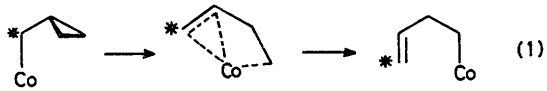
Rearrangements of Cyclopropylmethyl and But-3-enyl Cobaloximes

By MARTIN P. ATKINS, BERNARD T. GOLDING*, and PHILIP J. SELLARS
(*Department of Chemistry and Molecular Sciences, University of Warwick, Coventry* CV4 7AL)

Summary [1-^{13}C]-1-Cyclopropylmethyl(pyridine)cobaloxime (**1b**) rearranges (in $CDCl_3$ at 310 K) to [4-^{13}C]-but-3-enyl(pyridine)cobaloxime (**2b**); 1-methylbut-3-enyl-(pyridine)cobaloxime (**3**) rearranges to 2-methylbut-3-enyl(pyridine)cobaloxime (**4**) under the catalytic influence of trifluoroacetic acid in $CDCl_3$.

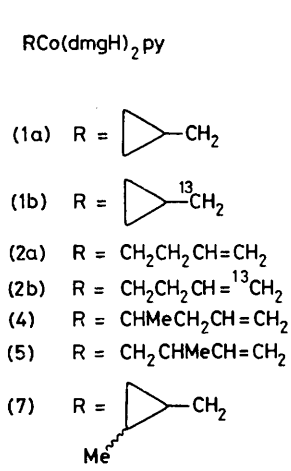
CHEMALY and PRATT[1] reported the thermal rearrangement of cyclopropylcarbinylcobalamin to but-3-enylcobalamin. This reaction was described as a carbon-skeleton rearrangement, the nature of which was unspecified. If it is an intramolecular reaction (but see later) and no shift(s) of hydrogen atoms occur, then a possible mechanism is *via* a homoallylic intermediate or transition state [equation 1)]. Continuing our investigations[2] with alkyl(base)-

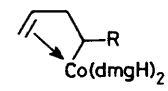


(1)

cobaloximes as models for alkylcobalamins, we have studied the reaction of ref. 1 with the corresponding cobaloximes (**1a**) and (**2a**). These compounds were prepared by the reaction of cyclopropylmethyl bromide and 4-bromobut-1-ene, respectively, with (pyridine)cobaloxime(I) in ethanol. To obtain pure (**1a**) it was necessary to carry out all operations in its preparation at 0 °C, because it is readily converted into (**2a**). This conversion is conveniently monitored by ^{1}H n.m.r. spectroscopy of (**1a**) in $CDCl_3$ at 310 K, whereupon it rapidly ($\tau_{\frac{1}{2}}$ *ca.* 3 h) is transformed to (**2a**).

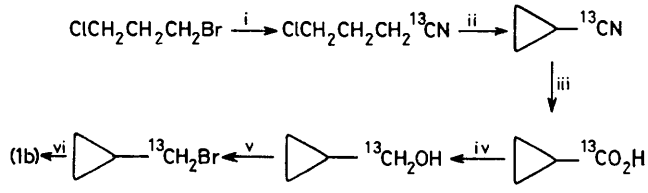
The mechanism of the conversion of (**1a**) into (**2b**) was studied with the specifically labelled cobaloxime (**1b**), synthesised as shown in the Scheme.[3] The intermediate [^{13}CN]-1-chloro-3-cyanopropane (95 atom % ^{13}C) was diluted with unlabelled material to a ^{13}C content of 32





(3) R = H
(6) R = Me

atom % in the cyano group. The {^{1}H}^{13}C n.m.r. spectra of (**1a**) and (**1b**) are shown in Figures A and B, respectively. Assignments of resonances (particularly important are peaks A—D) in these spectra are as follows: δ6·50 (A, 2 × cyclopropyl CH_2), 11·96 (B, 4 × dmgH Me), 14·04 (C, cyclopropyl *C*H), 38·09 (D, Co–CH_2, broad owing to coupling to Co), and 125·25, 137·47, 149·23, and 150·01 p.p.m. (4 × dmgH *C*=N and pyridine carbon atoms). In



Reagents: i, K^{13}CN (95 atom %); ii, NaOH; iii, aq. NaOH; iv, $LiAlH_4$–Et_2O; v, PBr_3–Et_2O; vi, (pyridine)cobaloxime(I).

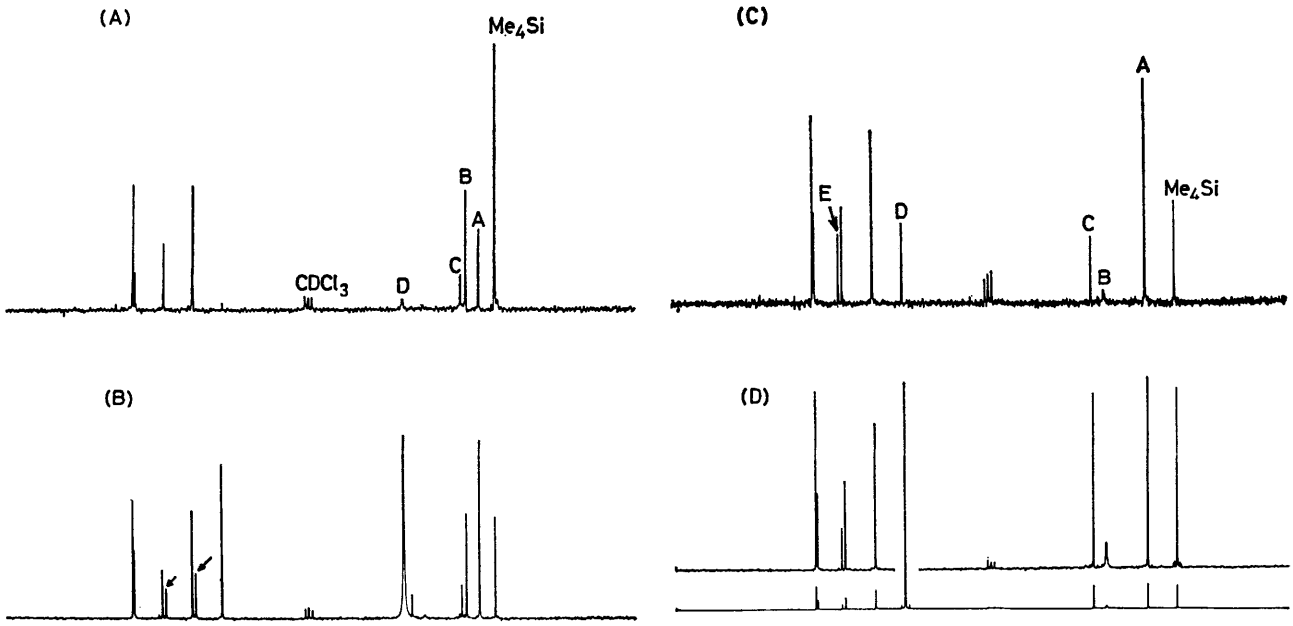


FIGURE. $\{^1H\}^{13}C$ n.m.r. spectra of compounds (**1a**) (A) (**1b**) (B), (**2a**) (C), and (**2b**) (D) in $CDCl_3$ (Me_4Si reference). For the purposes of obtaining the spectrum of (**1b**), a small amount of pyridine (arrowed peaks) was added to its solution in $CDCl_3$. At the time of running the sample of (**1b**), it already contains *ca.* 10% at (**2b**) [*cf.* (B) and (D)]. Although (**1b**) is largely labelled with ^{13}C at its Co–CH_2, there is probably a small amount of ^{13}C in the cyclopropyl methylene carbon atoms [*cf.* (A) and (B)] which arises during steps v and/or vi of its synthesis.

the spectrum (Figure B) of (**1b**) only the signal from the cobalt-bound carbon atom is of significantly enhanced intensity. A solution of (**1b**) (0·2 mol dm^{-3}) in $CDCl_3$ was incubated at 310 K in darkness and ^{13}C n.m.r. spectra were recorded at intervals.

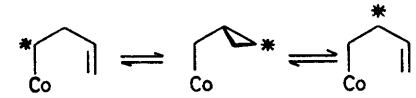
Signals from (**1b**) were replaced by signals due to (**2a**) and the spectrum after complete conversion (48 h) is shown in Figure D [this spectrum did not change after further incubation (1 week at 310 K, then 3 h at 333 K)]. Comparison of this spectrum with that (Figure C) of unlabelled authentic (**2a**) shows that only one signal from (**2b**) is of significantly enhanced intensity and this signal belongs to the olefinic methylene carbon (C-4) [assignments of the spectrum (Figure C) of (**2a**) are as follows: 12·09 (A, 4 × dmgH Me), 29·25 (B, Co–CH_2, broad), 34·51 (C, *C*-2), 112·90 (D, *C*-4), 139·09 (E, *C*-3), and 125·25, 137·53, 149·30, and 149·82 p.p.m. [*cf.* δ112·8 (*C*-1) and 140·2 (*C*-2) in the spectrum of but-1-ene]. These results are consistent with the mechanism of equation (1) and show that a cyclobutylcobalt species is not readily accessible from either (**1**) or (**2**) because this would have caused labelling at C-2 of (**2b**).

The conversion of (**1**) into (**2**) in $CDCl_3$ is arrested by addition of 1 mol. equiv. of pyridine. This suggests the intermediacy of a 5-co-ordinate species, as proposed by Dodd and Johnson[4] for the related degenerate rearrangement of allyl(pyridine)cobaloxime which is also suppressed by pyridine. The reversible loss of pyridine from (**1**) creates an additional co-ordination site on cobalt and permits the formation of the 18-electron homoallylic species[5] (**3**) [*cf.* equation (1)]. There is evidence for the production of 5-co-ordinate alkylcobaloximes in reactions of alkyl(aquo)cobaloximes which replace their water ligand with an amine.[6] An alternative mechanism[4] for the conversion of (**1**) into (**2**) is the intermolecular process in equation (2), which depends on the presence of adventitious traces of catalytic (pyridine)cobaloxime(II).† This

(2)

mechanism cannot be excluded by the present results (but see below).

If the transformation of (**1**) to (**2**) is reversible then a carbon-skeleton rearrangement can occur in which C-1 and C-2 of (**2**) will scramble according to equation (3).



(3)

This is because the methylene groups of the cyclopropyl group of (**1**) are enantiotopic. The consequences of such a process were demonstrated with 1-methylbut-3-enyl(pyridine)cobaloxime (**4**) and 2-methylbut-3-enyl(pyridine)cobaloxime (**5**), prepared from (pyridine)cobaloxime(I) and 4-bromopent-1-ene and 2-methylbut-3-enyl toluene-*p*-sulphonate, respectively. In the ^1H n.m.r. spectrum of (**4**) the 1-methyl group resonates at δ0·45 whereas the

† All cobaloximes in this paper were purified in darkness by column chromatography on silica gel using an eluting solvent containing 1% of pyridine. This procedure should remove cobaloxime(II) impurities. The resulting crystalline alkyl(pyridine)cobaloximes, pure by t.l.c. and ^1H n.m.r. spectroscopy after pumping, were used directly in the reactions described.

2-methyl group of (**5**) appears at $\delta 0{\cdot}91$, allowing their interconversion to be easily monitored. A slow transformation of (**4**) to (**5**) was observed in $CDCl_3$. This process was catalysed by trifluoroacetic acid {88% conversion of (**4**) into (**5**) with $[CF_3CO_2H]/[\text{total Co}] = 2{\cdot}29$, after 133 min at 310 K}. Using $CF_3CO_2{}^2H$ as catalyst no deuterium was incorporated into (**5**). Varying the concentration of (**4**) by a factor of 1·3, but keeping $[CF_3CO_2H]/[\text{total Co}]$ constant did not affect the rate of isomerisation of (**4**) to (**5**). These results indicate that the mechanism of conversion of (**4**) into (**5**) involves a 5-co-ordinate intermediate (**6**), the formation of which is facilitated by removal of co-ordinated pyridine as its trifluoroacetate. The intermediate (**6**) probably goes to the methyl cyclopropylcarbinylcobaloxime (**7**), which can ring open either to (**5**) or back to (**4**).

During the latter stages of the work described we learned that Dr. M. D. Johnson and his co-workers had also studied the rearrangement of (**4**) to (**5**). The importance of these findings to the mechanism of action of adenosylcobalamin-dependent enzymes is discussed in his paper.[7]

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[3] Based on the following papers in which the preparation of corresponding unlabelled material is described: C. F. H. Allen, *Org. Synth. Coll. Vol. I*, 1932, **156**; C. M. McCloskey and G. H. Coleman, *Org. Synth. Coll. Vol. III*, 1955, 221; J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, 1951, **73**, 2509.
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