CCCLXIX.—*The Synthesis of Di*isopropylmalonic* Acid and Some Related Compounds, with Observations on the Polar Character of the* iso*Propyl Radical.*

By FREDERICK C. B. MARSHALL.

RILEY (this vol., p. 1642) has studied the effect of alkylation on the stability of the dimalonatocupriate ion, and it was of interest to examine the di*iso*propyl compound with the view of determining whether it would exhibit the lesser degree of stability characteristic of the dialkylated complexes or whether the stabilising effect produced by one *iso*propyl radical would be intensified by the introduction of a second.

The first step was the preparation of *di*iso*propylmalonic acid* (VII), which is now described together with a number of new compounds produced during its synthesis. The stability, or rather instability, curves of disodium di*iso*propylmalonatocupriate and other " *iso* "-alkylated complexes will form the subject of a future communication with Dr. Riley.

The preparation of ethyl di*iso*propylmalonate was first attempted by treating ethyl *iso*propylmalonate with a molecular amount of sodium or potassium, either " molecularised " in ether or as ethoxide in alcohol, and *iso*propyl iodide, but the original ester was recovered in all cases, although *n*-propyl and many other iodides reacted normally.

Ethyl cyanoacetate, however, is readily alkylated (Hessler, *J. Amer. Chem. Soc.*, 1913, **35**, 990) under the conditions of Henry (*Jahresber.*, 1889, 637), and by modifying Hessler's conditions ethyl di*iso*propylcyanoacetate was obtained in large quantity. This ester could be converted almost quantitatively into the *cyano-acid*, but further hydrolysis to the malonamic or malonic acid could not be effected with alkali of any strength. Fusion of the cyano-acid with potassium hydroxide gave *di*iso*propylacetonitrile* (III) in excellent yield, together with a small amount of *di*iso*propylacetamide* (IV). The production of the latter is interesting, since prolonged boiling of the acetonitrile (from which it is presumably formed in the fusion) with caustic alkali solution or with constant-boiling hydrochloric acid failed to effect hydrolysis, and even the more drastic treatment with alkaline hydrogen peroxide at 50° (Radziszewsky, *Ber.*, 1885, **18**, 355) resulted only in slow amide formation.

The reverse process, loss of water from di*iso*propylacetamide, however, takes place with such readiness that some nitrile is formed even on sublimation. Hydrolysis of di*iso*propylacetamide to the corresponding acetic acid could be effected only by means of nitrous acid.

Di*iso*propylacetonitrile was also produced in small amounts when the cyano-acid was distilled alone, with much charring when the potassium salt was heated, and together with a solid, m. p. 72°, when di*iso*propylcyanoacetic acid was distilled with phosphoric oxide.

The action of concentrated sulphuric acid and alcohol (Harding, Haworth, and Perkin, J., 1908, **93**, 1947) on di*iso*propylcyanoacetic acid produced only a small quantity of the cyano-ester. Twenty-four hours' treatment with cold concentrated sulphuric acid left the cyano-acid unattacked, but the malonamic acid (II) was produced at 100° after 20 hours (compare Fischer and Flateau, *Ber.*, 1909, **42**, 2983; Curtius, *J. pr. Chem.*, 1930, **125**, 211): this was not further hydrolysed by caustic alkali (compare Robinson, J., 1924, **125**, 226).

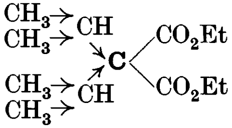
The hydrolysis of *di*iso*propylmalonamic acid* was ultimately achieved by means of nitrous acid in cold concentrated sulphuric acid (compare Bouveault, *Bull. Soc. chim.*, 1893, **9**, 370; Tafel and Thompson, *Ber.*, 1907, **40**, 4493), but it was never complete and the malonic acid (VII) could not be economically isolated.

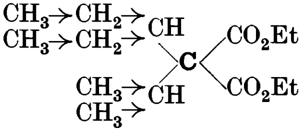
Di*iso*propylmalonamic acid was esterified neither by alcohol and hydrogen chloride after 50 hours nor by alcohol and sulphuric acid; the sole product after 4 days' treatment in the latter case was di*iso*propylacetamide in 8% yield. The methyl ester (V) was, however, prepared in good yield by means of diazomethane or methyl sulphate or by the action of methyl iodide on the *silver* salt.

The hydrolysis of *methyl di*iso*propylmalonamate* to *methyl hydrogen di*iso*propylmalonate* (VI) was best performed by Fischer's method (Fischer and Flateau, *loc. cit.*; Fischer and Brauns, *Ber.*, 1914, **47**, 3181) of passing nitrous fumes into an ethereal solution of the ester. The yield was good and separation from unreacted material facile. The methyl hydrogen ester was further hydrolysed by prolonged boiling with concentrated aqueous potassium hydroxide.

The inability to introduce a second *iso*propyl radical into *iso*propylmalonic ester under the usual conditions, a fact already observed by Thorpe (private communication), may be due to steric hindrance depending on the bulk of the groups about the central carbon atom **C** (IX) or to the polar * effect of the *iso*propyl group. Probably both factors are contributory to the inhibition, but that the " steric " factor is not alone responsible is demonstrable in several ways. First, the second *iso*propyl radical enters *iso*propylcyanoacetic ester almost as readily as the second methyl group enters methylcyanoacetic ester, for Hessler (*loc. cit.*) showed the reaction products to contain 10% and 12% of di*iso*propyl- and dimethyl-cyanoacetic ester respectively. Secondly, the point may be tested experimentally by endeavouring to introduce into *iso*propylmalonic ester a group whose " steric " effect is as great as or greater than that of the *iso*propyl group but which differs from it in polar nature. Such a combination is found in the group $(CH_3{\cdot}CH_2)_2CH^-$, where the electron sources (the methyl groups) are farther removed from the atom **C** (IX and X).

(IX.)





(X.)

Experiment showed that this group could be introduced—with some difficulty, it is true—into *iso*propylmalonic ester by the usual method. Further, the same *ester* could be prepared in the same yield by treating αγ-dimethyl*iso*propylmalonic ester with *iso*propyl iodide and sodium ethoxide.

It appears fairly evident, therefore, that (1) the inability to introduce a second *iso*propyl group into *iso*propylmalonic ester does not depend entirely on the size of this group, since an even larger one has been introduced, and (2) since, of the internally and the

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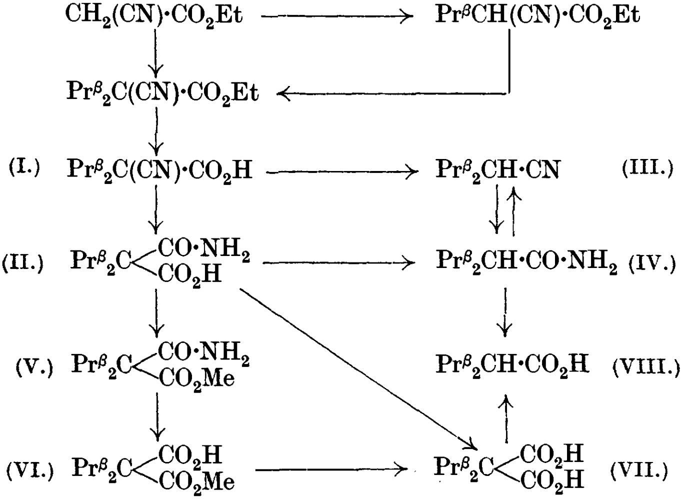
* " Polar " effect is intended to include all electronic disturbance—presumably due to the methyl groups—whether internally propagated through the valency linkings, or externally—" direct " effect.

externally transmitted effect of the methyl groups, it is the former which probably varies the more (from *I* to approx. 0) in the *iso*propyl and αγ-dimethyl*iso*propyl radicals, being almost negligible (Gane and Ingold, J., 1928, 1594) after transmission through more than two saturated bonds, the dominating factor controlling the introduction of the second *iso*propyl group is the polar effect of the methyl groups propagated through the valency linkings.

The complete series of reactions involved in the preparative portion of this paper is tabulated below.



EXPERIMENTAL.

*Ethyl Di*iso*propylcyanoacetate.*—The mixture of 90% of mono- and 10% of di-*iso*propylcyanoacetic ester produced by Hessler's method (*loc. cit.*) was treated with more sodium and *iso*propyl iodide (1 mol. of each) in the minimum quantity of alcohol. After a few hours, the alcohol was slowly distilled off on the steam-bath until the mixture had been concentrated to about one quarter of its original bulk; the product was then poured into water and the mixture of esters—now containing about 95% of di*iso*propylcyanoacetic ester—was extracted with ether and worked up in the usual way, unchanged mono*iso*propylcyano-ester being removed by shaking with cold 10% sodium hydroxide solution. The ester had b. p. 238—241° and was equal in weight to the original cyanoacetic ester.

By treating ethyl cyanoacetate with two equivalents of sodium ethoxide and *iso*propyl iodide in one operation the mixture of esters obtained contained 40% of the dialkylated ester. By using potassium ethoxide it is possible to keep the reactants more concentrated, so that reaction commences immediately on addition of the alkyl halide and is complete in a short time on the water-bath. The yield is identical with that above.

*Di*iso*propylcyanoacetic Acid.*—The ester was gently refluxed with 35% potassium hydroxide solution (3 vols.) and a little alcohol for 16 hours. On acidification, *di*iso*propylcyanoacetic acid* was obtained, m. p. 97·5° after recrystallisation from petroleum (b. p. 60—80°), in which it was sparingly soluble. The acid is easily soluble in alcohol, ether, and the usual organic solvents, but very sparingly soluble in water (Found: C, 63·8; H, 9·15; equiv., by titration 170. $C_9H_{15}O_2N$ requires C, 63·9; H, 8·9%; equiv., 169). The *silver* salt is insoluble in water, alcohol, and ammonia solution (Found: Ag, 39·1. $C_9H_{14}O_2NAg$ requires Ag, 39·1%).

Potash fusion. An intimate mixture of di*iso*propylcyanoacetic acid (5 g.) and molten potassium hydroxide (10 g.) on distillation gave two layers of distillate. The upper one, containing mainly *di*iso*propylacetonitrile* (III), was separated, washed with water, dried, and distilled; b. p. 170—171°. On evaporation the liquid deposited a few crystals of di*iso*propylacetamide, which could not be removed by distillation alone owing to their volatility in the vapour of the nitrile. The analytical specimen was obtained by distilling the nitrile over a little phosphoric oxide and retaining only the first two-thirds of the distillate (Found: C, 76·7; H, 12·1. $C_8H_{15}N$ requires C, 76·8; H, 12·0%). It had b. p. 170°, $d^{23°}$ 0·8105, $n_D^{23°}$ 1·4158, $[R_L]_D$ 38·8 (calc., 38·9). It was insoluble in water and had a camphoraceous odour resembling that of pinacolin.

*Di*iso*propylmalonamic Acid.*—Di*iso*propylcyanoacetic acid (20 g.) was heated with concentrated sulphuric acid (200 g.) at 100° for 20 hours. The brownish liquor obtained was cooled and poured on ice (500 g.), and the precipitated acid was washed with water, and dried at 100° (yield, 95% of the theoretical). It was a white powder, fairly easily soluble in ether, soluble in cold and very soluble in hot alcohol, and very sparingly soluble in cold water. Recrystallised from dilute sulphuric acid or from formic acid, washed with water, and dried in a vacuum, it formed large long prisms, m. p. 168° with evolution of carbon dioxide and formation of di*iso*propylacetamide (Found: C, 57·5; H, 9·3; CO_2 on melting, 23·8; equiv., by titration, 186·5. $C_9H_{17}O_3N$ requires C, 57·75; H, 9·1; CO_2, 23·55%; equiv., 187).

The *silver* salt is slightly soluble in water and easily in aqueous ammonia (Found: Ag, 36·5. $C_9H_{16}O_3NAg$ requires Ag, 36·7%). The ammonium salt is very soluble in water and crystallises in flat plates.

*Di*iso*propylacetamide* (IV).—The crude amide obtained by fusion of di*iso*propylmalonamic acid (above) was sublimed through filter-paper, care being taken to avoid dehydration. The pure *amide* formed long, white, prismatic needles, m. p. 149°, very soluble in alcohol, fairly easily soluble in ether, slightly soluble in hot water, and almost insoluble in cold (Found: C, 67·1; H, 12·0. $C_8H_{17}ON$ requires C, 67·1; H, 11·9%).

*Methyl Di*iso*propylmalonamate.*—(a) *By means of diazomethane.* Diazomethane from 6 g. of nitroso-*N*-methylurea * was distilled with ether during 2 hours into 5 g. of di*iso*propylmalonamic acid in a mixture of 200 c.c. of methyl acetate and 100 c.c. of ether cooled to − 15°. The mixture was kept for an hour and then freed from solvent by spontaneous evaporation. The residue was freed from acid by means of sodium carbonate solution and recrystallised from warm ether, from which the methyl ester separated in fine tetragonal prisms, m. p. 105°.

(b) *From the silver salt.* The dry silver salt reacted at once with methyl iodide (a slight excess in 3 vols. of ether) and after a few minutes the methyl ester was extracted with ether in almost theoretical yield.

(c) *By means of methyl sulphate.* A solution of 10 g. of the acid in more than twice the theoretical amount of 15% aqueous sodium hydroxide was shaken with an excess of methyl sulphate, with external cooling when necessary. The solid ester soon separated. Unchanged acid was recovered in the usual way and treated again with methyl sulphate. This method gives the purest product, but the yield is variable.

The *methyl di*iso*propylmalonamate* obtained by evaporation of the dried ethereal extract had m. p. 105°, unchanged by three recrystallisations. It was insoluble in water, easily soluble in alcohol, fairly easily soluble in ether, and sparingly soluble in petroleum (b. p. 60—80°) (Found: C, 59·6; H, 9·5; N, 6·6, 6·7. $C_{10}H_{19}O_3N$ requires C, 59·7; H, 9·45; N, 7·0%).

*Methyl Hydrogen Di*iso*propylmalonate* (VI).—Methyl di*iso*propylmalonamate (5 g.), suspended in a mixture of 60 c.c. of ether and 5 c.c. of water cooled in ice-water, was treated with nitrous fumes until a deep bluish-green solution was obtained. After some hours, more nitrous fumes were passed in and the process was repeated at intervals until the green colour was permanent. Ether was then removed under reduced pressure and the neutral ester was separated

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* Prepared by hypobromite oxidation of acetamide to acetylmethylurea, hydrolysis of this with boiling nitric acid, and treatment of the methylurea nitrate with ice-cold sodium nitrite solution by a modification of the details of Thorpe and Whiteley ("Manual of Organic Chemical Analysis," p. 136).

from the acid ester by cold dilute sodium carbonate solution and ether-extraction. The crude acid ester was precipitated in a fine state of division by excess of dilute sulphuric acid, traces of nitrous acid were removed by urea, and the *methyl hydrogen di*iso*propylmalonate* was extracted with ether and crystallised from petroleum (b. p. 60—80°); it separated from the hot solution in long slender prisms, m. p. 110°, and by slow evaporation in large cubical prisms (Found: C, 59·3; H, 9·1. $C_{10}H_{18}O_4$ requires C, 59·4; H, 8·9%).

*Di*iso*propylmalonic Acid* (VII).—The methyl hydrogen ester was boiled with 45% potassium hydroxide solution (3 mols.) for 36 hours, and any remaining unhydrolysed was separated by boiling petroleum (three extractions) from the acid obtained on acidification. Recrystallised from benzene–acetone or petroleum–acetone, *di*iso*propylmalonic acid* was obtained as a microcrystalline powder, m. p. 197° (decomp.), almost insoluble in light petroleum, benzene, or chloroform, easily soluble in alcohol and ether. The crystals from acetone–benzene contain benzene which is lost spontaneously on exposure to air (Found: C, 57·7; H, 8·5. $C_9H_{16}O_4$ requires C, 57·45; H, 8·5%).

The *silver* salt is fairly readily soluble in water, aqueous alcohol, and ammonia solution (Found: Ag, 53·6. $C_9H_{14}O_4Ag_2$ requires Ag, 53·75%). The copper salt, prepared by boiling the acid with copper oxide or carbonate and recrystallised from a large volume of water, is deep blue (compare Riley, *loc. cit.*). The sodium salt is soluble in water and aqueous alcohol; it is precipitated from aqueous solution by acetone.

*Di*iso*propylacetic acid* (VIII), obtained by heating di*iso*propylmalonic acid, was washed with water, dried, and distilled. It was a viscous liquid, very sparingly soluble in water, easily soluble in alcohol and ether; b. p. 214°/760 mm., $d^{20°}$ 0·9106, $n_D^{20°}$ 1·429 (Found: C, 66·6; H, 11·1; equiv., by titration, 142. $C_8H_{16}O_2$ requires C, 66·7; H, 11·1%; equiv., 144). The *silver* salt is insoluble in ammonia solution (Found: Ag, 43·25. $C_8H_{15}O_2Ag$ requires Ag, 43·0%).

Ethyl iso*Propyl-$\alpha\gamma$-dimethyl*iso*propylmalonate* (X).—This *ester* was obtained in 10% yield by either method mentioned on p. 2756, sodium ethoxide being used. When potassium ethoxide was used with *iso*propylmalonic ester and $\alpha\gamma$-dimethyl*iso*propyl iodide, the main reaction was between the ethoxide and the iodide, a considerable amount of Δ^{β}-pentene distilling with the alcohol during concentration of the mixture.

The fraction, b. p. 256—260°, was refluxed for 12 hours with dilute aqueous potassium hydroxide to remove traces of the monoalkylated ester. The pure compound has b. p. 258—259°/760 mm.,

$d^{20°}$ 0·9594, $n_D^{20°}$ 1·4380, $[R_L]_D$ 74·51 (calc., 74·54) (Found: C, 66·2; H, 10·4. $C_{15}H_{28}O_4$ requires C, 66·2; H, 10·3%).

Hydrolysis to the corresponding acid could not be effected, but the ester was further characterised by hydrolysis to the *ethyl hydrogen* ester, which was a viscous liquid, b. p. 152—158°/20 mm., $d^{18°}$ 1·015, $n_D^{18°}$ 1·455, $[R_L]_D$ 65·2 (calc., 65·3) (Found: C, 63·8; H, 10·1. $C_{13}H_{24}O_4$ requires C, 64·0; H, 9·8%).

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