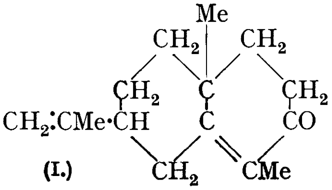
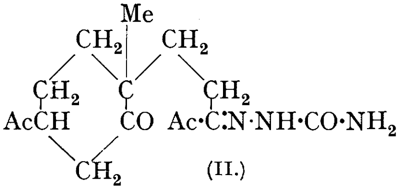
330. *Synthetic Cyperones and their Comparison with α- and β-Cyperones.*

By P. S. Adamson, F. C. McQuillin, Robert Robinson, and J. L. Simonsen.

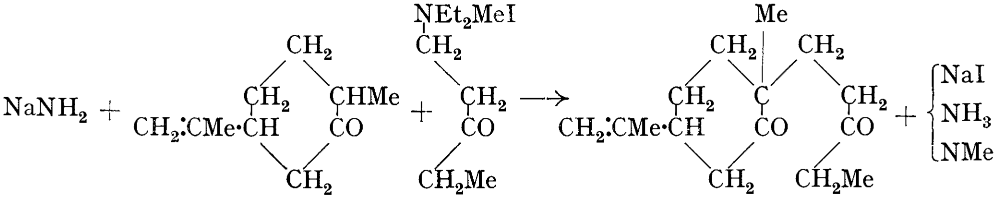
Suitable methods for the synthesis of certain sesquiterpene derivatives were independently devised in our two laboratories, and the present joint communication deals with the application of both processes to the synthesis of substances structurally identical with α- and β-cyperones. The respective oximes, semicarbazones, and 2 : 4-dinitrophenylhydrazones of the natural and the synthetic ketones exhibit undepressed melting points on admixture and closely resemble one another in most respects. They show, however, certain optical and crystallographic divergencies, so that complete identity is not claimed. A close scrutiny of the experimental details will, however, lead to the conviction that these syntheses establish the correctness of the constitution of the cyperones which was put forward by Bradfield, Pritchard, and Simonsen (this vol., p. 763).

α-Cyperone is the name given to a ketone, $C_{15}H_{22}O$, prepared by hydrolysing a semicarbazone, m. p. 216°, in its turn obtained from the oil of the tubers of *Cyperus rotundus* (Hegde and Rao, *J. Soc. Chem. Ind.*, 1935, **34**, 387T; Bradfield, Hegde, Rao, Simonsen, and Gillam, J., 1936, 667); β-cyperone is obtained from the α-isomeride by the action of aqueous oxalic acid or methyl-alcoholic potassium hydroxide. Bradfield, Pritchard, and Simonsen (*loc. cit.*), revising earlier work in some particulars, showed that α-cyperone should be represented by the expression (I). On ozonolysis, β-cyperone semicarbazone gave the same


(I.)

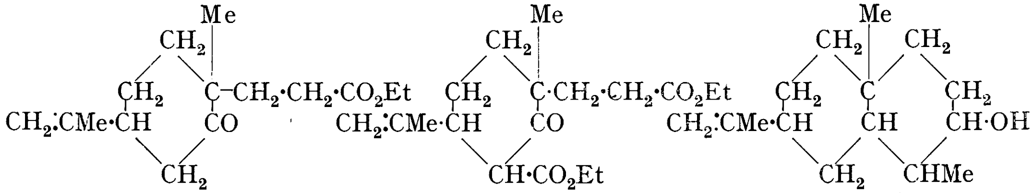

(II.)

product, $C_{15}H_{23}O_4N_3$ (probably II), as the α-isomeride, and the conclusion was drawn that the αβ-isomerism is confined to the stereochemistry of the methyl and the *iso*propenyl group. It is important to note that this evidence excludes isomerism due to a change in the position of the double bonds, and the formula (I) corresponds to no more than two optically inactive substances. In the oximes, semicarbazones, and dinitrophenylhydrazones there are naturally further possibilities of isomerism. Bradfield, Jones, and Simonsen (J., 1936, 1137) have already confirmed the essential correctness of (I) by a synthesis of a stereoisomeride of dihydrocyperone, and a similar process, described below, has now been extended to the synthesis of β-cyperone or a closely related stereoisomeride. Meanwhile, the unsaturated cyclic ketone synthesis of du Feu, McQuillin, and Robinson (this vol., p. 53) was being developed in a similar direction, so we decided to collaborate. The specimens of natural origin are designated Nα, Nβ; the synthetic specimens made in Bangor by way of the Reformatzky reaction are termed Bβ, and the synthetic specimens made by the more direct process in Oxford are termed Oα, Oβ.



(III.) (IV.)

We deal first with the latter section of the work. The condensation of the methiodide of 1-*diethylaminopentan*-3-*one* (III) and the sodio-derivative of *l*-dihydrocarvone was effected in ether–pyridine solution and afforded the solid *diketone* (IV). This was dehydrated with cyclisation by alcohol-free sodium ethoxide in benzene solution, with formation of a synthetic α-cyperone (Oα) (I), and by cold 50% sulphuric acid with formation of a synthetic β-cyperone (Oβ) (I). In the alternative method, the sodio-derivative of *l*-dihydrocarvone is condensed with ethyl β-chloropropionate with formation of *ethyl* 1-*methyl*-4-iso*propenyl*cyclo*hexan*-2-*one*-1-β-*propionate* (V). This ester was purified by condensation



(V.) (VI.) (VII.)

with ethyl oxalate in alcoholic sodium ethoxide solution; the α-keto-ester lost carbon monoxide on heating, and the distilled product was doubtless *ethyl* 3-*carbethoxy*-1-*methyl*-4-iso*propenyl*cyclo*hexan*-2-*one*-1-β-*propionate* (VI). From this the keto-acid corresponding to (V) was obtained on hydrolysis, and the acid was then esterified.

When the ester (V) was treated with zinc and ethyl α-bromopropionate in toluene solution, a mixture of products was obtained, which was repeatedly fractionated with continuous fall of the boiling points. On hydrolysis of the main product with methyl-alcoholic potassium hydroxide, a ketone, $C_{15}H_{22}O$, closely resembling β-cyperone, was obtained (Bβ) (I). On reduction with sodium and alcohol this synthetic ketone afforded 1 : 10-*dimethyl*-7-iso*propenyldecal*-2-*ol* (VII), the 3 : 5-*dinitrobenzoate* of which showed no depression of melting point in admixture with α-cyperyl 3 : 5 dinitrobenzoate.

Comparisons.—The superficial physical characteristics of the natural and the synthetic cyperones are the same. In regard to Nα and Oα the densities, refractive indices, and boiling points are almost identical, but the rotatory powers are divergent; for example, Nα, $[\alpha]_{5461}$ + 138°; Oα, $[\alpha]_{5461}$ + 68°. The melting points of the oximes and semicarbazones are not the same (differences 6° and 12° in the respective pairs) but those of the appropriate mixtures in the case of the oximes were that of the less fusible specimen (Nα), and in the case of the semicarbazones the m. p. of Oα was raised by admixture with Nα. Miss D. M.

Crowfoot reports that the oximes Nα and Oα were practically indistinguishable morphologically.

Similar resemblances and divergencies were noted in the β-series. For instance, Nβ has $[\alpha]_{5461}$ + 239°, Oβ has $[\alpha]_{5461}$ + 342°, and Bβ had $[\alpha]_{5461}$ + 111·7°. It should be noted that Nβ and Bβ were regenerated from the semicarbazones, whereas Oβ was not subjected to this treatment, and it would appear that racemisation of this ketone occurs with surprising facility. Again, the derivatives, *viz.*, the oximes, semicarbazones, and 2 : 4-dinitrophenylhydrazones, showed, on appropriate admixture, mixed melting points which were always intermediate between those of the individual specimens.

The semicarbazones Oβ, Bβ, and Nβ had practically identical melting points and undepressed mixed melting points, and moreover the rotatory powers were not very different: $[\alpha]_{5461}$ + 201° and + 217° for Oβ and Nβ respectively. On the other hand, Miss Crowfoot found all five semicarbazones to be crystallographically different, although polymorphism was not excluded. For other comparisons the experimental section may be consulted, but the conclusion we have reached is that our synthetic ketones are structurally identical with the natural compounds, the position being complicated by ready racemisation or partial racemisation.

EXPERIMENTAL.

1-*Diethylaminopentan*-3-*one*.—β-Chloroethyl ethyl ketone (E.P. 282,412; Kenner and Statham, *Ber.*, 1936, **69**, 19) (40 g.) in ether (100 c.c.) was added dropwise to diethylamine (48 g.) in ether (200 c.c.) with stirring and cooling in ice. After several hours, dilute sodium hydroxide solution was added, the ether separated, and dried, and on distillation 1-*diethylaminopentan*-3-*one* (27·7 g.) was obtained, b. p. 84°/13 mm., $n_D^{15^\circ}$ 1·4368 (Found: N, 8·8. $C_9H_{19}ON$ requires N, 8·9%). This substance when treated with methyl iodide, slightly in excess of the theoretical, with cooling, yielded the methiodide (III) as a very viscous fluid which could not be crystallised.

1-*Methyl*-1-γ-*ketopentyl*-4-iso*propenyl*cyclo*hexan*-2-*one* (IV).—*l*-Dihydrocarvone (32 g.) in ether (150 c.c.) was refluxed with powdered sodamide (9 g.) for 4 hours in a stream of dry nitrogen. 1-Diethylaminopentan-3-one methiodide (32·3 g.) in dry pyridine (50 c.c.) was then added dropwise with vigorous stirring. After the mixture had been kept overnight, the reaction was completed by refluxing for 5 hours. Water was added, the oil taken up in ether, and the extract dried and evaporated. On distillation of the residue, dihydrocarvone was first recovered, and a fraction then obtained, b. p. 146—150°/2 mm. (7·5 g.), which crystallised almost completely on cooling, and recrystallised from light petroleum in large, almost rectangular plates, m. p. 103° (Found: C, 76·8; H, 10·3. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%).

1 : 10-*Dimethyl*-7-iso*propenyl*-$\Delta^{1(9)}$-*octal*-2-*one and an Isomeride*.—(a) *Cyclisation of* (IV) *with sodium ethoxide*. The diketone, m. p. 103° (5 g.), was dissolved in dry benzene (50 c.c.), and alcohol-free sodium ethoxide (1·8 g.) added in small portions with shaking. After being kept for 24 hours at the room temperature, the brown solution was maintained at 60° for 1 hour; water was then added, and the benzene layer separated. The extract was dried and evaporated, yielding on distillation a pale yellow oil (3·2 g.), b. p. 160—163°/11 mm., $n_D^{14^\circ}$ 1·5299, $d_{18^\circ}^{18^\circ}$ 1·012, $[\alpha]_{5780}$ + 68°, $[\alpha]_{5461}$ + 88° (Found: C, 82·3; H, 10·1. $C_{15}H_{22}O$ requires C, 82·6; H, 10·1%).

The *oxime* (Oα) crystallised from aqueous methyl alcohol in long needles, m. p. 144° (Found: C, 77·4; H, 10·0. $C_{15}H_{23}ON$ requires C, 77·3; H, 9·5%); mixed with the oxime of α-cyperone, m. p. 151°, it had m. p. 150—151°. The *semicarbazone* (Oα) crystallised from methyl alcohol in colourless, irregular plates, m. p. 202°, $[\alpha]_{5461}$ + 91·5° (in chloroform; *c*, 3·6) (Found: C, 69·6; H, 9·0. $C_{16}H_{25}ON_3$ requires C, 69·8; H, 9·1%); mixed with the semicarbazone of α-cyperone, m. p. 216°, it melted at 205—206°.

(b) *Cyclisation of* (IV) *with sulphuric acid*. The diketone, m. p. 103° (1·8 g.), was treated with cold 50% sulphuric acid with cooling and vigorous shaking. After standing for an hour, the liquid was kept at 50° for 30 minutes, then cooled and mixed with ice-cold water and ether. The extract was washed with dilute sodium carbonate solution, dried, and evaporated, and on distillation the residue afforded an almost colourless oil (1·2 g.), b. p. 130°/1 mm., $n_D^{16^\circ}$ 1·5590, $d_{18}^{18^\circ}$ 0·999, $[\alpha]_{5461}$ + 342° (Found: C, 82·6; H, 10·3. $C_{15}H_{22}O$ requires C, 82·6; H, 10·1%).

The *oxime* (Oβ) crystallised from aqueous methyl alcohol in long colourless needles, m. p. 152—153°, $[\alpha]_{5461}$ 147° in ethyl alcohol (*c*, 1·9) (Found: C, 77·3; H, 10·0; N, 6·1. $C_{15}H_{23}ON$ requires C, 77·3; H, 9·9; N, 6·0%). Mixed with the oxime of β-cyperone, m. p. 139°, it melted at 139°, and no depression occurred on admixture with the synthetic oxime (Bβ) described below. The *semicarbazone* (Oβ) crystallised from methyl alcohol in colourless prisms, m. p.

204° (decomp.), which rapidly turned yellow in the light; $[\alpha]_{5461}$ + 201° in ethyl alcohol (*c*, 2·2) (Found : C, 69·8; H, 9·2; N, 15·0. $C_{16}H_{25}ON_3$ requires C, 69·8; H, 9·1; N, 15·3%). Mixed with the semicarbazone of β-cyperone, m. p. 207°, it had m. p. 206° (decomp.), and a mixture of the semicarbazones Oβ and Bβ showed the same behaviour. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl alcohol–ethyl acetate in scarlet prisms, m. p. 226° (Found : C, 62·8; H, 6·6; N, 14·1. $C_{21}H_{24}O_4N_4$ requires C, 63·3; H, 6·5; N, 14·1%). Mixed with the dinitrophenylhydrazone of β-cyperone, m. p. 218—219°, it melted at 222—223°.

Ethyl 1-*Methyl*-4-iso*propenyl*cyclo*hexan*-2-*one*-1-β-*propionate* (V).—A mixture of *l*-dihydrocarvone (60 g.) and sodamide (15·4 g.) in ether (800 c.c.) was refluxed for 10 hours, hydrogen being passed to remove the ammonia liberated. After cooling in ice, ethyl β-chloropropionate (54·8 g.) was added with vigorous shaking, sodium chloride separating. The reaction was completed by heating for 5 hours, ice was then added, the ethereal layer separated, dried, and the solvent evaporated. Distillation of the residual oil under 14 mm. pressure gave (i) *l*-dihydrocarvone (23 g.), (ii) b. p. 175—187° (41·5 g.), and (iii) b. p. 187—245° (12·5 g.).

To a cooled solution (salt-ice) of sodium (3·9 g.) in alcohol (90 c.c.) a similarly cooled mixture of the keto-ester (fraction ii) (43·3 g.) and ethyl oxalate (33·5 g.) was added. On being allowed gradually to attain the room temperature (48 hours), a brown solution was obtained, which was poured on crushed ice. The ethereal layer (A) was separated, the alkaline solution acidified with dilute sulphuric acid, and the resulting yellow oil dissolved in ether. The oil, remaining after the removal of ether from the dried solution, readily lost carbon monoxide on being heated for 1 hour (bath at 160—200°) at 18 mm., and then had b. p. 180—215°/3 mm. Redistillation gave *ethyl* 3-*carbethoxy*-1-*methyl*-4-iso*propenyl*cyclo*hexan*-2-*one*-1-β-*propionate* (VI) as a colourless viscid oil, b. p. 170—175°/3 mm., $[\alpha]_{5461}$ − 29·4° (in chloroform; *c*, 2·25) (Found : C, 66·8; H, 8·7. $C_{18}H_{28}O_5$ requires C, 66·7; H, 8·6%). The *semicarbazone* crystallised from aqueous alcohol in long needles, m. p. 147—148° (Found : C, 59·5; H, 7·9. $C_{19}H_{31}O_5N_3$ requires C, 59·8; H, 8·1%). From the neutral fraction of the oil (A) a further quantity of the ester was obtained on retreatment with ethyl oxalate.

Hydrolysis of the ester (60 g.) was effected by digestion with hydrochloric acid (270 c.c.) for 14 hours. The acid, which was a viscid oil, gave a *semicarbazone* crystallising from alcohol in well-formed cubes which were frequently twinned, decomp. 192—193°, after sintering at 184° (Found : C, 60·0; H, 8·1. $C_{14}H_{23}O_3N_3$ requires C, 59·8; H, 8·2%).

The acid (32·3 g.) was esterified with alcohol (320 c.c.) and sulphuric acid (57 g.) by heating for 20 hours; *ethyl* 1-*methyl*-4-iso*propenyl*cyclo*hexan*-2-*one*-1-β-*propionate* (V) had b. p. 181—182°/13 mm., $d_{25}^{25^\circ}$ 1·003, $n_D^{25^\circ}$ 1·4825, $[\alpha]_{5461}$ − 10·65° (in chloroform; *c*, 3·285) (Found : C, 71·0; H, 9·3. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·5%). The semicarbazone was an oil.

Condensation of the Ester (V) *with Ethyl α-Bromopropionate.*—1 : 10-*Dimethyl*-7-iso*propenyl*-$\Delta^{1(9)}$-*octal*-2-*one* (I). A mixture of the keto-ester (23·6 g.), ethyl α-bromopropionate (22·6 g.), and zinc (8·2 g.) in toluene (150 c.c.) was heated in an oil-bath, the vigorous reaction which ensued necessitating removal from the bath. After the reaction had moderated, the mixture was gently boiled (bath at 140—145°) for 15 hours. The zinc compound was decomposed with dilute sulphuric acid, the toluene separated and dried, and the solvent removed under diminished pressure. Distillation of the residual oil at 12 mm. gave three fractions : (i) b. p. up to 190° (1·8 g.), (ii) b. p. 190—200° (2·7 g.), (iii) b. p. 205—215° (19·3 g.). There was considerable decomposition during the distillation. Fractions (ii) and (iii), which gave with alcoholic ferric chloride brownish-green colorations, were repeatedly refractionated, during which process a continual fall in boiling point was observed; ultimately a large fraction, b. p. 170—190°/15 mm., was obtained.

This fraction, from several condensations (40 g.), was mixed with a methyl-alcoholic solution of potassium hydroxide (20 g.) and heated on the steam-bath for 2 hours; addition of water to the cooled solution caused the separation of an oil, which was collected in ether. Evaporation of the solvent from the dried solution gave the ketone, b. p. 170—180°/13 mm. (7·1 g.). From the alkaline solution the acid was recovered. This, after esterification, gave a further quantity of the ketone on treatment with ethyl α-bromopropionate in the presence of zinc. The ketone is also obtained in poor yield if the acid is digested with acetic anhydride, and the product distilled under diminished pressure.

For purification the ketone was converted into the *semicarbazone*, which was slowly deposited from the aqueous methyl-alcoholic solution; it crystallised from methyl alcohol in rosettes of colourless prisms, decomp. 209—210° after sintering at 195° (Found : C, 69·8; H, 9·1. $C_{16}H_{25}ON_3$ requires C, 69·8; H, 9·1%). It was highly phototropic, becoming bright yellow on exposure to light. On admixture with β-cyperone semicarbazone, decomposition occurred at 207—208°

after sintering at 195°. 1 : 10-*Dimethyl*-7-iso*propenyl*-$\Delta^{1(9)}$-*octal*-2-*one*, regenerated from the semicarbazone by digestion with oxalic acid in acetone solution and distillation in steam, was a colourless oil, b. p. 173—175°/14 mm., $d^{25^\circ}_{25^\circ}$ 0·9947, $n_D^{25^\circ}$ 1·5565, $[\alpha]_{5461}$ + 111·7° (Found : C, 82·2; H, 9·9. $C_{15}H_{22}O$ requires C, 82·6; H, 10·1%). The *oxime* crystallised from methyl alcohol in long, fine needles, m. p. 141—144°, not altered by further crystallisation; $[\alpha]_{5461}$ + 112° (in alcohol; *c*, 2·035) (Found : C, 77·1; H, 9·6. $C_{15}H_{23}ON$ requires C, 77·3; H, 9·9%). In admixture with β-cyperone oxime it had m. p. 138°. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate–alcohol in red leaflets with a bright metallic reflex, m. p. 225—227°, not depressed in admixture with β-cyperone 2 : 4-dinitrophenylhydrazone, m. p. 218—219° (Found : C, 63·3; H, 6·5. $C_{21}H_{26}O_4N_4$ requires C, 63·3; H, 6·5%).

1 : 10-*Dimethyl*-7-iso*propenyldecal*-2-*ol* (VII).—The ketone (I) (2 g.) in alcohol (80 c.c.) was treated with sodium (8 g.). After completion of the reaction, water was added, the ethyl alcohol removed in steam, and the *decalol* collected in ether. Removal of the solvent left a very viscid oil (1·6 g.), b. p. 160°/12 mm., $n_D^{20^\circ}$ 1·5032 (Found : C, 81·3; H, 11·7. $C_{15}H_{26}O$ requires C, 81·1; H, 11·7%). The 3 : 5-*dinitrobenzoate*, prepared by treating the alcohol with 3 : 5-dinitrobenzoyl chloride in pyridine solution, crystallised from alcohol in fine needles, m. p. 150—152° (Found : C, 63·8; H, 6·8. $C_{22}H_{28}O_6N_2$ requires C, 63·5; H, 6·7%). In admixture with α-cyperyl 3 : 5-dinitrobenzoate it had m. p. 150—153°.

On heating the alcohol with potassium hydrogen sulphate at 190—200° for 4 hours, elimination of water occurred and an oil, b. p. 148°/22 mm., was obtained. After distillation over sodium it had $d^{25^\circ}_{25^\circ}$ 0·9181, $n_D^{25^\circ}$ 1·4992, $[\alpha]_{5461}$ + 47·0°, but analysis showed the *hydrocarbon* to be impure (Found : C, 86·6; H, 11·7. $C_{15}H_{24}$ requires C, 88·2; H, 11·8%). With hydrogen chloride, in either ether or acetic acid, it gave a liquid hydrochloride.

The following report has been furnished by Miss D. M. Crowfoot, to whom we are greatly indebted.

Oximes.—Five preparations were examined, *viz.*, those termed Nα, Oα, Nβ, Oβ, and Bβ. The first three were triclinic lath-shaped crystals on (001) elongated along (010). They were practically indistinguishable morphologically. *X*-Ray photographs [(010) ″ (001)] showed complete identity between Nα and Oα. There seemed to be a slight difference in the *c* spacing of the β-compounds when compared with the α-, though for the rest the photographs showed essential identity. The difference seems to be too small to indicate the presence of a different molecular species. It is more of the order of magnitude one would associate with the presence of a mixed crystal, mainly α. In any case it could not be due to a molecule with a completely different stereochemical configuration.

The synthetic β-specimens differed crystallographically from the above and also from one another. They were both orthorhombic, but the Oβ preparation showed positive birefringence, the Bβ negative. They may, however, be polymorphs, since from the melt in both cases orthorhombic negative crystals were obtained, but these were too small to be measured accurately.

2 : 4-*Dinitrophenylhydrazones.*—Three preparations were examined, *viz.*, Nα, Nβ, Oβ. All three were plates, lath-shaped on (001), elongated along (010), showing straight extinction and very marked yellow-red pleochroism. The birefringence was very high, the slow direction being along (001). The crystals were probably all orthorhombic. In the two β-preparations the plates were commonly bounded by the edges (110), (100), the angle between which was *ca.* 40′. The same angle was measured in the case of the α-preparation, though the crystals here, which were much stouter, were commonly bounded by (010) and (100). The morphological and optical evidence does not therefore distinguish between these three compounds; it would, of course, be possible to do so by the *X*-ray method.

Semicarbazones.—Five preparations were examined, *viz.*, Nα, Oα, Nβ, Oβ, Bβ and all were crystallographically different. Nα consisted of plates bounded by edges inclined at *ca.* 43° to each other; slow extinction along one edge. Through the plane of the plate a very much inclined biaxial figure is visible. Oα formed irregular plates through which a biaxial figure is visible with the acute bisectrix normal to the plane. The birefringence is positive. From the melt the crystals obtained from these preparations are very similar, but further evidence would be necessary to establish identity.

The three β-*semicarbazones* show very distinct forms. Nβ occurs as thick plates on (010) bounded by edges at an angle of 55°, the slow extinction lying in the acute angle at 35° to one edge. Through (010) a positive (or negative, optic axial very large) biaxial figure is visible showing γ nearly perpendicular to (010). The crystals may be monoclinic or triclinic.

Bβ forms thin lath-shaped plates, probably orthorhombic. The dispersion is extremely marked. Through the *c* face a negative biaxial figure with very small optic axial angle is visible. Oβ forms lath-shaped, thickish plates. One eye of a biaxial figure is visible nearly normal to (001).

These three preparations were then studied on melting between two glass surfaces. All three decomposed visibly, and all crystallised in platy forms, of which that from Nβ and one of those from Bβ seemed possibly identical.

It is not possible to draw any definite conclusions as to the identity of any of these five semicarbazones until identical crystals have been obtained either from melts or from solutions, seeded if necessary.

We are indebted to the Government Grants Committee of the Royal Society for a grant. One of us (P. S. A.) desires to thank the Department of Scientific and Industrial Research for a maintenance grant.

UNIVERSITY COLLEGE OF N. WALES, BANGOR.
DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.

[*Received, July 24th,* 1937.]