248. *Fused Carbon Rings. Part V. Methods for the Synthesis of Reduced Dicyclic Systems.*

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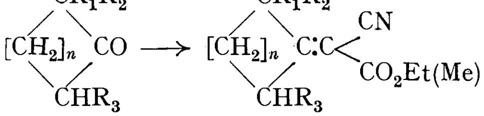
IN view of the lack of general methods for the synthesis of the important alicyclic systems containing two or more fused ortho-rings, a number of processes have been under review, and experiments along three lines are now described.

(1) We first attempted to generalise the method by which the β-*bicyclo*octanones had been prepared (Linstead and Meade, J., 1934, 935), depending primarily upon the condensation of cyanoacetic ester with a cyclic ketone containing an aliphatic ester group on the α-carbon atom. We now find that the ease with which this condensation proceeds depends upon the degree of substitution of the ring carbon atoms adjoining the keto-group. The reaction may be represented as

(I.)



(II.)

When R_1 is of the type $[CH_2]_x{\cdot}CO_2Et$ or $[CH_2]_x{\cdot}CO_2Me$ ($x = 0, 1,$ or 2), condensation occurs if R_2 and R_3 are both hydrogen, but if *either* R_2 *or* R_3 is an alkyl group, condensation either does not occur or is extremely slow. This is illustrated in the following table.

	Substituents in I.					
n.	R_1.	R_2.	R_3.	Amount of catalyst, %.*	Time of reaction.	Yield of II, %.
2	H	H	H	15	4 hours	75
2	$CH_2{\cdot}CO_2Et$	H	H	4	14 days	41
2	$CH_2{\cdot}CH_2{\cdot}CO_2Et$	H	H	5	5 ,,	33
3	$CH_2{\cdot}CH_2{\cdot}CO_2Me$	H	H	18	42 ,,	17
2	CO_2Et	Me	H	8	8 months	3
2	$CH_2{\cdot}CO_2Me$	Me	H	27	6 ,,	nil
2	$CH_2{\cdot}CO_2Me$	H	Me	27	6 ,,	,,
3	$CH_2{\cdot}CH_2{\cdot}CO_2Me$	Me	H	28	6 ,,	,,
3	$CH_2{\cdot}CH_2{\cdot}CO_2Me$	H	Me	27	6 ,,	,,

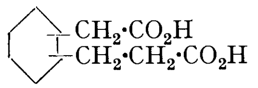
* The amount of catalyst (piperidine) is given as a percentage of the weight of cyanoacetic ester.

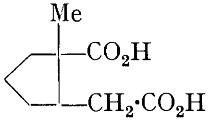
The fact that keto-esters in which R_2 is methyl do not condense prevents the use of the method for the synthesis of dicyclic compounds containing a bridge methyl group. The inhibiting effect of the alkyl groups can scarcely be due to a suppression of enolisation, and must therefore be attributed to steric hindrance. A methyl group on the β-carbon atom does not prevent condensation (unpublished work by Dr. R. L. Jones). When condensation occurs, the process is more efficient than the above yields indicate, for a large proportion of the uncombined reagents can be recovered. When condensation is inhibited, the piperidine and cyanoacetic ester—particularly the methyl ester—combine to give *cyanoacetopiperidide*.

cis-β-Decalone was synthesised from *cyclo*hexanone by this method as follows. The ketone was converted into methyl *cyclo*hexanone-2-β-propionate (cf. Haworth and Mavin, J., 1933, 1012), and this was condensed to *dimethyl*cyclo*hexylidene*-1-*cyanoacetate*-2-β-*propionate*. The saturated cyano-ester obtained from this yielded with boiling hydrochloric acid a little *cis*-β-decalone and mainly *cis*-*cyclo*hexane-1-acetic-2-β-propionic acid (III) (Hückel, *Annalen*, 1925, **441**, 1), which gave *cis*-β-decalone on cyclisation with baryta.

The unsaturated cyano-ester from ethyl 2-methyl*cyclo*pentanone-2-carboxylate, on reduction and hydrolysis, yielded 1-*methyl*cyclo*pentane*-1-*carboxy*-2-*acetic acid* (probably *cis*-) (IV), which contains an arrangement of substituents identical with that postulated for ring C of ætiobilianic acid.

(III.)





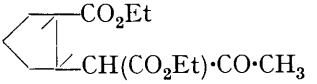
(IV.)

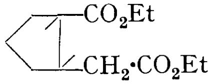
(2) The second method examined was the Michael addition of sodio-esters to unsaturated cyclic ketones and esters. Kon and Khuda (J., 1926, 3071) prepared decalin-1 : 3-dione from acetyl*cyclo*hexene by this process, which has been extended to the synthesis of alkyldecalins by Ruzicka, Koolhaas, and Wind (*Helv. Chim. Acta*, 1931, **14**, 1151; cf. Clemo, *Chem. and Ind.*, 1935, **54**, 314). Kon and Khuda's oxidations of decalin-1 : 3-dione were anomalous, for sodium hypobromite was stated to yield *cis*-*cyclo*hexane-1-carboxy-2-acetic acid and permanganate to give *trans*-*cyclo*hexane-1 : 2-dicarboxylic acid. The first of these results was doubtful, because the dicyclic substance must be mainly *trans*-, as deduced from the method of preparation and the physical measurements of Ruzicka, Koolhaas, and Wind. Repetition of these oxidations showed that, in fact, *both* the acids were of the *trans*-series, that obtained by the use of hypobromite being the *trans*-*cyclo*hexane-1-carboxy-2-acetic acid (m. p. 156—157°) of Windaus, Hückel, and Reverey (*Ber.*, 1923, **56**, 91).

A promising line of attack was blocked by the fact that a partial Clemmensen reduction of decalin-1 : 3-dione only yielded a trace of mono-ketone. This reduction might be accompanied by rearrangement of the ring, as in the analogous formation of trimethyl*cyclo*pentanone and trimethyl*cyclo*pentane from dimethyl*cyclo*hexanedione (Dey and Linstead, preceding paper), but there is no evidence of this from the physical properties of the fully reduced hydrocarbon (Ruzicka, Koolhaas, and Wind, *loc. cit.*). This difference between the simple and the fused *cyclo*hexane ring may be due to the fact that the formation of an intermediate three-membered ring is easier in the case of the less rigid single ring.

Ethyl sodioacetoacetate added to ethyl Δ^1-*cyclo*pentenecarboxylate to yield a mixture of *ethyl* trans-cyclo*pentane*-1-*carboxylate*-2-*acetoacetate* (V) and ethyl *trans-cyclo*pentane-1-carboxylate-2-acetate (VI), formed by ketonic fission of the primary addition product, but

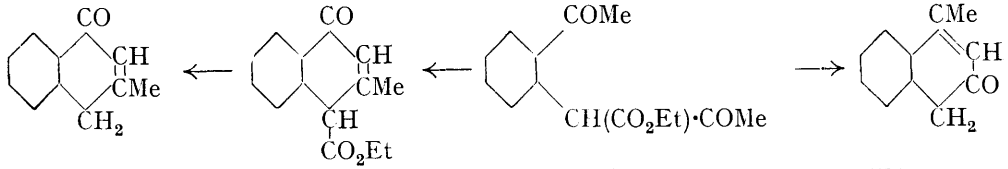
(V.)





(VI.)

little or no dicyclic material. Ethyl sodioacetoacetate reacted with acetyl*cyclo*hexene, on the other hand, to yield trans-3-*methyl*-Δ^2-*octal*-1-*one* (VII) and the corresponding keto-ester (VIII). The intermediate (IX) might cyclise in two ways to yield ultimately the ketones (VII)



(VII.) (VIII.) (IX.) (X.)

or (X). The ketone was reduced successively to trans-3-*methyl*-α-*decalone* and *trans*-2-methyldecalin, the latter resembling the material prepared by Ruzicka by a different method. The physical properties of both ketone and hydrocarbon placed them in the *trans*-series, as anticipated from the method of formation. Rather surprisingly, the hydrocarbon was dehydrogenated by selenium at 320—350° to 2-methylnaphthalene. This proved that the unsaturated ketone had the structure (VII) and not the alternative, (X). In agreement with this, it did not yield a benzylidene compound.

(3) In view of the recent extension of the Friedel–Crafts reaction to the alicyclic series, the ring-closure of cyclo*pentane*-β-*propionyl chloride* to α-*bicyclo*octanone was attempted. The *acid* was easily prepared by reduction of *cyclo*pentanone-2-β-propionic acid, but no simple ketone could be obtained by its dehydration or through the acid chloride. In view of this failure and that recorded by Bradfield, Jones, and Simonsen (J., **1934**, 1810), this line of attack was not pursued.

EXPERIMENTAL.

(1) cis-β-*Decalone*.—*cyclo*Hexanone-2-β-propionic acid melted at 66° in agreement with Haworth and Mavin. A mixture of 84 g. of its methyl ester (b. p. 140°/10 mm.), 46 g. of methyl cyanoacetate, and 8 g. of piperidine was left for 6 weeks at room temperature. Distillation of the dark red mixture gave (i) a little water and piperidine; (ii) 70% of unreacted esters, b. p. 108°/30 mm.—145°/15 mm.; (iii) cyanoacetopiperidide, b. p. 150—160°/1 mm., *ca.* 8 g.; (iv) the unsaturated cyano-ester, b. p. 175—185°/1·5 mm. On redistillation, fraction (iv) gave 20 g. (17%) of *dimethyl* cyclo*hexylidene*-1-*cyanoacetate*-2-β-*propionate* (II; $n = 3$, $R_1 = CH_2{\cdot}CH_2{\cdot}CO_2Me$; $R_2,R_3 = H,H$), b. p. 178—180°/1·5 mm., unsaturated to permanganate and stable on keeping (Found: C, 63·6; H, 7·25. $C_{14}H_{19}O_4N$ requires C, 63·4; H, 7·2%). Fraction (iii) solidified rapidly; the *cyanoacetopiperidide* crystallised from aqueous alcohol in large prisms, m. p. 88—89°. It yielded piperidine in quantity when boiled with alkali, and appears to be identical with Guareschi's product (Beilstein, III Edn., IV, 12) (Found: C, 63·0; H, 7·8. $C_8H_{12}ON_2$ requires C, 63·2; H, 7·9%).

The unsaturated cyano-ester was reduced by aluminium amalgam in moist ether, giving 13 g. (65%) of *dimethyl* cyclo*hexane*-1-*cyanoacetate*-2-β-*propionate*, a thick colourless oil, b. p. 165°/1 mm. (Found: C, 63·0; H, 7·8. $C_{14}H_{21}O_4N$ requires C, 62·9, H, 7·9%). 12 G. of this ester were hydrolysed (20 hrs.) with 36 c.c. of concentrated hydrochloric acid, the product distilled in steam until the distillate no longer smelt of ketone, and the residue evaporated to dryness under reduced pressure. The distillate on neutralisation, etc., gave 0·4 g. of *cis*-β-decalone semicarbazone, prisms from dilute alcohol, m. p. 183° (decomp.). The residue was dissolved in aqueous sodium carbonate and freed from neutral impurities with ether. The alkaline solution was then acidified, and the acid isolated by means of ether as a thick oil which deposited clusters of hard crystals after a few weeks. These were freed from oil and crystallised thrice from dilute alcohol. *cis-cyclo*Hexane-1-acetic-2-β-propionic acid (III) formed small prisms, m. p. 109—110° (cf. Hückel, *loc. cit.*) (Found: C, 61·6; H, 8·4; equiv., 106·5. Calc. for $C_{11}H_{18}O_4$, dibasic: C, 61·7; H, 8·4%; equiv., 107). The yield of solid acid was 42%; no *trans*-

acid could be isolated from the residual oil. The *cis*-dianilide melted at 165° (Hückel, 163°) after two crystallisations from dilute methanol. 1·5 G. of the *cis*-acid were ketonised smoothly at 280—300° in the presence of a few crystals of baryta. The *cis*-β-decalone was identified as the semicarbazone, m. p. 182—183° (decomp.) (Hückel, 182°), identical with that obtained in the steam distillation above (Found: N, 20·4. Calc. for $C_{11}H_{19}ON_3$: N, 20·1%). The yield of pure semicarbazone was 73%, and 2% of *cis*-acid was recovered.

The condensation of 2-methyl*cyclo*hexanone with ethyl β-bromopropionate gave a considerably better yield (83%) of mixed 2-methyl*cyclo*hexanone-2- and -6-propionic esters than that reported by Ruzicka, Koolhaas, and Wind (*loc. cit.*, p. 1169). These were separated by Ruzicka's method. Both failed to condense with cyanoacetic ester under the conditions given in the table. The corresponding methyl 2-methyl*cyclo*pentanone-2- and -5-β-propionates were prepared by the usual procedure from 2-methyl*cyclo*pentanone, sodamide, and methyl chloroacetate (40% yield), and were separated by Ruzicka's method into 43% of the 2 : 2-ester and 8% of the 2 : 5-ester, both of which boiled at 110°/12 mm. Neither ester condensed with cyanoacetic ester under the conditions given in the table.

200 G. of ethyl 2-methyl*cyclo*pentanone-2-carboxylate, 130 g. of ethyl cyanoacetate, and 10 c.c. of piperidine gave after 8 months 10 g. of condensation product, b. p. 150—157°/1 mm., which was reduced to the saturated cyano-ester, b. p. 148—150°/1 mm. (7 g.). Hydrolysis in the usual way gave a gum which slowly crystallised. The solid 1-*methyl*cyclo*pentane*-1-*carboxy*-2-*acetic acid* (IV) crystallised in small cubes from benzene–petroleum, m. p. 124—125° (125—126° after a further crystallisation from water, in which it was quite soluble) (Found: C, 58·0; H, 7·6; equiv., 94. $C_9H_{14}O_4$, dibasic, requires C, 58·1; H, 7·5%; equiv., 93).

(2) *Michael Additions.*—Decalin-1 : 3-dione, obtained as a crystalline solid, m. p. 142°, in agreement with Kon and Khuda (contrast Ruzicka, Koolhaas, and Wind, *loc. cit.*), was oxidised with sodium hypobromite by their method. The carboxy-acetic acid after crystallisation melted at 156—157° (Windaus, Hückel, and Reverey, *loc. cit.*). Permanganate oxidation of the dione yielded *trans*-hexahydrophthalic acid, m. p. and mixed m. p. 220°, sparingly soluble in ether.

Ethyl $\triangle^1$-*cyclo*pentenecarboxylate (Cook and Linstead, J., 1934, 959) was refluxed overnight with equimolecular amounts of ethyl acetoacetate and alcoholic sodium ethoxide (steam-bath). The product was separated by distillation into 23% of ethyl *trans*-*cyclo*pentane-1-carboxylate-2-acetate (VI), b. p. 148°/16 mm. (Cook and Linstead, *loc. cit.*), and 8% of *ethyl* trans-cyclo*pentane*-1-*carboxylate*-2-*acetoacetate* (V), b. p. 176°/16 mm. (Found: C, 62·6; H, 8·1. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·1%). A small amount of a solid, m. p. 64°, which was soluble in alkali and probably dicyclic, was also isolated.

Acetyl*cyclo*hexene (Darzens, *Compt. rend.*, 1910, **150**, 707) was similarly condensed with ethyl sodioacetoacetate (1 mol.; 5 hrs.). Scarcely any acidic product was formed, and the neutral material consisted of 15% of unchanged reactants, 10% of trans-3-*methyl*-Δ^2-*octal*-1-*one* (VII) and 30% of *ethyl* trans-3-*methyl*-Δ^2-*octal*-1-*one*-4-*carboxylate* (VIII). The former (Found: C, 80·3; H, 9·6. $C_{11}H_{16}O$ requires C, 80·5; H, 9·8%) boiled at 110—111°/10 mm. and immediately reduced neutral permanganate. The latter (Found: C, 70·9; H, 8·6. $C_{14}H_{19}O_3$ requires C, 71·2; H, 8·5%) boiled at 180°/9 mm., was unsaturated to permanganate, and gave a violet colour with ferric chloride. Catalytic reduction of the ketone in alcohol over Adams's platinum gave a 45% yield of trans-3-*methyl*-α-*decalone*, together with some high-boiling auto-condensation products. The *semicarbazone* formed small needles, m. p. 203—205°, from dilute pyridine (Found: C, 65·1; H, 9·5. $C_{12}H_{21}ON_3$ requires C, 64·6; H, 9·4%); from this, the ketone was regenerated, b. p. 120°/8 mm., $n_D^{17·4°}$ 1·4853, $d_{4°}^{17·4°}$ 0·9815, $[R_L]_D$ 48·58 (calc., 48·61) (Found: C, 79·1; H, 11·0. $C_{11}H_{18}O$ requires C, 79·5; H, 10·8%). The semicarbazone, on distillation with potash and a little palladised barium sulphate, yielded *trans*-2-methyldecalin, which after purification in the usual way (cf. J., 1934, 956) had b. p. 78°/14 mm., $n_D^{17·4°}$ 1·4761, $d_{4°}^{17·4°}$ 0·8712, $[R_L]_D$ 48·84 (calc., 48·60) (Found: C, 86·5; H, 13·0. Calc. for $C_{11}H_{20}$: C, 86·8; H, 13·2%). These constants are in reasonably good agreement with those of Ruzicka, Koolhaas, and Wind (*loc. cit.*, p. 1154), who give b. p. 76°/12 mm., $n_D^{20°}$ 1·4681, $d_{4°}^{20°}$ 0·8670; $[R_L]_D$ 48·75. The hydrocarbon was dehydrogenated over selenium for 18 hrs. at 320—350° (bath temp.). The product, isolated in the usual way, gave a poor yield of an oil which readily formed a picrate. This crystallised from alcohol in yellow needles, m. p. 115° alone or admixed with the picrate of authentic β-methylnaphthalene.

(3) 60 G. of *cyclo*pentanone-2-β-propionic acid (Cook and Linstead, J., 1934, 953) were refluxed for 6 hrs. with 200 c.c. of concentrated hydrochloric acid and 200 g. of amalgamated zinc. The reduced acid, isolated by means of ether, gave on fractionation 29 g. of cyclo*pentane*-2-

β-*propionic acid* as a colourless mobile liquid which solidified in ice; b. p. 131°/6 mm., $n_D^{17.4°}$ 1·4594, $d_{4°}^{17.4°}$ 1·0100, $[R_L]_D$ 38·51 (calc., 38·52) (Found: C, 68·0; H, 10·0. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%). 17 G. of unchanged keto-acid (b. p. 175°/10 mm.) were recovered. The following derivatives of *cyclo*pentanepropionic acid were prepared: *ethyl* ester (88% yield, Fischer–Speier method at room temperature), pleasant-smelling liquid, b. p. 90°/9 mm. (Found: C, 70·5; H, 10·6. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·6%); *acid chloride* (thionyl chloride at 90°), b. p. 66°/1·5 mm. (Found: Cl, 21·7. $C_8H_{13}OCl$ requires Cl, 22·1%); *anilide* (from the acid chloride), long needles from dilute acetic acid, m. p. 110° (Found: C, 77·5; H, 8·5. $C_{14}H_{19}ON$ requires C, 77·4; H, 8·8%). The acid yielded no α-*bicyclo*octanone when distilled over phosphoric oxide. The acid chloride reacted vigorously when treated with aluminium chloride in light petroleum, but only a yellow waxy solid could be isolated from the product.

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