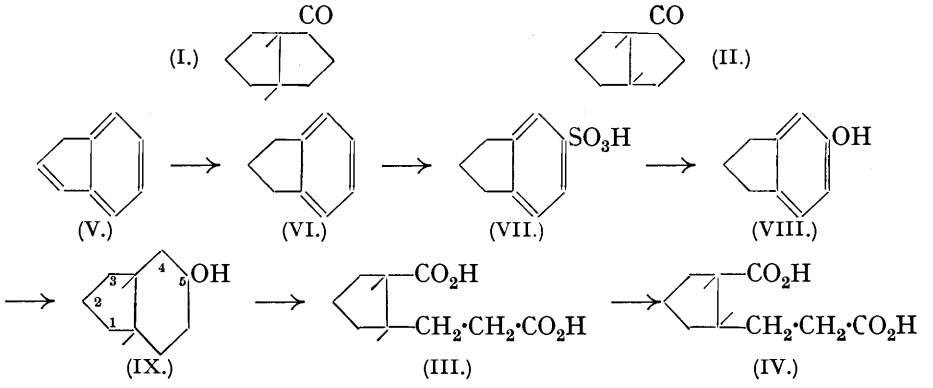
198. *Fused Carbon Rings. Part II. The Synthesis of* cis-α-0 : 3 : 3-bicyclo*Octanone and Related Compounds.*

By A. H. Cook and R. P. Linstead.

As was indicated in the introduction (preceding paper), the special interest of α-*bicyclo*-octanone is that the adjacence of the carbonyl group to the central bridge renders possible a direct interconversion of the two stereoisomeric forms (I) and (II) which is not possible in the β-ketones.

The cis- and trans-cyclo*pentane*-1-*carboxy*-2-*propionic acids* (III and IV) required for

the preparation of the α-ketones were synthesised from indene by the method indicated below :



The most attractive methods for the conversion of indane * (hydrindene) (VI) into the phenol (VIII) are : (1) the reduction of 5- and 6-hydroxyindanones, themselves prepared (a) by ring closure of the chloride of *m*-methoxy-β-phenylpropionic acid or (b) from phenyl α-bromopropionate by molecular rearrangement and ring closure (v. Auwers and Hilliger, *Ber.*, 1916, **49**, 2410); (2) the nitration, reduction, and diazotisation of indane; and (3) the sulphonation of indane, followed by potash fusion. After preliminary experiments method (3) was developed to give the phenol in satisfactory quantity.

Indane-5-sulphonic acid (VII) was readily prepared and separated from the 4-isomeride by a modification of Spilker's method (*Ber.*, 1893, **26**, 1538), but in our hands the process of Borsche and Pommer (*Ber.*, 1921, **54**, 102) was unsatisfactory. The sodium salt of (VII) gave a good yield of (VIII) on fusion with potash, the product being identical with that of Borsche and John (*Ber.*, 1924, **57**, 656). The hydroxyl group is therefore certainly in position 5. Catalytic reduction of the phenol to cis-5-*hydrindanol* (IX) was readily effected with platinum in acetic acid solution. (The term *cis* here refers to the linking of the rings and not to the position of the hydroxyl group with respect to the second ring, which is unknown.) A small amount of *cis*-hydrindane, but no hydrindanone, was formed in this reduction.

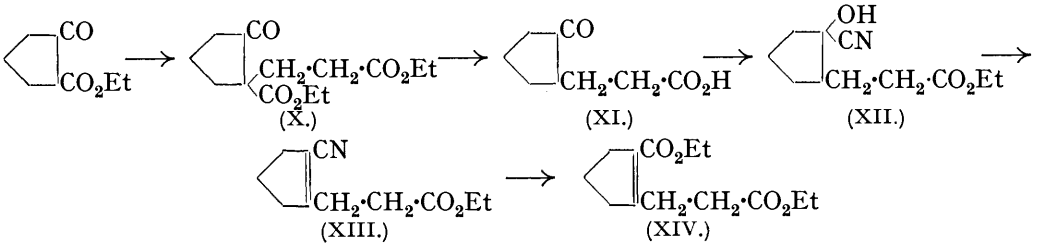
When this work was put in hand it was expected that the alcohol (IX) would simulate *cis*-β-decalol on oxidation and yield mainly *cis-cyclo*pentane-1 : 2-diacetic acid (see Part I) and only a small amount of the isomeric *carboxy-propionic acid* (III). Oxidation, however, gave exclusively the latter product, and no trace of the diacetic acid was found, although its detection would have been simple owing to its comparative insolubility. The oxidation was best carried out with warm concentrated nitric acid; the hot dilute acid gave a poorer yield, Beckmann's mixture formed the hydrindanone (p. 948), and potassium permanganate broke the molecule completely.

The *cis*-configuration of the acid was shown in two ways. On treatment with hydrochloric acid at 180° an isomeric *acid* was obtained, which is accordingly given the *trans*-configuration (IV). The same change was effected by a modification of the excellent method of Hückel and Goth (*Ber.*, 1925, **58**, 447), the *diethyl* ester of the *cis*-acid being converted into the *trans*-isomeride by the action of potassium in ether, followed by acidification. These configurational changes were obscured at first owing to the remarkable coincidence that the two acids (III and IV) melted at the same temperature and their *dianilides* behaved similarly. The acid stable to hydrochloric acid, however, depressed the melting point of the parent compound and also showed characteristic differences in solubility and crystalline form. As the two anilides also depressed each other's melting points and the diethyl esters differed in physical properties, no doubt remained that the acids were stereoisomeric and not identical.

The structure of these acids was practically certain from the method of formation,

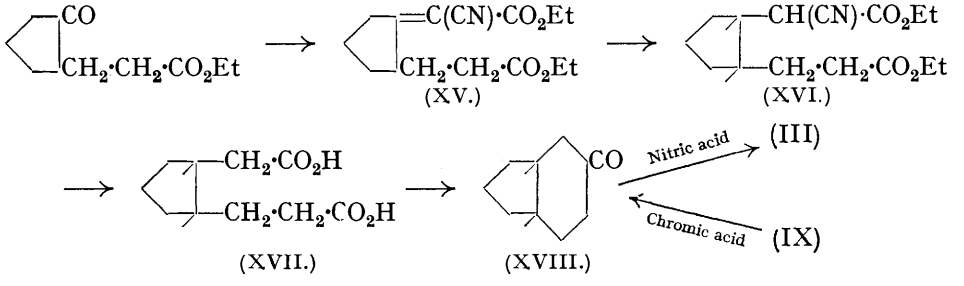
* Nomenclature following Hückel; see p. 935.

from the production of a dicyclic ketone on pyrolysis (see below), and from their non-identity with the diacetic acids of Part I, but in view of the fact that they had been formed by a destructive reaction it was considered advisable to carry out an independent synthesis from a *cyclo*pentane compound. The process indicated below was first examined :



The *cyanohydrin* of *ethyl* cyclo*pentanone*-2-β-*propionate* * (XII) was dehydrated to *ethyl* 1-*cyano*-cyclo*pentene*-2-β-*propionate* (XIII), which could not be reduced by aluminium amalgam or catalytically. Hydrolysis of (XIII) with alcoholic acid led to the *unsaturated* ester (XIV), and a small quantity of the corresponding acid was obtained by treatment of (XIII) with alkali. The ester (XIV) could not be reduced satisfactorily with platinum and hydrogen or with aluminium amalgam, although it was unsaturated to permanganate. It is therefore possible that the double bond in (XIII) and (XIV) is in reality in the side chain, whence the compounds will be of the Δ^{β}-dihydromuconic class, which are known to be difficult to reduce.

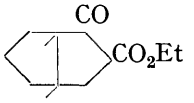
In view of these difficulties it was decided to synthesise a suitable hydrindanone from ethyl *cyclo*pentanonecarboxylate and oxidise it to *cis-cyclo*pentane-1-carboxy-2-propionic acid. For this purpose the method of Linstead and Meade (preceding paper) was applied to *cyclo*pentanone-2-propionic ester, and cis-cyclo*pentane*-1-*acetic*-2-*propionic acid* (XVII) obtained without difficulty. This acid was smoothly converted at 315—320° in the presence of baryta into cis-5-*hydrindanone* (XVIII), which was oxidised by nitric acid to *cis-cyclo*pentane-1-carboxy-2-propionic acid identical with that prepared from indene. The connexion between the two series of compounds was consolidated by the oxidation of the 5-hydrindanol (IX) prepared from indene into the ketone (XVIII) identical with that synthesised from *cyclo*pentanone-2-propionic ester. As far as we are aware, the identity of the products formed by the two routes supplies the first proof by degradation of the presence of the five-membered ring in indene.



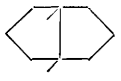
The structure of the carboxy-propionic acids being established, we can now consider their conversion into dicyclic compounds. The *cis*-acid gave a good yield of cis-α-0 : 3 : 3-bicyclo*octanone* (I) when heated with baryta at 280—290°. When its ester was heated with sodium in benzene, it gave *ethyl* cis-α-bicyclo*octanone*-β-*carboxylate* (XIX), which, from its physical constants and intense colour with ferric chloride, existed in the

* We find that acids of the type of (XI) and their esters yield derivatives by substitution, such as hydrazones and semicarbazones, but these are not given by keto-esters of type (X). On the other hand, both types, and even the highly enolic ethyl *cyclo*pentanonecarboxylate itself, yield cyanohydrins with ease.

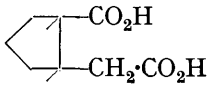
enolic form like the isomeric β-keto-α-carboxylate (p. 945). On hydrolysis the keto-ester yielded *cis*-α-*bicyclo*octanone.



(XIX.)



(XX.)



(XXI.)

*trans-cyclo*Pentane-1-carboxy-2-propionic acid (IV) *gave the same* α-bicyclo*octanone* when heated with baryta. The yield was of the same order, but a slightly higher temperature (*ca.* 320°) was necessary to bring about the ring closure. The ketone obtained by both methods was the practically pure *cis*-isomeride : it differed very little in properties from material regenerated from the pure *cis*-semicarbazone and its derivatives separated in an almost pure condition. When the ester of the *trans*-acid was submitted to the Dieckmann reaction, the *cis*-keto-ester (XIX) was formed, identical with that obtained from the *cis*-ester. This presents an instructive contrast with the *trans*-diacetic ester of Part I, in which no change of configuration is possible and no ring closure occurs.

trans-α-*bicyclo*Octanone has therefore not been obtained and it appears improbable that it will be capable of preparation by the cyclisation of *cyclo*pentane derivatives.

When the *semicarbazone* of the *cis*-ketone was distilled with caustic potash, *cis-bicyclo*-octane (XX) was evolved together with nitrogen and ammonia (this modification of the Kishner–Wolff reaction appears to be an improvement on the customary process).

The *cis*-α-ketone in both the " crude " and the regenerated condition was oxidised by nitric acid to *cis-cyclo*pentane-1-carboxy-2-acetic acid (XXI) identical with that synthesised by Linstead and Meade (see also Part III).

The α-*bicyclo*octanone series therefore *resembles* the α-decalone series in the fact that both *cis*- and *trans*-monocyclic 1-carboxy-2-propionic (or -butyric) acids yield the same dicyclic α-ketone, but *differs* in that this ketone is of the *cis*-series, whereas with α-decalone the ketone has the *trans*-configuration.

It will be convenient to summarise at this stage the evidence for the configuration of the *bicyclo*octanes. No absolute determination of configuration has yet been achieved and the evidence is based on a number of analogies which support one another and are almost certainly correct.

(1) The configuration of the two *cyclo*pentane-1-carboxy-2-acetic acids is based on their relative stability to hydrochloric acid, that unstable being given the *cis*-structure by analogy with all other known acids containing a carboxyl group directly attached to the rings.

(2) As this acid is formed by the oxidation of both α-*bicyclo*octanone (semicarbazone, m. p. 180°) and β-*bicyclo*octanone (semicarbazone, m. p. 197°), these also are given the *cis*-configuration, and the same is assigned to the hydrocarbon which they both yield on reduction.

(3) The third isomeric *bicyclo*octanone (semicarbazone, m. p. 251°) is given the *trans*-β-structure from its non-identity with the above and because (*a*) it is a saturated dicyclic ketone, (*b*) from its method of formation it contains a *cyclo*pentane ring with a fused ring in the 1 : 2 position, and (*c*) it is a β-ketone because it is not readily isomerised into a *cis*-form.

(4) Catalytic reduction (platinum) of 2-carbethoxy*cyclo*pentenylcyanoacetic ester yields a product undoubtedly having the *cis*-configuration, because it is hydrolysable to the *cis*-1 : 2-carboxy-acetic acid. Hence it is reasonable to suppose that other 2-substituted cyanoacetic esters will be reduced to *cis*-1 : 2-*cyclo*pentane derivatives. This leads to configurations for the *cyclo*pentanediacetic acids and β-*bicyclo*octanones in agreement with those deduced above. It also leads to a *cis*-configuration for the *cyclo*pentaneacetic-propionic acid and the derived 5-hydrindanone described on p. 948.

(5) By analogy with Hückel's results, platinum reduction of 5-hydroxyindane should give a *cis*-hydrindanol. In agreement, this alcohol is oxidised to the 5-hydrindanone for which the *cis*-configuration is deduced in (4) above.

(6) The ease of formation of ketones from all four of the 1 : 2-adipic acids derived from *cyclo*pentane is in agreement with these configurations. So also is the inability of the *trans*-diacetic ester to yield a cyclic keto-ester.

Physical Constants of bicyclo*Octane Derivatives.*—The samples of *bicyclo*octane prepared from the α- and the (*cis*-)β-ketone were almost identical in physical properties. The hydrocarbon was optically normal and therefore resembled *cis*-rather than *trans*-decalin :

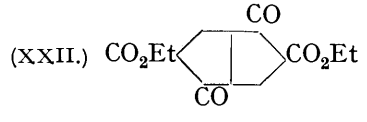
Hydrocarbon.	$d_{4^\circ}^{t^\circ}$.	$n_D^{t^\circ}$.	*t.*	$[R_L]_D$ found.	$[R_L]_D$ calc.	EM_D.
cis-Decalin (Hückel)	0·898	1·4823	20°	43·88	43·98	−0·10
trans-Decalin (Hückel)	0·872	1·4713	20	44·26	43·98	+0·28
*cis-bicyclo*Octane (*ex* α-)	0·8699	1·4614	18·1	34·76	34·75	+0·01
*cis-bicyclo*Octane (*ex* β-)	0·8702	1·4609	16·2	34·71	34·75	−0·04

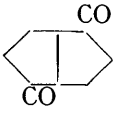
In general the physical constants of the ketones also support the configurations assigned above. The densities * of all *cis*-dicyclic ketones (tabulated below) are greater than unity, whereas the densities of their *trans*-isomerides, where known, are below 0·99. In both the decalone and the *bicyclo*octanone series, the α-ketone is denser than the β-. Both the *bicyclo*octanones show a slight exaltation in molecular refractivity, which also appears in *cis*-2-hydrindanone and *cis*-5-hydrindanone. The exaltation of the known *trans*-dicyclic ketones is, of course, greater.

Ketone.	$d_{4^\circ}^{t^\circ}$.	$n_D^{t^\circ}$.	*t.*	$[R_L]_D$, found.	$[R_L]_D$, calc.	EM_D.
cis-α-Decalone (Hückel)	1·0077	1·4936	21°	43·90	43·99	−0·09
trans-α-Decalone (Hückel)	0·9846	1·4849	21·5	44·27	,,	+0·28
cis-β-Decalone (Hückel)	1·0038	1·4927	20	44·02	,,	+0·03
trans-β-Decalone (Hückel)	0·9790	1·4834	16	44·34	,,	+0·35
cis-2-Hydrindanone (Hückel).....	1·001	1·4846	16·7	39·51	39·37	+0·14
trans-2-Hydrindanone (Hückel)...	0·9807	1·4769	17	39·78	,,	+0·41
cis-5-Hydrindanone (C. & L.)	1·0034	1·4848	18·1	39·43	,,	+0·06
cis-α-*bicyclo*Octanone (C. & L.) ...	1·0097	1·4790	20	34·91	34·76	+0·15
cis-β-*bicyclo*Octanone (L. & M.) ...	1·0084	1·4799	19	34·96	,,	+0·20

These new results have a bearing on the work of Ruzicka, de Almeida, and Brack (*Helv. Chim. Acta*, **1934**, **17**, 183), who cyclised both *cis*- and *trans*-hexane-1 : 3 : 4 : 6-tetracarboxylic ester with an excess of sodium in benzene to the same *bicyclo*octane-1 : 4-dione-2 : 5-dicarboxylate (XXII), which was hydrolysed to *bicyclo*octane-1 : 4-dione (XXIII). The configuration of this was left uncertain, but in view of the similarity in

(XXII.)





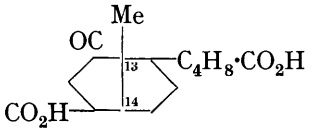
(XXIII.)

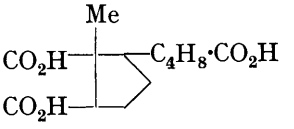
method of formation with that of *cis*-α-*bicyclo*octanone there seems no doubt that both products belong to the *cis*-series. In agreement with this, the physical properties recorded for the diketone (XXIII) give by extrapolation a value at 20° for $[R_L]_D$ of 34·93, which is very close to that found for our *cis*-derivatives. (Direct comparison is possible because there is scarcely any difference between the Eisenlohr constants for the CO and the CH_2 group. The necessity for extrapolation is shown by the variation in the experimental values for $[R_L]_D$ with temperature; *loc. cit.*)

α-*bicyclo*Octanone is the parent of the acid $C_{15}H_{22}O_5$ (XXIV) obtained by Wieland and Schlichting (*Z. physiol. Chem.*, 1924, **134**, 276) by the degradation of desoxycholic acid.

* Attention may be drawn to a number of textual errors in previous papers. Hückel (*Annalen*, 1925, **441**, 20) gives $d_D^{16^\circ}$ 1·4834 in place of $n_D^{16^\circ}$ 1·4834 for *trans*-β-decalone. Kandiah (J., 1931, 947) gives for *trans*-2-hydrindanone $n_D^{20\cdot2^\circ}$ 1·0021. Thakur (J., 1932, 2128) gives $[R_L]_D$ calc. for *trans*-β-decalone as 44·11 instead of 43·99 and (*ibid.*, p. 2152) for *trans*-2-hydrindanone 39·51 instead of 39·37. Hückel and Friedrich (*Annalen*, 1926, **451**, 132) refer to "*cyclohexane-1-essig-2-propionsaure*" throughout p. 159, whereas "*cyclohexane-1-essig-2-carbonsaure*" is obviously intended.

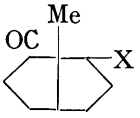
This acid can in turn be oxidised to the important tribasic acid $C_{13}H_{20}O_6$ (XXV). Wieland and Dane have shown (*Z. physiol. Chem.*, 1933, **216**, 91) that the acid (XXV) has the

(XXIV.) 

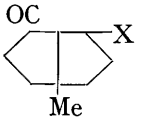


(XXV.

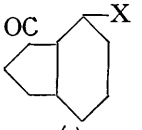
trans-configuration, which must therefore also be applied to the parent keto-acid (XXIV). Three types of ring are possible :



(*a*)



(*b*)



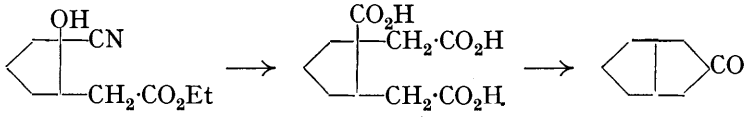
(*c*)

It is argued that, of these, (*c*) is excluded, because it has no methyl group attached to C_{13} (employing the conventional numbering of the bile-acid skeleton); hence free configurational change is possible, so that the keto-acid (XXIV) would be *cis*. It is similarly assumed that an α-*bicyclo*octanone would not be isolated in the *trans*-form unless the bridge carried a methyl group on the carbon atom adjoining the keto-group to prevent enolisation and consequent change of configuration. As (XXIV) is a stable *trans*-compound, type (*b*) is excluded and type (*a*) confirmed.

The present work provides strong support for this assumption and hence for the structure proposed by Wieland and Dane for ring D of the bile acids. It may be pointed out, however, that the instability of *trans*-α-hydrindanones is not yet conclusively established and that type (*c*) is therefore not rigidly excluded from this line of evidence. The same element of uncertainty also applies to Windaus's deduction concerning the mode of linking of rings A and B in the cholestanes and lithobilianic acids (compare Ruzicka, Furter, and Thomann, *Helv. Chim. Acta*, 1933, **16**, 327).

The following experiments of subsidiary importance were also carried out in the course of the present investigations. The ring of ethyl *cyclo*pentanone-2-carboxylate-2-propionate (X) was opened by sodium ethoxide to yield *ethyl γ-carbethoxysuberate*. The corresponding *acid* on distillation with baryta yielded *cyclo*pentanone-2-β-propionic acid and no trace of *cyclo*heptanone. This, we believe, is a unique case of direct competition between the formation of a five- and a seven-membered ring and shows clearly that it is the 6- rather than the 9-carbon atom which is more accessible for cyclisation involving the 1-carbon atom. By the Dieckmann reaction, γ-carbethoxysuberic ester yielded *ethyl* cyclo*pentanone-2-carboxylate-5-β-propionate*, which has synthetic possibilities.

The condensation of the cyanohydrin of ethyl *cyclo*pentanone-2-acetate (XXVI) with ethylsodiocyanoacetate, following Higson and Thorpe (J., 1906, **89**, 1455), was also examined in the hope of introducing a second acetic residue and thus synthesising a carboxylated 1 : 2-diacetic acid and thence a β-*bicyclo*octanone :

(XXVI.) 

The yield of ketone obtained by this process was very small; it appeared to be mainly *trans*-β-*bicyclo*octanone.

Experimental.

1. *Preparation of* cyclo*Pentanecarboxypropionic Acids from Indene.*—Indane was prepared from indene by catalytic reduction over nickel (compare Goth, *Ber.*, 1928, **61**, 1459) in an apparatus made by Technical Research Works, Ltd. This was kindly placed at our disposal by Dr. J. W. Cook, to whom our thanks are due. The indene was allowed to flow over the catalyst at a rate of 4 drops/sec. at 170—175° under a hydrogen pressure of 150 lb./sq. in.

Reduction was complete, as the product gave only a light yellow colour with sulphuric acid and boiled at 176—178°. Yield, 86%.

50 C.c. of concentrated sulphuric acid were added dropwise with shaking and cooling to an equal volume of indane. After 12 hours, the thick syrup was poured into 25 c.c. of water, and then set to a crystalline mass. This was drained and crystallised from 250 c.c. of 20% (vol.) sulphuric acid. The trihydrate of indane-5-sulphonic acid crystallised (m. p. 92°; yield, 80%) and was converted into the sodium salt, which was thoroughly dried, finally over a free flame.

The sodium salt from 150 c.c. of indane was mixed with 5% of zinc dust (Borsche and John, *loc. cit.*) and added in small portions with gentle stirring during 20 minutes to 1 kg. of potash contained in a pot with a narrow neck and kept at 285°. After a further 25 minutes, the melt was cooled, dissolved in water, and acidified at 0° with concentrated hydrochloric acid. The phenol was extracted with ether (steam distillation was unnecessary), and the extract washed with sodium carbonate solution and dried over calcium chloride. The residue from the ether was distilled at 135°/21 mm. or 110°/8 mm.; a crystalline mass of 5-hydroxyindane (VIII) was obtained, which formed white needles (88 g.), m. p. 54—55° (lit., 56°), from light petroleum. The phenol gave a faint blue colour with ferric chloride and an intense magenta with warm concentrated sulphuric acid. The benzoyl derivative melted at 111—112° (Borsche and John give 106—107°). The yield was considerably less when the fusion was carried out in a wide-mouthed shallow pot or when no zinc was used.

Catalytic reduction. The catalyst was prepared essentially by Adams's method (" Organic Syntheses," VIII, 92), but a more active product was always obtained by the use of potassium nitrate in place of sodium nitrate. The glacial acetic acid used as solvent was distilled over permanganate, purified by freezing, and redistilled. For reductions under pressure the hydrogen was contained in a small steel cylinder joined by a four-way connection to the reaction vessel, the charging cylinder, and a stout glass capillary manometer. The pressure in the apparatus was calculated from the manometer readings and the relative volumes of the apparatus and of the closed arm of the manometer. The results of a number of reductions are tabulated below. In all cases the product was filtered from the catalyst, diluted with water (3 vols.), and neutralised with concentrated aqueous caustic soda. The reduction products were isolated by means of ether and separated by distillation into hydrindane, b. p. about 52°/12 mm., and 5-hydrindanol, b. p. about 112°/15 mm. Although absorption became slow after the theoretical quantity of hydrogen had been taken up, some unchanged phenol was always recovered (10—15%).

Pressure in expts. 1—5, 1 atm.; in expts. 6—10, 2·8 atms.

Expt.	Hydroxy-indane used, g.	Acetic acid, c.c.	Catalyst, g. PtO_2.	Rate of uptake, c.c./hr.	Product (g.). Hydrindane.	5-Hydrindanol.
1	4·3	10	0·5	300	0·4	1·8
2	17·0	35	1·0	500	3·7	7·6
3	28·0	60 c.c. ether	1·0	nil	—	—
4	22·0	30 c.c. alcohol	1·0	200	6·0	14·0
5	26·0	50	0·7	500	3·0	13·0
6	20·0	25 c.c. alcohol	0·5	800	3·8	14·8
7	30·0	30	0·75	800	3·0	18·5
8	30·0	30 (Skita Pt)	0·6	nil	—	—
9	30·0	30	1·0	1000	12·0	48·0
10	30·0	30	1·0	1000		

These figures show that the reduction is slowed by the use of alcohol and stopped by ether, but that increase of pressure, besides increasing the rate of reaction, also decreases the formation of hydrocarbon. The hydrindane formed boiled at 163·5—164°/768 mm., 52°/12 mm., and did not react with metallic sodium or with permanganate.

cis-5-*Hydrindanol* (IX) was obtained as a colourless viscous liquid, b. p. 113°/15 mm., $n_D^{20\cdot5°}$ 1·4931, $d_{4°}^{20\cdot5°}$ 1·0062, $[R_L]_D$ 40·50 (calc., 40·87). It set to a crystalline mass in solid carbon dioxide–ether, and gave no definite colour with concentrated sulphuric acid and no trace of a semicarbazone (Found : C, 76·7; H, 11·4. $C_9H_{16}O$ requires C, 77·1; H, 11·4). A *phenylurethane* was formed readily from 0·7 g. of the alcohol and 0·6 g. of phenylcarbimide and yielded delicate needles, m. p. 121°, from benzene–petroleum (Found : C, 74·1; H, 8·2. $C_{16}H_{21}O_2N$ requires C, 74·1; H, 8·2%).

Oxidation. Into 80 c.c. of concentrated nitric acid, stirred mechanically, 20 g. of 5-hydrindanol were dropped so that the temperature was kept at about 40° (*ca.* 1 hour). After a further 30 minutes' stirring, the liquid was diluted with 40 c.c. of water and concentrated to

75 c.c. An almost pure acid, m. p. 101°, separated from the solution over-night in rosettes of needles which were only slightly contaminated with a yellow nitro-compound. (This nitro-compound, which was obtained in larger amount if the mixture was not well stirred, crystallised from alcohol in yellow needles, m. p. 153°, and dissolved in alkali with deepening of colour.) The mother-liquors from the acid contained much oxalic acid and little useful material. Consistent yields of 43—45% of pure acid were obtained. When the oxidation mixture was not diluted before evaporation, the yield was not improved and the separation was made more difficult; this was also true when a little mercury or ammonium vanadate was added to the oxidation mixture.

cis-cyclo*Pentane*-1-*carboxy*-2-*propionic acid* (III) crystallised from water or, better, from hydrochloric acid in rosettes of needles, m. p. 101°, and was stable to permanganate in acid solution [Found: C, 58·1; H, 7·6; equiv. by titration, 93·5. $C_9H_{14}O_4$ (dibasic) requires C, 58·1; H, 7·6%; equiv., 93·0]. The *dianilide*, prepared from the acid chloride in ether, crystallised from dilute alcohol in small needles, m. p. 190° (Found: C, 74·9; H, 6·9. $C_{21}H_{24}O_2N_2$ requires C, 75·0; H, 7·1%). The *silver* salt (Found: Ag, 53·6. $C_9H_{12}O_4Ag_2$ requires Ag, 53·9%), prepared from 12·5 g. of the acid and 24 g. of silver nitrate, gave with 30 c.c. of ethyl iodide in 125 c.c. of ether the *diethyl* ester (10 g. after redistillation), b. p. 160°/20 mm., $n_D^{23·4°}$ 1·4670, $d_{4°}^{23·4°}$ 1·0626, $[R_L]_D$ 63·10 (calc., 63·35) (Found: C, 64·2; H, 9·0. $C_{13}H_{22}O_4$ requires C, 64·4; H, 9·1%). The ester regenerated the parent acid on hydrolysis.

Conversion into the trans-*form*. 2 G. of the *cis*-acid were heated for 5 hours with 5 c.c. of concentrated hydrochloric acid in a sealed tube at 180°. The somewhat charred product was washed out with water, decolorised with charcoal, and concentrated to 8 c.c.; trans-cyclo*pentane*-1-*carboxy*-2-*propionic acid* (IV) separated; m. p. 99° (crude), 101·5° after crystallisation from water or hydrochloric acid (Found: C, 58·4; H, 7·6. $C_9H_{14}O_4$ requires C, 58·1; H, 7·6%). This differed from the *cis*-isomeride as follows:

cis-Acid.	*trans*-Acid.
Easily soluble in water.	Sparingly soluble in cold water.
Crystallises slowly from water; crystals form first on the surface, often only on seeding.	Crystallises normally in the bulk of the solution.
Rosettes or spherical cushions of needles, m. p. 101°.	Clumps of stout needles, m. p. 101·5°.

A mixture of the acids melted at about 80°.

The *dianilide* of the *trans*-acid melted at 192° alone, and at 166—168° when mixed with the *cis*-dianilide (Found: C, 75·0; H, 7·0. $C_{21}H_{24}O_2N_2$ requires C, 75·0; H, 7·1%).

3·0 G. of ethyl *cis-cyclo*pentane-1-carboxylate-2-propionate were added drop by drop to a suspension of 0·5 g. of molecular potassium in 50 c.c. of dry ether. A vigorous reaction occurred, hydrogen was liberated, and a deep orange suspension of a potassio-compound formed. After 15 minutes the mixture was acidified (the colour then completely disappeared), washed with sodium bicarbonate solution and water, and dried over sodium sulphate. Removal of the ether and distillation of the residue yielded the *diethyl* ester of trans-cyclo*pentane*-1-*carboxy*-2-*propionic acid* in good yield, b. p. 161°/19 mm., $n_D^{23·4°}$ 1·4655, $d_{4°}^{23·4°}$ 1·0540, $[R_L]_D$ 63·58 (calc., 63·35) (Found: C, 64·3; H, 9·1. $C_{13}H_{22}O_4$ requires C, 64·4; H, 9·1%). On being hydrolysed with boiling hydrochloric acid, this yielded the pure *trans*-acid, m. p. 101° alone or mixed with the *trans*-acid prepared above, but 79—80° in admixture with the *cis*-acid. The above procedure is an improvement on the method of Hückel and Goth (*loc. cit.*) based on the work of Scheibler and his co-workers on the formation of potassio-compounds of aliphatic esters (*Ber.*, 1920, **53**, 388; 1925, **58**, 1198).

2. *Preparation of* cis-cyclo*Pentanecarboxypropionic Acid from Ethyl* cyclo*Pentanone*-2-β-*propionate*.—208 G. of ethyl *cyclo*pentanone-2-carboxylate were added to 31 g. of molecular sodium in 1·5 l. of benzene (steam-bath). After 1 hour the sodio-compound was cooled and slowly treated with 163 g. of ethyl β-chloropropionate (see p. 954). After being heated for a further 5 hours on the steam-bath, the mixture was acidified and the benzene layer washed with sodium bicarbonate solution. The residue from the benzene yielded 32 g. of unchanged keto-ester and 240 g. (75%) of *ethyl* cyclo*pentanone*-2-*carboxylate*-2-β-*propionate* (X), b. p. 189°/18 mm., $n_D^{19·4°}$ 1·4563, $d_{4°}^{19·4°}$ 1·1004, $[R_L]_D$ 63·33 (calc., 63·35) (Found: C, 60·8; H, 8·0. $C_{13}H_{20}O_5$ requires C, 60·9; H, 7·9%). This ester yielded no ketonic derivatives. 220 G. were boiled under reflux with 250 c.c. of concentrated hydrochloric acid for 9 hours. On removal of the mineral acid in a vacuum and cooling in ice, the residue solidified to a hard crystalline mass of cyclo*pentanone*-2-β-*propionic acid* (XI), which could be purified by distillation or esterified direct. The pure acid boils at 175°/10 mm., distils without decomposition at atmospheric

pressure, and crystallises from ice-cold benzene–petroleum in hexagonal plates, m. p. 37° (Found : C, 61·4; H, 7·9; equiv., 157. $C_8H_{12}O_3$ requires C, 61·5; H, 7·8%; equiv., 156). The *semicarbazone* is formed readily and crystallises from dilute acetic acid in small needles, m. p. 219° (slight decomp.) (Found : C, 50·7; H, 7·1. $C_9H_{15}O_3N_3$ requires C, 50·7; H, 7·1%). On treatment with 2 : 4-dinitrophenylhydrazine in alcoholic sulphuric acid the acid gave the dinitrophenylhydrazone of the ethyl ester (see below).

As suggested by the last result, the acid was readily esterified. The crude product from 220 g. of (X) was dissolved in 300 c.c. of alcohol, dry hydrogen chloride passed in for 30 minutes, *ethyl* cyclo*pentanone*-2-β-*propionate* isolated after 12 hours, b. p. 150°/18 mm., $d_{4^\circ}^{19\cdot4^\circ}$ 1·0410, $n_D^{19\cdot4^\circ}$ 1·4514, $[R_L]_D$ 47·67 (calc., 47·84). The over-all yield from (X) was 80—83% (Found : C, 65·2; H, 8·6. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%). Unlike the ester (X), this readily yielded ketonic derivatives and dissolved in concentrated hydrochloric acid with evolution of heat. The *semicarbazone* separated from dilute alcohol in long needles, m. p. 153·5° (Found : C, 54·8; H, 7·8. $C_{11}H_{19}O_3N_3$ requires C, 54·8; H, 7·9%), and the 2 : 4-*dinitrophenylhydrazone* from alcohol in long orange-yellow needles, m. p. 92·5° (Found : C, 52·5; H, 5·5. $C_{16}H_{20}O_6N_4$ requires C, 52·7; H, 5·5%).

Ethyl *cyclo*pentanone-2-propionate (1 mol.) was warmed with sodium ethoxide (1 mol.) in 500 c.c. of absolute alcohol for 5 hours on the steam-bath, a quantitative yield of *ethyl γ-carbethoxysuberate* being obtained, b. p. 186°/9 mm. (Found : C, 59·6; H, 8·5. $C_{15}H_{26}O_6$ requires C, 59·6; H, 8·6%). The same ester was formed to a considerable extent in the preparation of (X) if ethyl β-chloropropionate was added quickly to hot ethyl sodio*cyclo*pentanonecarboxylate. The ester was hydrolysed with boiling concentrated hydrochloric acid (2 vols., 4 hours), and the acid isolated by removal of the mineral acid under reduced pressure. *γ-Carboxysuberic acid* crystallised from ethyl acetate–petroleum in clusters of stout prisms, m. p. 111° (yield, 85%). It was very soluble in water and organic solvents except ether, chloroform, and the hydrocarbons [Found : C, 49·4; H, 6·4; equiv., 72·6. $C_9H_{14}O_6$ requires C, 49·5; H, 6·5%; equiv. (tribasic), 72·7]. It was stable at 230°, but at 300° with 10% of baryta it yielded carbon dioxide, water, and pure *cyclo*pentanone-2-β-propionic acid (semicarbazone, m. p. 218°).

Ethyl carbethoxysuberate (20 g.) was refluxed with molecular sodium (2·0 g.) in benzene (50 c.c.) for 5 hours. After the usual treatment, 2·2 g. of *ethyl* cyclo*pentanone*-2-*carboxylate*-5-*propionate*, b. p. 186°/20 mm., were isolated (Found : C, 60·8; H, 7·9. $C_{13}H_{20}O_5$ requires C, 60·9; H, 7·9%). The ester gave an intense violet colour with ferric chloride, a solid copper derivative, and a dinitrophenylhydrazone.

Cyanohydrin of ethyl cyclo*pentanone*-2-β-*propionate* (XII). The keto-ester together with a few drops of aqueous caustic potash was added to liquid hydrogen cyanide cooled in a freezing mixture. The mixture was left over-night, treated with a few drops of concentrated sulphuric acid, and distilled under reduced pressure. The *cyanohydrin* boiled at 154°/8 mm. or 182°/18 mm. Yield, about 90% (Found : C, 62·7; H, 8·2. $C_{11}H_{17}O_3N$ requires C, 62·5; H, 8·1%). It was dehydrated in ether–pyridine by the *slow* addition of thionyl chloride to *ethyl* Δ^1(or Δ^5)-1-*cyano*cyclo*pentene*-2-β-*propionate* (XIII), b. p. 173°/17 mm., yield 75—80% (Found : C, 68·5; H, 7·7. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8%). This was hydrolysed with boiling 10% aqueous potash (3 mols.) for 30 hours to *cyclo*pentene-1-carboxy-2-propionic acid, which was only sparingly soluble in cold water and was crystallised from hot water or hydrochloric acid, m. p. 122° (Found : equiv., 92·7. Calc., 92·0).

50 G. of the unsaturated cyano-ester (XIII) were hydrolysed and esterified by a mixture of 33 c.c. of concentrated sulphuric acid, 75 c.c. of alcohol, and 2 c.c. of water (20 hours at b. p.). By redistillation of the fraction of b. p. 165—170°/21 mm., 15 g. of *ethyl* cyclo*pentene*-1-*carboxylate*-2-*propionate* were isolated, b. p. 171—172°/20 mm. (Found : C, 64·9; H, 8·4. $C_{13}H_{20}O_4$ requires C, 64·9; H, 8·4%). The ester was free from nitrogen and was unsaturated, but could not be reduced. It readily absorbed hydrogen bromide in ethereal solution, but reduction of the bromo-ester obtained (b. p. 197°/15 mm.) with zinc and acetic acid gave indefinite unsaturated esters, from which solid products were not obtained on hydrolysis.

Ethyl cyclo*pentylidene*-1-*cyanoacetate*-2-β-*propionate* (XV). A mixture of 61·5 g. of ethyl *cyclo*pentanone-2-β-propionate, 38 g. of ethyl cyanoacetate, and 2 g. of piperidine was kept at 0° for 24 hours, 7 g. of anhydrous sodium sulphate added to clarify the cloudy solution, which, after remaining for 4 days at 0° and for 2 hours on the steam-bath, was washed with acid and with sodium bicarbonate solution, dried, and distilled. It yielded 22 g. of unchanged cyanoacetic ester, 25 g. of keto-ester, and 30·7 g. (33%) of the unsaturated *cyano*-ester (XV) as a thick colourless oil, b. p. 220°/17 mm. (Found : C, 64·5; H, 7·5. $C_{15}H_{21}O_4N$ requires C, 64·5; H, 7·5%). 70 G. of the above ester in 1 l. of moist ether were reduced during 2 days with 70 g

of amalgamated aluminium (Vogel, J., 1927, 594). The sludge of alumina was removed and washed with ether, and *ethyl* cis-cyclo*pentane*-1-*cyanoacetate*-2-β-*propionate* (XVI) isolated from the filtrate and washings in the usual way. Yield, 46 g.; b. p. 202°/12 mm. (Found : C, 64·0; H, 8·1. $C_{15}H_{23}O_4N$ requires C, 64·1; H, 8·2%). 43 G. of the saturated ester were refluxed with 50 c.c. of concentrated hydrochloric acid for 12 hours, the dark solution becoming light brown; 24·8 g. (81%) of an oil separated from the cooled solution and rapidly solidified to a mass of crystals. cis-cyclo*Pentane*-1-*acetic*-2-β-*propionic acid* (XVII) crystallised from water or, better, benzene in rosettes of needles, m. p. 98°, sparingly soluble in cold water and cold benzene, very soluble in acetone (Found : C, 59·9; H, 8·2. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·0%).

cis-5-*Hydrindanone* (5-*Keto*-cis-0 ; 3 : 4-bicyclo*nonanone*) (XVIII).—20 G. of the acetic-propionic acid were smoothly ketonised by 2 g. of baryta at 315—320° to 8·3 g. of the crude ketone, b. p. 98·5—99°/12 mm., which was converted in bulk into the *semicarbazone*. This was much less soluble in alcohol than the semicarbazone of α-*bicyclo*octanone and crystallised from dilute acetic acid in small feathery needles, m. p. 203° (Found : C, 61·5; H, 8·8. $C_{10}H_{17}ON_3$ requires C, 61·6; H, 8·7%). From this derivative the pure cis-5-*hydrindanone* was regenerated with oxalic acid, b. p. 96·5°/11 mm., $n_D^{18\cdot1°}$ 1·4848, $d_{4°}^{18\cdot1°}$ 1·0034, $[R_L]_D$ 39·43 (calc., 39·37) (Found : C, 78·1; H, 10·1. $C_9H_{14}O$ requires C, 78·2; H, 10·1%). The 2 : 4-*dinitrophenylhydrazone*, which was readily produced, formed golden-yellow plates from much alcohol, m. p. 163° (Found : C, 56·4; H, 5·5. $C_{15}H_{18}O_4N_4$ requires C, 56·6; H, 5·7%).

1·5 G. of *cis*-5-hydrindanone were added dropwise with vigorous shaking to 6 c.c. of boiling concentrated nitric acid; 10 c.c. of water were then added, and the mixture boiled for a few minutes, concentrated to 10 c.c., and allowed to cool. After 3 days, 0·90 g. of a solid acid separated on the surface of the liquid in the rosettes of needles characteristic of *cis-cyclo*pentane-1-carboxy-2-propionic acid. It melted at 99—100°, alone or mixed with the *cis*-acid prepared from indene.

As an attempt to reduce *cis*-5-hydrindanone to the corresponding alcohol failed, the reverse reaction was carried out. 2·0 G. of the alcohol (IX) (from indene) were added to 1·5 g. of potassium dichromate in 30 c.c. of 50% acetic acid and a little sulphuric acid. After 1 hour on the steam-bath the ketone was distilled in steam and identified as the semicarbazone, m. p. 203° alone or mixed with the material made from *cyclo*pentanonecarboxylate.

3. *Formation of* bicyclo*Octane Derivatives*.—(1) 19·0 G. of *cis-cyclo*pentane-1-carboxylic-2-propionic acid and 1 g. of baryta were heated to 280—290°; ketone was then smoothly evolved. If the ketone was not rapidly removed, extensive oxidation occurred and succinic acid was produced. The distillate was washed with sodium bicarbonate solution and water, dried, and redistilled. Yield, 8·9 g. (70%); b. p. 58—60°/5 mm. On redistillation cis-α-bicyclo*octanone* (I) was obtained as a colourless liquid with a pronounced ketonic odour; b. p. 71°/15 mm., $n_D^{15\cdot85°}$ 1·4797, $d_{4°}^{18\cdot5°}$ 1·0099, $[R_L]_D$ 34·91 (calc., 34·76). It was very volatile in steam and sparingly soluble in water (Found : C, 77·6; H, 9·8. $C_8H_{12}O$ requires C, 77·4; H, 9·8%). It gave an almost quantitative yield of *semicarbazone*, m. p. (crude) 170°, which formed large white leaflets from absolute alcohol; these became opaque and chalky on drying, m. p. 180° (decomp.) (Found : C, 60·0; H, 8·3. $C_9H_{15}ON_3$ requires C, 59·6; H, 8·3%). The 2 : 4-*dinitrophenylhydrazone* formed golden-yellow plates, m. p. 115—116°, from alcohol (Found : C, 54·8; H, 5·3. $C_{14}H_{16}O_4N_4$ requires C, 55·2; H, 5·3%).

7·2 G. of the redistilled ketone were converted into the semicarbazone (10·25 g.), which was decomposed with oxalic acid in the usual way. The regenerated ketone had b. p. 72°/12 mm., $n_D^{20\cdot0°}$ 1·4790, $d_{4°}^{20\cdot0°}$ 1·0097, practically identical with the figures given above.

(2) The same ketone was obtained in approximately the same yield from *trans-cyclo*pentane-1-carboxy-2-β-propionic acid at 310—315°. The semicarbazone melted at 174·5° (crude) and at 181° after crystallisation (mixed m. p. 180—181°).

(3) 4·0 G. of ethyl *cis-cyclo*pentane-1-carboxylate-2-propionate were cyclised with 0·4 g. of molecular sodium in 25 c.c. of benzene (3 hours, steam-bath). The mixture was worked up in the usual way to yield 1·7 g. of the keto-ester (XIX), b. p. 140°/20 mm., $n_D^{23\cdot4°}$ 1·4797, $d_{4°}^{23\cdot4°}$ 1·0825, $[R_L]_D$ 51·40 (calc. for keto-ester, 50·26; for enol-ester, 51·31) (Found : C, 67·4; H, 8·4. Calc. for $C_{11}H_{16}O_3$: C, 67·3; H, 8·2%).

An equal yield of the same ester was obtained from *trans-cyclo*pentane-1-carbethoxy-2-propionic ester by the same method. Both keto-esters were hydrolysed by boiling hydrochloric acid to *cis*-α-*bicyclo*octanone, identified by means of the semicarbazone.

Both keto-esters gave intense violet colours with ferric chloride, turning pink on dilution, amorphous dinitrophenylhydrazones and the same *basic copper* derivative, which was formed

by shaking with neutral copper acetate solution as an apple-green powder, m. p. 106° after crystallisation from dilute alcohol (Found : Cu, 23·5. $C_{11}H_{15}O_3$·CuOH requires Cu, 23·1%).

cis-bicyclo*Octane*. The following process avoided the sealed tube used in Wolff's method and was rapid and convenient. 5·0 G. of the regenerated ketone were converted into the semicarbazone, which was washed thoroughly, roughly dried, and heated (free flame) in a distilling flask with 7·5 g. of caustic potash. The mass fused and ammonia was given off. At 200—210° a second reaction set in, nitrogen being evolved, and oily drops of hydrocarbon began to distil. There was no charring, the residue being colourless. The distillate was shaken with sodium bisulphite solution, taken up in ether, dried with calcium chloride, and evaporated. Yield of crude hydrocarbon 4·0 g. (90%), 2·8 g. of which boiled sharply at 137—138°. When this portion was redistilled over sodium, cis-bicyclo*octane* was collected as a colourless mobile oil, b. p. 138—138·5°/768 mm., $n_D^{18\cdot1°}$ 1·4614, $d_4^{18\cdot1°}$ 0·8699, $[R_L]_D$ 34·82 (calc. 34·75) (Found : C, 87·2; H, 12·8. C_8H_{14} requires C, 87·2; H, 12·8%).

Oxidation of cis-α-bicyclo*octanone*. A solution of 0·5 g. of the distilled ketone in 3 c.c. of glacial acetic acid was added to a mixture of 0·4 c.c. of fuming nitric acid and 1·6 c.c. of glacial acetic acid. After 2 days at room temperature the acetic acid was removed over potash, in a vacuum desiccator, and the acid constituent of the residue extracted with aqueous sodium bicarbonate. Acidification and ether extraction of the bicarbonate solution yielded an oil which soon solidified. On crystallisation from much petroleum *cis-cyclo*pentane-1-carboxy-2-acetic acid was obtained, m. p. and mixed m. p. 87° (Found : equiv., 87·3 Calc., 86·0). This result was confirmed by a similar oxidation of the regenerated ketone.

We thank the Chemical Society and the Royal Society for grants.

IMPERIAL COLLEGE, LONDON, S.W. 7. [*Received, April 11th*, 1934.]