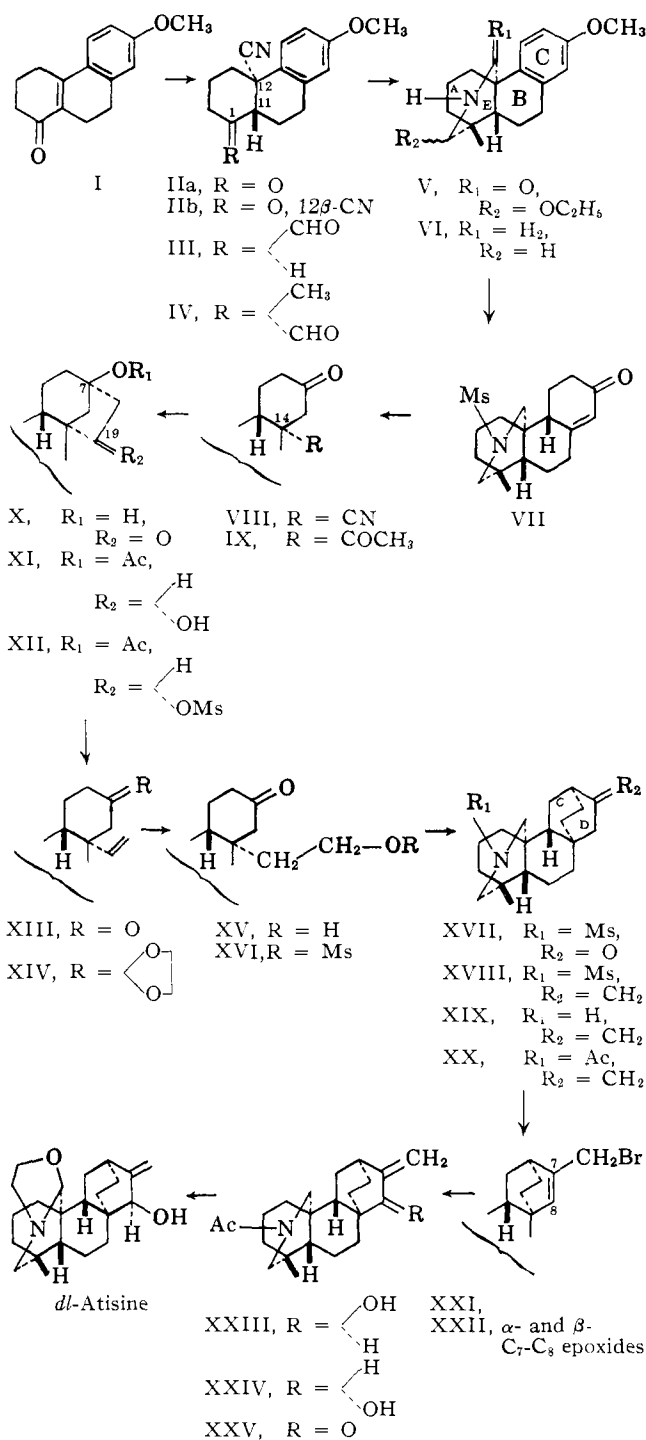
### Stereospecific Total Synthesis of *dl*-Atisine<sup>1</sup>

Sir:

Although several efforts<sup>2</sup> have been made recently to synthesize diterpene alkaloids, no successful total synthesis of them has been reported. We wish to describe here the total synthesis of atisine, one of the most important aconite alkaloids, in the racemic form.

Hydrocyanation<sup>3</sup> of the tricyclic conjugated ketone<sup>4</sup> I, prepared from 6-methoxy-1-tetralone through four steps, with hydrogen cyanide and diethyl aluminum chloride afforded a mixture of the *trans*- and *cis*-cyano ketones,<sup>5</sup> IIa, m.p. 148–150°, and IIb, m.p. 134–135°, in 72% yield. Recrystallization of this mixture in the presence of hydrochloric acid caused epimerization and gave the *trans* epimer IIa as the sole product in 94% yield. Wittig reaction<sup>7</sup> of IIa with *p*-tolylloxymethylene triphenylphosphorane followed by acid hydrolysis gave the formyl derivative III, m.p. 138–140°, which was stereoselectively methylated to give the  $\beta$ -methyl derivative IV, m.p. 163–164°. Alkaline hydrolysis of IV, followed by ethylation, yielded a mixture of the 16-epimeric ethoxy lactams V, m.p. 234–248°, which was reduced with lithium aluminum hydride at 105–110° to the cyclic secondary amine VI, m.p. 92–93° (hydrochloride, m.p. 275°). The free base underwent the modified Birch reduction to afford the dienol ether, m.p. 117–118°, which after mesylation with mesyl chloride and alkali (mesylamide, m.p. 164.5–165°) was converted by acid treatment into the conjugated ketone VII, m.p. 200–202°,  $\lambda_{\text{max}}^{\text{EtOH}}$  243 m $\mu$  ( $\epsilon$  15,400). The last compound was obtained in 36% over-all yield from the *trans*-cyano ketone IIa through eight steps. Alternatively, reduction of IV and cyclization of the dimesyl derivative, m.p. 147–149°, of the resulting amino alcohol, m.p. 138–139.5°/149–150°, with potassium carbonate afforded the *N*-mesyl derivative of VI, m.p. 143–144.5°, which on Birch reduction was converted into the dienol ether described earlier.

In order to construct ring D, the tetracyclic conjugated ketone VII was hydrocyanated<sup>8</sup> to give in 60% yield the *trans*-cyano ketone VIII, m.p. 222–223.5°, together with a small amount of the *cis*-epimer, m.p. 209–211°. Conversion<sup>9</sup> of the highly hindered cyano group of the former into the methyl ketone was effected by treatment of the corresponding ketal, m.p. 267–268°, with methyl lithium followed by acid hydrolysis to give the diketone IX, m.p. 228–230°, in 46% over-all yield (3 steps). This was readily cyclized<sup>9</sup> with dilute alkali to the hydroxy ketone X, m.p. 207–210°, which after acetylation (acetate, m.p. 254–255°) was stereoselectively reduced with sodium borohydride to the 19 $\alpha$ -



alcohol XI, m.p. 206–207°. Refluxing the methanolic dioxane solution of the mesyl derivative XII, m.p. 237–238°, of the last compound with aqueous potassium hydroxide caused hydrolysis and simultaneous degradation to give in excellent yield the 14 $\alpha$ -vinyl 7-ketone XIII, m.p. 207–209°, which was then converted into the vinyl ketal XIV, m.p. 196–197° (75% yield from IX). Hydroboration and subsequent oxidation of XIV afforded the hydroxy ketal, m.p. 190–193°, in 80% yield, which after deketalization (XV, m.p. 167–169°) and mesylation (XVI) was smoothly cyclized with potassium *tert*-butoxide to the desired pentacyclic ketone XVII, m.p. 183–185°, in 54% over-all yield. Construction of the skeleton of the alkaloid was thus completed.

Wittig reaction of XVII afforded the *exo*-methylene derivative XVIII, m.p. 127–128°, in 73% yield, which by Birch reduction (XIX, m.p. 78–81°) and subsequent

(1) Angularly Substituted Polycyclic Compounds, XI.

(2) (a) J. W. Apsimon and O. E. Edwards, *Can. J. Chem.*, **40**, 896 (1962); (b) I. Iwai, A. Ogiso, and B. Shimizu, *Chem. Ind. (London)*, 1288 (1962); (c) J. A. Findlay, W. A. Henry, T. C. Jain, Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Letters*, No. 19, 869 (1962); (d) R. A. Bell and R. E. Ireland, *ibid.*, No. 4, 269 (1963).

(3) W. Nagata, M. Yoshioka and S. Hirai, *ibid.*, No. 11, 461 (1962).

(4) G. Stork, *J. Am. Chem. Soc.*, **69**, 2936 (1947).

(5) The stereochemical assignment of these epimeric cyano ketones was performed by comparison of their CN-band intensities in the infrared [*cis*: 24.2, *trans*: 17.4 (in CHCl<sub>3</sub>, lit.<sup>3</sup>)] as well as of the relative rates of lithium aluminum hydride reduction of the cyano groups in the corresponding ethylene ketals (*k*<sub>*cis*</sub>/*k*<sub>*trans*</sub> ~ 8). Cf. W. Nagata, *et al.*, *J. Org. Chem.*, **26**, 2413 (1961).

(6) All compounds reported give satisfactory compositional analyses and show reasonable infrared spectra.

(7) G. Wittig, W. Böll, and K. H. Krück, *Chem. Ber.*, **95**, 2514 (1962).

(8) The configurations of these cyano ketones were assigned from their dipole moments ( $\mu_{\text{cis}}$ : Calcd., 5.84 D., found, 5.20 D.,  $\mu_{\text{trans}}$ : Calcd. 8.42 D., found, 6.32 D.) and their CN-band intensities in the infrared (*cis*/*trans* = 20.0/12.1 (in CHCl<sub>3</sub>). The intensity ratio of about 1.5/1.0 has been found to be generally applicable to pairs of angularly substituted *cis* and *trans* cyano compounds. Cf. W. Nagata, N. Yoshioka, and M. Narisada, to be published).

(9) Cf. R. D. Haworth, B. G. Hutley, R. G. Leach, and G. Rodgers, *J. Chem. Soc.*, 2720 (1962).

