Reaction of *trans*-1,4-Dichlorobutene and Diethyl Acetamidomalonate. Formation of a New Lysine Intermediate

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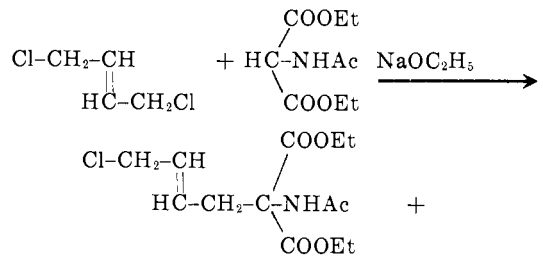
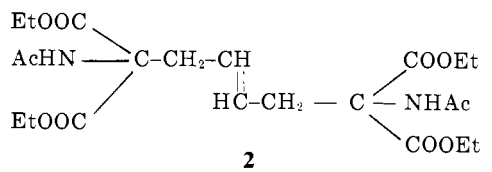
***trans*-1,4-Dichlorobutene and diethyl acetamidomalonate condensed to form *trans*-diethyl 4-chloro-2-butenyl acetamidomalonate and *trans*-1,4-(diethyl acetamidomalonyl)butene-2. Amination of the former gave an amine that could be converted to lysine.**

IN CONNECTION with a study involving synthetic approaches to certain amino acids, two hitherto unreported compounds were prepared, one a new lysine precursor. Thus, *trans*-1,4-dichlorobutene underwent condensation with diethyl acetamidomalonate to give a mixture of *trans*-diethyl 4-chloro-2-butenyl acetamidomalonate, **1**, and *trans*-1,4-(diethyl acetamidomalonyl)-butene-2, **2**.



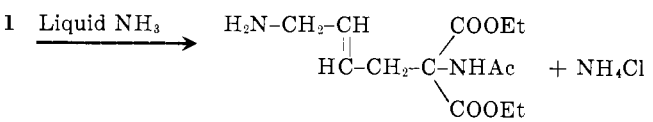
1



2

The formation of **1**, a new lysine intermediate, was favored by the use of excess halide and by the gradual addition of the sodio malonate solution to the halide.

Amination of the allylic chloride was readily accomplished to give *trans*-diethyl 4-amino-2-butenyl acetamidomalonate, **3**, in high yield.



3

Birkofer and Hempel (*1*) prepared this amino ester by a less direct route and converted it to a tritiated lysine.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were made using a Perkin-Elmer Model 21 recording spectrograph. PMR spectra were obtained with a Varian Associates A 56/60 analytical NMR spectrometer operating at 60 MHz. All PMR spectra were run on $CDCl_3$ solutions of approximately 10% w./w. concentration and containing a trace of tetramethyl silane (TMS) for internal referencing of peaks in parts per million δ.

Condensation of *trans*-1,4-Dichlorobutene and Diethyl Acetamidomalonate. Sodium (2.0 grams, 0.0875 gram atom) was dissolved in 100 ml. of ethanol, and 19.0 grams (0.0875 mole) of diethyl acetamidomalonate added. After strring and refluxing for 1 hour, a pale yellow solution resulted. This was cooled to 25° C., transferred under nitrogen to a dry addition funnel, and added during 1 hour with rapid stirring, to 55.0 grams (0.44 mole) of *trans*-1,4-dichlorobutene at 45° to 50° C. The resulting mixture was stirred and refluxed for 8 hours. After cooling, sodium chloride was removed and the filtrate evaporated on a rotary evaporator to leave 26.0 grams of a sirup. Distillation of a 6.6-gram aliquot produced 5.25 grams (77.5%) of **1**, b.p. 144–5° C./0.3 mm.). This rapidly solidified and was recrystallized from ether-hexane, m.p. 63.5–64° C.

Anal. Calcd. for $C_{13}H_{20}ClNO_5$: C, 51.07; H, 6.59; Cl, 11.62; N, 4.58.

Found: C, 51.62; H, 6.82; Cl, 12.10; N, 4.57. ν^{neat} 9.73 (trans olefin), 685 (possibly C—Cl), 1752 (ester carbonyl), 3280 (secondary amide NH), 1525, 1665 (secondary amide carbonyl).

PMR. 1.26 (t, 6.2, J = 7Hz, $COOCH_2CH_3$), 2.03 (S, 3.0 $NCOCH_3$), 3.08 (d-m, 1.8, Jd = 5.5Hz, $=CCH_2C$), 3.99 (d-m, 2.0, Jd = 5.5 Hz, $ClCH_2C=$), 4.24 (q, 4.0, J = 7Hz $COOCH_2$), 5.66 (m, 1.8, CH=CH), 7.02 (S, 0.9, CONH).

The residue in the distilling flask, when triturated with ether, gave 1.3 gram of **2**, m.p. 121.5–22° C. (from ether).

Anal. Calcd. for $C_{22}H_{34}N_2O_{10}$: C, 54.31; H, 7.04; N, 5.76.

Found: C, 53.94; H, 6.86; N, 5.72. ν^{neat} 957 or 978 (trans olefin), 1752 (ester carbonyl), 3280 (secondary amide NH), 1535, 1670 (secondary amide carbonyl).

PMR. 1.24 (t, 12.0, J = 7Hz, $COOCH_2CH_3$), 2.04 (S, 6.4, $NCOCH_3$), 2.98 (d-m, 4.0, Jd = 6Hz, $CH_2C=$), 4.23 (q, 8.0, J = 7Hz, $COOCH_2$), 5.27 (m, 1.8, CH=CH), 6.67.

Amination of *trans*-Diethyl 4-Chloro-2-butenyl Acetamidomalonate. The halide (4.0 grams, 0.012 mole) was added to 50 ml. of liquid ammonia and the mixture allowed to stand overnight at room temperature in a bomb. Following evaporation of the ammonia, the residue was taken up in chloroform and the ammonium chloride removed by filtration. Evaporation of the chloroform left the amino ester, **3**, as an oil, 3.5 grams, 94.5% yield.

ν^{neat} 973 (trans olefin), 1752 (ester carbonyl), 3380 (secondary amide and primary amide NH), 1515, 1680

(secondary amide carbonyl), 1620 (primary amine NH).

The amine was converted quantitatively to the known (*1*) hydrochloride by dissolving in chloroform, saturating with hydrogen chloride, and adding ether to precipitate the solid. M.p. 170–172° C. (from ethanol-ether). Lit. (*1*), 172° C.

PMR. 1.27 (t, 5.6, J = 7Hz, $COOCH_2CH_3$), 2.12 (S, 3.2, $NCOCH_3$), 3.07, (w.m., 2.1, $=\overline{CCH_2}C$), 3.66 (w.m., 2.5, $NCH_2C=$), 4.27 (q, 3.8, J = 7Hz, $COOCH_2$), 5.78 (w.m., 1.8, CH=CH), 7.4 and 8.25 (Broad, NH and CONH).

ACKNOWLEDGMENT

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LITERATURE CITED

(1) Birkofer, L., Hempel, K., *Ber.* **93**, 2282 (1960).

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Potential Inhibitors of Cholesterol Biosynthesis Phosphonates Derived from Geraniol and Congeners

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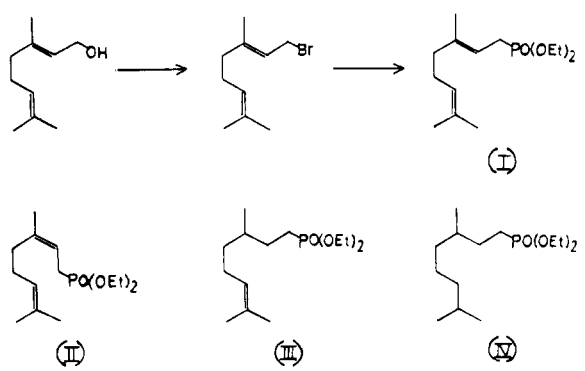
Diethyl (*E*)-3,7-dimethylocta-2,6-diene-1-phosphonate (I), diethyl (Z)-3,7-dimethylocta-2,6-diene-1-phosphonate (II), diethyl 3,7-dimethyloct-6-ene-1-phosphonate (III), and diethyl 3,7-dimethyloctane-1-phosphonate (IV) were prepared from geraniol, nerol, citronellol, and tetrahydrogeraniol, respectively. Under conditions used previously with geraniol, nerol was converted to the corresponding bromide with hydrogen bromide or phosphorus tribromide at low temperatures. Reaction of these allylic bromides with triethyl phosphite gave approximately equal amounts of phosphonates by substitution, and of unsaturated hydrocarbons by elimination. The allylic phosphonates were obtained without cis-trans or allylic rearrangement. The nonallylic phosphonates derived from citronellol and tetrahydrogeraniol were obtained in good yields.

MOST of the cholesterol-lowering agents used therapeutically exert their effect after the cyclization of squalene oxide to lanosterol, which often results in the accumulation of undesirable sterols. It seems desirable to develop inhibitors which affect the synthesis earlier in the sequence. This paper describes the synthesis of certain acyclic phosphonates, which might be expected to inhibit the condensation of geranyl pyrophosphate with isopentenyl pyrophosphate mediated by prenyltransferase.

The choice of phosphonates for study was based on the consideration that the nonbonding electrons on the oxygen atoms of geranyl and dimethylallyl pyrophosphates are undoubtedly involved in enzyme-substrate complexes. The external electron distribution in phosphonates, $RPO(OH)_2$, and thus their ability to bind to an enzyme site through magnesium, is similar to that in phosphates. However, the carbon-phosphorus bonds are not expected to cleave in enzymic reactions catalyzed by esterases or prenyltransferase. With regard to the steric requirements of the prenyltransferase surface, citronellyl pyrophosphate and terpene phosphates inhibit the coupling of geranyl pyrophosphate with isopentenyl pyrophosphate in vitro (*4*). The effectiveness of phosphonates as inhibitors of enzymic reactions involving organic phosphates as substrates has been demonstrated recently in a study of the phosphonate analog of pyridoxal phosphate (*1*).



The phosphonates of the terpenes were prepared by the Michaelis-Arbuzov reaction: $RBr + P(OEt)_3 \rightarrow RPO(OEt)_2 + EtBr$. The required terpene bromides were obtained from the alcohols either with phosphorus tribromide or hydrogen bromide. In the presence of appropriate amounts of tertiary amine, phosphorus tribromide is known to convert geraniol to its bromide without cis-trans or allylic rearrangement (*6*, *8*). With