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_8 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 8β- and 8α-hydroxy compounds. This mixture was separated by alumina chromatography into each epimer, XXIII, m.p. 198–199° ($\lambda_{max}^{CHCl_3}$ 3604, 1625, 906 cm.$^{-1}$) and XXIV m.p. 198–200° ($\lambda_{max}^{CHCl_3}$ 3611, 1627, 907 cm.$^{-1}$). Both XXIII and XXIV were proved to be the racemic forms of the naturally derived materials[10] by the complete identity of infrared spectra (CHCl₃).

The 8α-epimer XXIV was oxidized to the corresponding enone XXV, m.p. 160–168° (λ_{max}^{EtOH} 208 mμ (ϵ 13,100), 232 mμ (shoulder); $\lambda_{max}^{CHCl_3}$ 1703, 1628, 942 cm.$^{-1}$). The complete identity of the infrared (CHCl₃) and ultraviolet spectra of this enone with those of an authentic sample of the optically active compound[10] again establishes the suggested configuration of the skeleton of atisine. Since reconversion of the enone to the allylic 8β-alcohol XXIII and its epimer XXIV, and transformation of the former to atisine in the natural series have already been performed by Pelletier and co-workers,[10,11] 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).

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Concerning the Mechanism of a Reaction Catalyzed by Coenzyme B₁₂

Sir:

There are several biochemical transformations requiring coenzyme B₁₂ as co-factor which lack ready precedent in organic chemistry. We wish to propose a detailed mechanism for one of these, the coenzyme B₁₂ intermediated interconversion of methylmalonyl and succinyl CoA (Scheme 1). This mechanism finds direct analogy in the observation by Heck and Breslow[1–3]
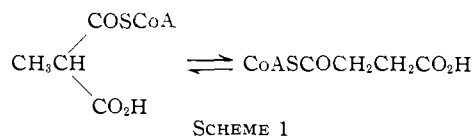
$$\underset{CO_2H}{\overset{COSCoA}{CH_3CH}} \rightleftharpoons CoASCOCH_2CH_2CO_2H$$

SCHEME 1

that carbonylation of methyl acrylate, by cobalt hydrocarbonyl under carbon monoxide at 0°, 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[4] 1,2 shift of CoA bound carboxyl[5–7]

(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°.[2] The succinate–methylmalonate ratio found in the biochemical equilibrium is 10.5 at 25°.[3]
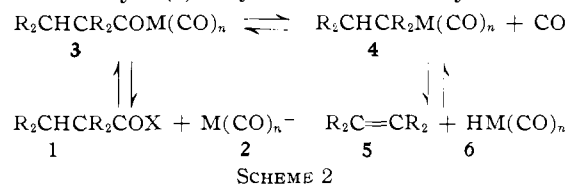
(2) H. Adkins and G. Krsek, ibid., 71, 3051 (1949).

(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.[7]

Consider first some reactions which are exhibited by derivatives of metal carbonyls (Scheme 2). Acyl metal carbonyls (3) may be formed readily either from

$$R_2CHCR_2COM(CO)_n \rightleftharpoons R_2CHCR_2M(CO)_n + CO$$

$$\text{3} \qquad\qquad\qquad \text{4}$$

$$R_2CHCR_2COX + M(CO)_n^- \qquad R_2C{=}CR_2 + HM(CO)_n$$

$$\text{1} \qquad\qquad \text{2} \qquad\qquad \text{5} \qquad\qquad \text{6}$$

SCHEME 2

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.[1,8–12] 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.[1] The most striking feature of acyl metal carbonyls, however, is their facile reversible decarbonylation to form alkyl metal carbonyls (3 ⇌ 4).[9,10,12–15] In particular, acetyl manganese pentacarbonyl (and presumably the cobalt analog) containing ^{14}C in the acetyl carbonyl group is decarbonylated to produce ^{14}C-free carbon monoxide, while carbonylation of methyl manganese pentacarbonyl with ^{14}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 B₁₂ catalyzed isomerization is similar to that of the prosaic carbonylation of olefins (Scheme 2) and that the chemistry of cobalt in coenzyme B₁₂ (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 B₁₂ to form methylmalonyl B₁₂ 9, reshuffling of this as in Scheme 2 to produce succinyl B₁₂ 14 and cleavage of 14 to CoA to produce succinyl CoA and regenerate the reduced coenzyme B₁₂. Since it is known that cobalamines (e.g., 15) may be reduced to a grey–green species which exhibits a nucleophilic coördinated cobalt
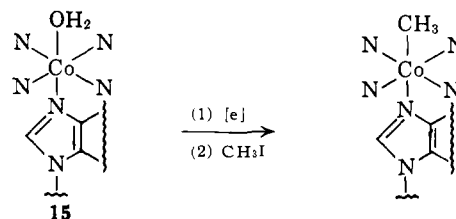
atom,[16,17] it is reasonable to presume that coenzyme B₁₂

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

(6) C. S. Hegre, S. J. Miller and D. Lane, Biochem. Biophys. Acta., 56, 538 (1962).

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

(8) For 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).

(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, 14231f (1954).

SCHEME 3

may be similarly reduced to a nucleophilic species (7 ⇌ 8) which may then be acylated by methylmalonyl CoA to form methylmalonyl coenzyme B_{12} (9). The second stage of the proposed mechanism is initiated by an intramolecular transcarbonylation (9 ⇌ 10 ⇌ 11) wherein no over-all ligand loss from cobalt occurs. Theoretical justification of this lies in the above discussed decarbonylation of acyl metal carbonyls and in the ready formylation of primary and secondary amines by metal carbonyls.[8,18] The flexibility of the strained corrin

$$R_2N-M(CO)_n \xrightarrow{\text{CO}} R_2\overset{i}{N}COM(CO)_n \longrightarrow R_2NCHO$$
$$\overset{i}{} \qquad \overset{ii}{}$$

ring system must play a large part in this transcarbonylation. Inspection of models reveals that one of the hydropyrrole rings may become approximately perpendicular to the plane of the other three. This affords a means of lengthening the cobalt nitrogen distance to accommodate the carbonyl group of 10 which would not be available in a rigid prophyrin ring system. The remainder of the mechanism is straightforward and parallels Scheme 2. Transient loss of acrylic acid from 10 to produce 12, re-addition of 12 to acrylic acid in the opposite sense to produce 13, recarbonylation of 13 to produce succinyl B_{12} 14 and cleavage of 14 by CoA will produce succinyl CoA and regenerate a molecule of reduced coenzyme B_{12}.

The proposed mechanism is completely consistent with results obtained from labeling experiments and in addition predicts a reduced form of coenzyme B_{12} as the active agent and the intermediacy of acyl derivatives of the coenzyme.

Among other biochemical transformations which require coenzyme B_{12} are the isomerization of propylene

(18) This reaction, which frequently occurs under quite mild conditions, probably proceeds *via* intermediates i and ii.[19]

(19) H. W. Sternberg and I. Wender, Abstracts of Papers, International Conference on Coördination Chemistry, London, April, 1959.

glycol to propionaldehyde[20,21] and the interconversion of glutamic and β-methylaspartic acid.[22,23] The last of these (Scheme 4) is superficially similar to the methylmalonyl–succinyl CoA rearrangement. However, from labeling experiments[23] (an over-all 1,2 shift of the glycine residue) and the observation that more

$$\overset{\pm}{HO_2CCH_2CH_2CHNH_2CO_2H} \rightleftharpoons \overset{\pm}{HO_2CCHCHNH_2CO_2H}$$
$$\overset{\underset{\displaystyle |}{}}{CH_3}$$

SCHEME 4

than one enzyme is necessary for this reaction,[23] the assumption that these two rearrangements are mechanistically closely related is not warranted at present.

(20) A. M. Brownstein and R. H. Abeles, *J. Biol Chem.*, **236**, 1199 (1961).

(21) R. H. Ables and H. A. Leed, Jr., *ibid.*, **236**, 2347 (1961).

(22) A. Munch-Petersen and H. A. Barker, *ibid.*, **230**, 649 (1958).

(23) H. A. Barker, *Fed. Proc.*, **20**, 956 (1961).

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A New Type of "Cyclonucleoside" Derived from 2-Chloro-8-mercapto-9-β-D-xylofuranosyladenine

Sir:

We wish to report a new type of compound, "8,2'-cyclonucleoside," in the purine series and a synthesis of 2'-deoxyadenosine *via* a route involving this compound.

In the purine nucleoside series the cyclonucleoside salt has been reported by Clark, *et al.*,[1] though the cyclonucleoside derived from 2-keto or thioketopyrimidine has been reported[2] by many investigators. The configurational similarity of the 8-hydroxy or 8-mercapto group of purine nucleoside to the 2-keto

(1) V. M. Clark, A. R. Todd and J. Zussman, *J. Chem. Soc.*, 2959 (1951).

(2) A. M. Michelson and A. R. Todd, *ibid.*, 816 (1955); D. M. Brown, D. B. Parihar and A. R. Todd, *ibid.*, 3035, 4242 (1958); G. Shaw and R. N. Warrener, *ibid.*, 50 (1959); J. F. Codington, R. Fecher and J. J. Fox, *J. Am. Chem. Soc.*, **82**, 2792 (1960); *ibid.*, **83**, 1889 (1961); N. C. Jung and J. J. Fox, *ibid.*, **83**, 3060 (1961).