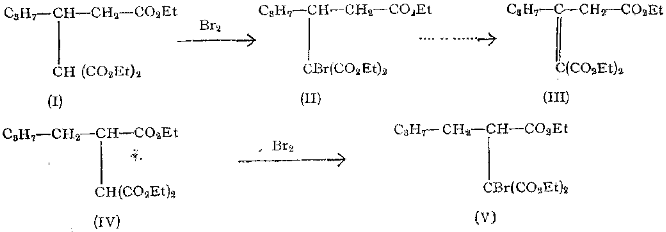
SYNTHETICAL INVESTIGATIONS IN THE THUJANE SERIES. PART XI.

Synthesis of an isomer of *a*-Thujadicarboxylic Acid (1-*iso*butyl-*cyclo*propane-1:2-dicarboxylic acid).

By P. C. Guha and M. S. Nande.

The application of the new method of synthesis of umbellularic acid (Guha and Muthanna, *Ber.*, 1938, **71**, 2668), was sought to be tried for the synthesis of thujadicarboxylic acid by the action of diazomethane upon *β*-*iso*propyl-*a*-carbethoxyglutaconic ester (III). The preparation of the compound (III) was tried by the action of diethylaniline, quinoline, pyridine, alcoholic potash, etc. upon *β*-*iso*-propyl-*a*′-carbethoxy-*a*′-bromoglutaric ester (II) by Guha and Muthanna (loc. cit.) without success.

With a view to elucidating whether the nonformation of III is due to the attachment of the bromo-malonic ester residue to the *β*-carbon atom of isocaproic acid, the compound (V) with the bromo-malonic ester group attached to the *a*-carbon atom has been synthesised by condensing ethyl *a*-bromo-*iso*caproate with sodio-malonic ester giving rise to (IV), and subsequent treatment of IV with bromine. The bromo-derivative on elimination of HBr with diethylaniline has given the desired unsaturated tri-ester (VI). This reacting with diazomethane gives the *cyclo*propane tri-ester (VII) readily, which on hydrolysis and decarboxylation furnishes the isomeric thuja-dicarboxylic acid (VIII).

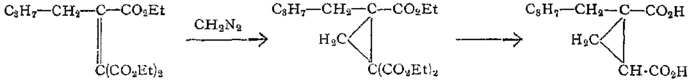


$$C_3H_7{-}\underset{\displaystyle CH(CO_2Et)_2}{\underset{|}{CH}}{-}CH_2{-}CO_2Et \xrightarrow{Br_2} C_3H_7{-}\underset{\displaystyle CBr(CO_2Et)_2}{\underset{|}{CH}}{-}CH_2{-}CO_2Et \dashrightarrow C_3H_7{-}\underset{\displaystyle C(CO_2Et)_2}{\underset{\|}{C}}{-}CH_2{-}CO_2Et$$

(I) (II) (III)

$$C_3H_7{-}CH_2{-}\underset{\displaystyle CH(CO_2Et)_2}{\underset{|}{CH}}{-}CO_2Et \xrightarrow{Br_2} C_3H_7{-}CH_2{-}\underset{\displaystyle CBr(CO_2Et)_2}{\underset{|}{CH}}{-}CO_2Et$$

(IV) (V)



(VI) (VII) (VIII).

EXPERIMENTAL.

*Ethyl α-bromo-*iso*butylacetate* was prepared via., *iso*butyl acetic acid starting from *iso*amyl alcohol according to the method of Noyes (*J. Amer. Chem. Soc.*, 1901, **23**, 392).

*Ethyl α-*iso*butyl-α′-carbethoxysuccinate* (IV).—Ethyl α-bromo-*iso*butyl acetate (136 g.) was treated with sodium malonic ester obtained from ethyl malonate (100 g.) and sodium (15.5 g.) in absolute alcohol (162 g.) and heating the mixture under reflux during 7 hours. Alcohol was removed under suction and the residual liquid treated with water. The oily layer thus obtained was washed with acidulated water and dil. sodium carbonate solution, ether extracted, dried, ether removed and the residual liquid distilled under reduced pressure, b.p. 175-176°/19 mm. (cf. Beatty, *J. Amer. Chem, Soc.*, 1908, **30**, 239).

*Bromination of ethyl-α-*iso*butyl-α′-carbethoxysuccinate* (IV): *Formation of ethylα-*iso*butyl-α′-carbethoxy-α′-bromosuccinate* (V).—To ethyl α-isobutyl-α′-carbethoxy succinate (105 g.) dissolved in an equal volume of carbon tetrachloride and warmed to 70°, dry bromine (20 c.c.) was added dropwise. After the evolution of hydrogen bromide ceased, the reaction mixture was heated under reflux on water-bath for about 3 hours, when the colour of the bromine nearly disappeared. The mixture was poured in ice-cold water and the separated oil washed with dil. sodium carbonate solution (5%), dried and fractionally distilled and the portion coming over at 175°/5 mm. was collected; yield 112 g. (68% of theory).

Action of diethylaniline on the bromo compound (V): *Formation of ethyl α-*iso*butyl-α′-carbethoxy-fumarate* (VI).—Ethyl α-*iso*butyl-α′-carbethoxy-α′-bromsuccinate (50 g.) was heated under reflux with freshly distilled diethylaniline (50 g.) on a metal bath during 8 hours. The product after cooling was treated with hydrochloric acid

(1 : 1) and the mixture extracted thoroughly with ether, the extract washed successively with dil. hydrochloric acid, sodium carbonate solution and water, dried, ether removed and the residual liquid distilled under reduced pressure, and the fraction coming between 112°-115°/2 mm. collected ; yield 15 g. This decolorised neutral potassium permanganate and bromine in carbon tetrachloride solution.

*Action of diazomethane on ethyl a-*iso*butyl-a′-carbethoxy-fumarate* (VI) *Formation of the* cyclo*propane ester* (VII).—The unsaturated ester (VI, 15 g.) was treated with diazomethane in ethereal solution (obtained from 6 g. of nitrosomethyl urea by the usual method) and allowed to stand in an ice chamber for one month. After removal of ether, the residue was distilled at reduced pressure, with frothing, when nitrogen was eliminated. It was then heated directly on a metal bath at 165-170° when the elimination of nitrogen was complete. The liquid when distilled under reduced pressure boiled at 108°-109°/2 mm.; yield 10 g.

*Hydrolysis of ethyl-a-*iso*butyl-a′-*cyclo*propanetricarboxylate* (VII) : *Formation of isomeric thujadicarboxylic acid* (VIII).—The above tricarboxylic ester was heated under reflux with hydrochloric acid (1 : 1) during 8 hours and the clear solution evaporated to dryness. The crude acid thus obtained crystallised from water, m.p. 98-99° (Found : C, 57.63 ; H, 7.89 ; Eq. Wt. 92.43. $C_9H_{14}O_4$ requires C, 58.06 ; H, 7.53 per cent. ; Eq. Wt. 93).

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