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RADICAL REARRANGEMENT OF A THIOESTER MEDIATED BY COBALAMIN

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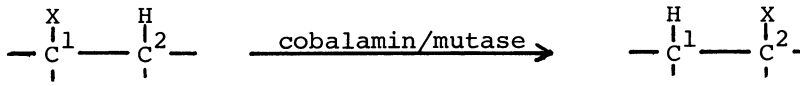
Zinc-reduction of 2-(ethylthio)carbonyl-2-phenylpropyl bromide in the presence of cobalamin gave the products formed by the migration of the thioester group. The formation of olefinic products excludes an anion mechanism and the rearrangement is concluded to be a radical rearrangement under the assistance of cobalamin.

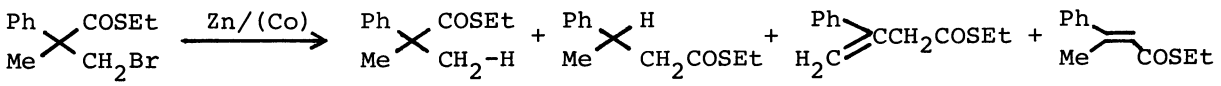
In biological system cobalamin catalyzes the isomarization of variety of compounds as shown in Eq. 1 (X=OH, NH_2, $C(CH_2)COOH$, $CH(NH_2)COOH$, COSCoA).[1] We have been concerned with model studies of the conversion of methylmalonyl-CoA into succinyl-CoA, and have proposed a radical mechanism assisted by cobalt complex.[2] An anion mechanism has also been proposed by Schrauzer et al.[3] We like to report here the experimental findings which support the radical rearrangement of a thioester group.



(1)

The reaction of 2-(ethylthio)carbonyl-2-phenylpropyl bromide (**1**)[4] with zinc in the presence of cobalamin, (Co), gave non-rearranged product **2** and (ethylthio)-carbonyl-rearranged products **3**-**5** (Eq. 2).[5] On the other hand the reaction without cobalamin gave only **2** in much slower rate. When the reaction was carried out in 10% NH_4Cl/MeOH, only reduction products **2** and **3** were obtained. However, the reaction in 10% AcOH/MeOH gave olefinic products **4** and **5** beside **2**. Under the former reductive conditions (NH_4Cl/MeOH) isolated **4** and **5** were further reduced to **3**. The reaction of bromide **1** with tributylstannane in benzene gave the non-rearranged product **2** and a phenyl-rearranged product **6**,[2] and contrary to the zinc-reduction mediated by cobalamin, no thioester migrated product was obtained as in the case the zinc-reduction without cobalamin.

In a similar model study Schrauzer et al.[3] obtained reduction products **8** and **9** on the reaction of 2-ethoxycarbonyl-2-(ethylthio)carbonylpropyl bromide (**7**, Y=Br) with zinc in the presence of cobalamin (Eq. 3). They got the similar result on the zinc reduction of the corresponding organo-cobalamin (**7**, Y=(Co)). These

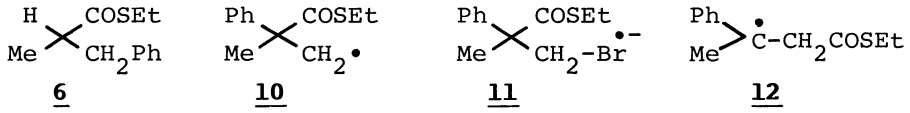


(2)

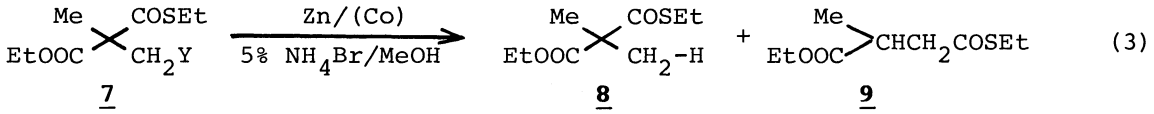
	1	**2**	**3**	**4**	**5**
In 10% NH_4Cl/MeOH		32%	56%	0%	0%
In 10% AcOH/MeOH		23%	trace	31%	32%

results led them to the proposal of an anion mechanism for the migration of the thioester group. However, it is notable that an alkyl-cobalt complex gives an alkyl radical as a primary reaction intermediate under reductive conditions ($NaBH_4$) and the radical intermediate is further reduced to a carbanion.[6] Murakami et al. have recently proposed an anion mechanism for the rearrangement of an ester group[7] and we agree to this proposal in the case of ester migration since the ester group does not rearrange through a radical intermediate.[8]

Our experimental findings suggest that the primary intermediate in the reaction shown in Eq. 2 is a radical species **10**. This redical intermediate can be formed by a single electron transfer from cobalamin(I) to give a radical anion **11** followed by the rupture of bromide ion,[9] or by the homolysis of the organo-cobalamin intermediate corresponding to **7** (Y=(Co)) under reductive conditions. The radical **10** isomerizes to radical **12** by the migration of the thioester group and collapses into the olefinic products **4** and **5**. The formation of **4** and **5** excludes the intervention of an anion intermediate, and suggests that a radical intermediate is involved in the cobalamin-mediated reaction of bromide **1** and that the rearrangement of the thioester group takes place in radical state under the influence of cobalamin(II).



6 **10** **11** **12**



7 **8** **9** (3)

References

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2) M. Tada, K. Inoue, K. Sugawara, M. Hiratsuka, and M. Okabe, Chem. Lett., 1985, 1821.
3) J. H. Grate, J. W. Grate, and G. N. Schrauzer, J. Am. Chem. Soc., 104, 1588 (1982).
4) Compound **1** (bp 95.5 °C/0.01 mmHg), prepared by bromomethylation of S-ethyl 2-phenylpropanethioate, was homogeneous from spectroscopic and chromatographic analyses. The structure was ascertained by the transformation into the corresponding methyl ester by the treatment with Na_2CO_3/MeOH.
5) A mixture of hydroxocobalamin (0.02 mmol) and 80 mg of zinc powder in 1 ml of methanol containing NH_4Cl or acetic acid was dipped in an ultrasonic bath to make cobalamin(I). The mixture was then treated with bromide **1** (0.03 mmol) and further exposed to ultrasonic agitation for 30 min. Products **2**, **3**, and **5** were identified with authentic samples and **4** was transformed into **3** by hydrogenation.
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