## 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> Ha,<sup>6</sup> m.p.  $148\text{-}150^\circ$ , and Hb, m.p.  $134\text{-}135^\circ$ , 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-tolyloxymethylene triphenylphosphorane followed by acid hydrolysis gave the formyl derivative III, m.p. 138-140°, which was stereoselectively methylated to give the 1\beta-methyl derivative IV, m.p. 163-164°. Alkaline hydrolysis of IV, followed by ethylation, yielded a mixture of the 16epimeric 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°,  $\lambda_{\max}^{\text{EtOH}}$  243 mµ ( $\epsilon$  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.  $147-149^{\circ}$ , of the resulting amino alcohol, m.p.  $138-139.5^{\circ}/149-150^{\circ}$ , 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>3</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°.<sup>8</sup> 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 methyllithium 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  $19\alpha$ -

(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  $[\epsilon_{cis}: 24.2, \epsilon_{trans}: 17.4$  (in CHCls. lit.<sup>8</sup>)] as well as of the relative rates of lithium aluminum hydride reduction of the cyano groups in the corresponding ethylene ketals ( $k_{cis}/k_{trans} \sim 8$ ). 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 ( $\mu_{nis}$ : Calcd., 6.84 D., found, 5.20 D.,  $\mu_{trans}$ : Calcd. 8.42 D., Found, 6.32 D.) and their CN-band intensities in the infrared ( $\epsilon_{cis}/\epsilon_{trans} = 20.0/12.1$  (in CHCls). 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).



alcohol XI, m.p.  $206-207^{\circ}$ . Refluxing the methanolic dioxane solution of the mesyl derivative XII, m.p.  $237-238^{\circ}$ , 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.  $207-209^{\circ}$ , which was then converted into the vinyl ketal XIV, m.p.  $196-197^{\circ}$  (75% yield from IX). Hydroboration and subsequent oxidation of XIV afforded the hydroxy ketal, m.p.  $190-193^{\circ}$ , in 80% yield, which after deketalization (XV, m.p.  $167-169^{\circ}$ ) and mesylation (XVI) was smoothly cyclized with potassium *tert*-butoxide to the desired pentacyclic ketone XVII, m.p.  $183-185^{\circ}$ , 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.  $127-128^{\circ}$ , in 73% yield, which by Birch reduction (XIX, m.p. 78–81°) and subsequent

acetylation was converted into the N-acetyl compound XX, m.p. 152.5–153°, in 86% over-all yield.

Finally, introduction of the hydroxy group at C<sub>8</sub> was accomplished as follows: bromination of the *exo*-cyclic olefin XX with N-bromo succinimide afforded mainly the rearranged allylic bromide XXI which after epoxidation (XXII) was treated with zinc and ethanol to give a mixture of the allylic 8 $\beta$ - and 8 $\alpha$ -hydroxy compounds. This mixture was separated by alumina chromatography into each epimer, XXIII, m.p. 198–199° ( $\lambda_{max}^{CHCls}$  3604, 1625, 906 cm.<sup>-1</sup>) and XXIV m.p. 198– 200° ( $\lambda_{max}^{CHCls}$  3611, 1627, 907 cm.<sup>-1</sup>). Both XXIII and XXIV were proved to be the racemic forms of the naturally derived materials<sup>10</sup> by the complete identity of infrared spectra (CHCl<sub>8</sub>).

The  $8\alpha$ -epimer XXIV was oxidized to the corresponding enone XXV, m.p.  $160-168^{\circ}$  ( $\lambda_{max}^{EtOH}$  208 m $\mu$  ( $\epsilon$ 13,100), 232 m $\mu$  (shoulder);  $\lambda_{max}^{CHCl_3}$  1703, 1628, 942 cm.<sup>-1</sup>). The complete identity of the infrared (CHCl<sub>3</sub>) and ultraviolet spectra of this enone with those of an authentic sample of the optically active compound<sup>10</sup> again establishes the suggested configuration of the skeleton of atisine. Since reconversion of the enone to the allylic 8 $\beta$ -alcohol XXIII and its epimer XXIV, and transformation of the former to atisine in the natural series have already been performed by Pelletier and coworkers,<sup>10,11</sup> the present work represents a stereospecific total synthesis of *dl*-atisine.

(10) (a) S. W. Pelletier and P. C. Parthasarathy, *Tetrahedron Letters*, **No. 4**, 205 (1963). We are very grateful to Prof. S. W. Pelletier for the authentic samples of the natural compounds, XXIII, XXIV, and XXV, a copy of the paper prior to publication, and valuable discussions; (b) S. W. Pelletier, *Chem. Ind.*, (London), 1116 (1958).

(11) S. W. Pelletier and W. A. Jacobs, J. Am. Chem. Soc., **78**, 4144 (1956). Shionogi Research Laboratory Shionogi & Co., Ltd. Fukushima-ku, Osaka, Japan Masayuki Narisada

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## Concerning the Mechanism of a Reaction Catalyzed by Coenzyme $B_{12}$

Sir:

There are several biochemical transformations requiring coenzyme  $B_{12}$  as co-factor which lack ready precedent in organic chemistry. We wish to propose a detailed mechanism for one of these, the coenzyme  $B_{12}$ intermediated interconversion of methylmalonyl and succinyl CoA (Scheme 1). This mechanism finds di-

 $COSCOA \\ CH_{3}CH \implies COASCOCH_{2}CH_{2}CO_{2}H$ 

CO<sub>2</sub>H

## SCHEME 1

rect analogy in the observation by Heck and Breslow  $1^{-3}$  that carbonylation of methyl acrylate, by cobalt hydrocarbonyl under carbon monoxide at  $0^{\circ}$ , affords after methanolysis a 5:1 mixture of methyl methylmalonate and methyl succinate. The proposed mechanism is consistent with known chemistry of transition metal organometallic complexes and with results obtained from labeling experiments, which indicate that the methylmalonyl-succinyl CoA interconversion is an intramolecular<sup>4</sup> 1,2 shift of CoA bound carboxyl<sup>5-7</sup>

(1) R. F. Heck and D. S. Breslow, J. Am. Chem. Soc., 83, 4023 (1961). The observed product ratio is the reverse of that found at  $120^{\circ}$ ? The succinate-methylmalonate ratio found in the biochemical equilibrium is 10.5 at  $25^{\circ}$ .<sup>3</sup>

(2) H. Adkins and G. Krsek, *ibid.*, **71**, 3051 (1949).

(3) R. Stjernholm and H. G. Wood, Proc. Natl. Acad. Sci. U. S., 47, 303 (1961).

(4) R. W. Kellermeyer and H. G. Wood, Biochemistry, 1, 1124 (1962).

unaccompanied by exchange with added acrylic acid.<sup>7</sup> Consider first some reactions which are exhibited by

derivatives of metal carbonyls (Scheme 2). Acyl metal carbonyls (3) may be formed readily either from



acid halides (1) and metal carbonyl anions (2, M = Mn, Co, Re) or from olefins (5) and metal hydrocarbonyls (6) followed by carbonylation of the intermediate alkyl metal carbonyls 4.<sup>1,8-12</sup> Cleavage of 3 to form acid derivatives is also well authenticated.8 Thermal decomposition of ethyl cobalt tetracarbonyl (4, R = H, M = Co, n = 4) produces ethylene.<sup>1</sup> The most striking feature of acyl metal carbonyls, however, is their facile reversible decarbonylation to form alkyl metal carbonyls  $(3 \rightleftharpoons 4)$ .<sup>9,10,12-15</sup> In particular, acetyl manganese pentacarbonyl (and presumably the cobalt analog) containing <sup>14</sup>C in the acetyl carbonyl group is decarbonylated to produce 14Cfree carbon monoxide, while carbonylation of methyl manganese pentacarbonyl with <sup>14</sup>C carbon monoxide introduces no radioactivity into the acetyl group.15 The acyl carbonyl group remains attached to the metal during decarbonylation.

It is our contention that the mechanism of this coenzyme  $B_{12}$  catalyzed isomerization is similar to that of the prosaic carbonylation of olefins (Scheme 2) and that the chemistry of cobalt in coenzyme  $B_{12}$ (especially when reduced) will resemble that of metal carbonyls and other low valence transition metal complexes. The proposed mechanism is presented in Scheme 3.

This mechanism may be divided into three stages: acylation of a molecule of reduced coenzyme  $B_{12}$  to form methylmalonyl  $B_{12}$  9, reshuffling of this as in Scheme 2 to produce succinyl  $B_{12}$  14 and cleavage of 14 to CoA to produce succinyl CoA and regenerate the reduced coenzyme  $B_{12}$ . Since it is known that cobalamines (e.g., 15) may be reduced to a grey-green species which exhibits a nucleophilic coördinated cobalt



atom,  $^{16,17}$  it is reasonable to presume that coenzyme  $B_{12}$ 

(5) H. Eggerer, P. Overath, F. Lynen and E. R. Stadtman, J. Am. Chem. Soc., 82, 2643 (1960).

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(7) R. W. Swick, Proc. Natl. Acad. Sci. U. S., 48, 288 (1962).

(8) Fot a general discussion of carbonylation reactions see C. W. Bird, Chem. Rev., 62, 294 (1962).

(9) R. F. Heck and D. S. Breslow, J. Am. Chem. Soc., 83, 1097 (1961).

(10) R. F. Heck and D. S. Breslow, *ibid.*, **84**, 2499 (1962).

(10) R. T. Heck and D. S. Bleslow, Bids, 64, 2455 (1962).
 (11) W. Beck, W. Hieber and H. Tengler, Chem. Ber., 94, 862 (1961).

(12) T. H. Coffield, J. Kozikowski and R. D. Closson, J. Org. Chem., 22, 598 (1957).

(13) F. Calderozo and F. A. Cotton, Inorg. Chem., 1, 30 (1962).

(14) G. Both and J. Chatt, Proc. Chem. Soc., 67 (1961).

(15) T. H. Coffield, et al., Abstracts of Conference Papers, International Conference on Coördination Chemistry, London, April 6-11, 1959, Paper No. 26.

(16) E. L. Smith, L. Mervyn, A. W. Johnson and N. Shaw, Nature, 194, 1175 (1952).

(17) E. L. Smith and L. Mervyn, *Biochem. J.*, **86**, 2p (1963); see also patent claims that cobalt phthalocyanine dyes may be vatted, *e.g.*, *Chem. Abstr.*, **48**, 14231*f* (1954).