265. *The Alkaloids of* Alstonia *Barks. Part II.* A. macrophylla, *Wall.*, A. somersetensis, *F. M. Bailey*, A. verticillosa, *F. Muell.*, A. villosa, *Blum.*

By Thomas M. Sharp.

The search for anti-malarial drugs in the genus *Alstonia* (Part I, this vol., p. 287) has been continued by the examination of four more species. *A. somersetensis*, *A. verticillosa*, and *A. villosa* are Australian species, the last occurring also in Java, whilst *A. macrophylla* is a native of Malaya and the Philippine Islands. Of these, the first two do not appear to have been examined before, but the other two are known to contain alkaloids, and in particular not to contain echitamine, the characteristic alkaloid of a number of African and other *Alstonias* (Goodson, J., 1932, 2626).

A. verticillosa contains a considerable amount of a mixture of sterols the separation of which has not been attempted, and in addition a small amount of echitamine. It is very similar to "dita-bark" (*A. scholaris*) examined many years ago by Jobst and Hesse (*Annalen*, 1875, **178**, 49). The other three barks all contain, in addition to much amorphous base, an alkaloid which forms well-defined crystalline salts and for which the name *villalstonine* is suggested, as it was first isolated from *A. villosa*. *A. macrophylla* contains, besides villalstonine, three other alkaloids, for which the names *macralstonine*, *macralstonidine*, and base M are suggested. The last is present in exiguous amount. Macralstonidine is also present in *A. somersetensis*, and a new base, isolated in comparatively small amount, and provisionally named base V, has been obtained from *A. villosa*.

Villalstonine, $C_{40}H_{50}O_4N_4$, has two basic and two non-basic nitrogen atoms, forms

salts of the general formula B,2HA, and yields a *dimethiodide*. It contains one methoxy- and two methylimino-groups, and this precludes the possibility of the simpler formula $C_{20}H_{24(26)}O_2N_2$. It forms, moreover, a *mono*-N-*benzyl* derivative, and final confirmation of the more complex formula is afforded by molecular-weight determination cryoscopically in benzene. The methoxy-group appears to exist as a methyl ester, since hydrolysis with alcoholic potassium hydroxide furnishes an amphoteric *substance*, $C_{39}H_{48}O_4N_4$, which does not contain a methoxy-group. The other bases are present in much smaller amounts. Macralstonine, $C_{44}H_{52}O_5N_4$, is crystalline and forms a crystalline *sulphate* but has not yielded any other crystalline salt. The base is very sparingly soluble in the common organic solvents except pyridine and chloroform, and has one methoxy- and three methylimino-groups. It is noteworthy that the optical rotation of the base and sulphate are opposite in sign, as is the case, *e.g.*, with aconitine and emetine. Its molecular weight has not been confirmed by direct determination owing to the lack of a suitable solvent, but the methoxyl content and phytochemical considerations leave little doubt as to its complexity. Macralstonidine, $C_{41}H_{50}O_3N_4$, is crystalline and forms crystalline salts. It is soluble in most organic solvents, contains two methylimino-groups but no methoxy-group, and appears to have a dioxymethylene group since it gives a red colour with Gaebel's reagent. Satisfactory molecular-weight determinations could not be obtained; it appears to be associated in benzene. Alkaloids M and V are crystalline, but owing to the very small quantity available neither formulæ nor names are suggested for them. The formulæ put forward for macralstonine and macralstonidine are to be regarded as provisional, for, although the analytical figures are in good agreement with those suggested, it is desirable to have more derivatives in order definitely to establish formulæ of such complexity. All the new alkaloids described give colour reactions characteristic of indole derivatives. The high molecular weight of these alkaloids is reminiscent of recent work on a number of *iso*quinoline alkaloids such as emetine, and more especially oxyacanthine, *iso*chondodendrine, curine, etc., which were at first thought to contain one *iso*quinoline group, but are now known to contain two such nuclei, and of calycanthine which is now considered to contain two indole nuclei.

Pharmacological experiments have been carried out with villalstonine hydrochloride by Dr. A. C. White of the Wellcome Physiological Research Laboratories. He found that a concentration of 1 : 6,500 to 1 : 12,500 caused a slight increase in the movement of the isolated rabbit uterus; a concentration of 1 : 25,000 had no action on the isolated guinea-pig uterus, and 1 : 50,000 none on the isolated rabbit intestine; a dose of 2 mg. per kg. caused, in the anæsthetised cat, a fall in blood pressure, which was unaffected by atropine. This fall was less than that caused by the same dose of alstonine sulphate. The action on bird malaria has not yet been determined. The other alkaloids have not been tested, as they occur in too small amount to be of practical importance.

The genus *Alstonia* is widely distributed throughout the tropical parts of the Old World and Australia and, with the exception of a small number of species occurring in China and New Caledonia, representative species have now been examined from all the districts from which it has been reported (for literature, see Part I, and Goodson and Henry, J., 1925, **127**, 1640). The alkaloids which have been isolated fall into three groups represented by (*a*) echitamine, occurring in many species from Africa, the East Indies, and Australia, (*b*) villalstonine, from a number of Australian and East Indian species, and (*c*) alstonine, which has only been found in one species, *viz.*, *A. constricta* from Australia. These three types of alkaloid appear to have little in common except that both villalstonine and echitamine appear to be indole derivatives, whilst alstonine does not give any of the usual indole colour reactions.

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Experimental.

The barks were finely ground and, with the exception of *A. verticillosa*, which required a preliminary extraction with petroleum, exhausted with alcohol. The alcoholic solutions were

divided into convenient-sized batches, and concentrated to the consistency of thick syrups, extracted with sufficient cold 0·5% sulphuric acid to render the solutions faintly acid to Congo-red, filtered, diluted with an equal volume of water, filtered again from precipitated impurities, and worked through by appropriate methods as described below.

A. macrophylla.—The acid liquor was extracted with ether to remove impurities, made strongly alkaline with sodium carbonate and shaken with ether. During this process a large amount of buff to greyish-green, granular, amorphous solid separated and formed a middle layer on standing. After a few extractions, the solid was collected by filtration and reserved (A), and the clear filtrate exhausted with ether. Occasionally the early ethereal extracts deposited crystals which were collected; when none appeared, the ether, after drying, was concentrated and left over-night. The colourless crystals which separated were filtered off, and consisted of crude macralstonine mixed with base M. The filtrate was evaporated and the residual resinous base converted into oxalate and dissolved in alcohol. From this solution, villalstonine oxalate separated in an almost pure condition, and a further, less pure, amount was obtained on concentration. After standing until no more oxalate separated, the solution was evaporated, the residue dissolved in water, treated with potassium carbonate, and shaken with ether. A portion of the liberated base failed to dissolve in ether, and was obtained by subsequent extraction with chloroform. After evaporation and solution in dry alcohol, both the ether-soluble and the chloroform-soluble part deposited crude macralstonidine as a colourless, crystalline powder. An additional quantity of this base was also obtained after conversion of the amorphous residue into perchlorate, and recovery of the base in the usual manner. The amorphous solid A (above) was dried in a desiccator, mixed with half its weight of powdered quick-lime, and exhausted in a Soxhlet extractor with benzene. The benzene solution was extracted with *N*-sulphuric acid, and the acid liquor basified with sodium carbonate and extracted with ether. This solution on concentration deposited macralstonine, and the filtrate after evaporation and solution in dry alcohol furnished macralstonidine. A further small amount of each of these bases was obtained by extraction of the residue from the benzene extracts with chloroform. The yields of the alkaloids from all the barks are given in the following table; the figures in parentheses are percentage yields.

Bark.	*A. macrophylla.*	*A. villosa.*	*A. somersetensis.*	*A. verticillosa.*
Weight, kg.	53·5	4·58	3·45	3·0
Total base, g.	496 (0·93)	66·4 (1·45)	47·8 (1·39)	8·0 (0·27)
Villalstonine oxalate, g.	216·9 (0·405)	19·7 (0·43)	3·05 (0·088)	—
Macralstonine, g.	18·8 (0·035)	—	—	—
Macralstonidine, g.	21·6 (0·0407)	—	2·13 (0·062)	—
M. sulphate, g.	1·03 (0·0019)	—	—	—
Base V, g.	—	0·65 (0·014)	—	—
Echitamine HCl, g.	—	—	—	4·7 (0·16)

A. villosa.—Macralstonine was not isolated from this bark, but apart from this, the method for the isolation of villalstonine oxalate was the same as that described above. The residual amorphous oxalate was converted into the more soluble sulphate, and its aqueous solution treated with 10% sodium perchlorate solution so long as a precipitate formed. This precipitated perchlorate failed to yield any crystalline substance. The filtrate was made alkaline with sodium carbonate and extracted with ether; this solution on standing for a short time deposited crystals of base V, which were collected, and a further small amount was obtained from the filtrate. The amorphous granular solid corresponding with A (see above) was extracted with dilute sulphuric acid, basified with sodium carbonate, and extracted with ether. After conversion into oxalate, it furnished a small amount of villalstonine oxalate together with amorphous material.

A. somersetensis.—The process described for the isolation of alkaloids from the two previous barks was not applicable to this bark owing to the formation of persistent and intractable emulsions. The acid solution of the alkaloids was treated with excess of sodium carbonate, the slimy precipitate filtered off, dried in a desiccator, and exhausted with ether (Soxhlet). On evaporation, this left a syrupy base which was made into oxalate but failed to crystallise. Villalstonine was obtained, however, after conversion into hydrobromide. The amorphous part was converted into the more soluble sulphate, and treated with sodium perchlorate. The base recovered from the precipitated perchlorate deposited crystals of macralstonidine after solution in dry alcohol.

A. verticillosa.—This bark (3 kg.) was exhausted with petroleum (b. p. 60—80°), the marc

air-dried, and then extracted with industrial methylated spirit. The petroleum extract on evaporation left a yellowish elastic mass (228·5 g.) which was partly soluble in alcohol; the residue from this extraction was grey and of a rubbery consistency, with physical properties very similar to those of Hesse's echikautschin (*loc. cit.*), although not necessarily identical with it. The alcoholic solution deposited colourless crystals which were obviously mixtures and gave colorations characteristic of sterols with Liebermann's reagent. No further attempt at purification was made. One crop of crystals appeared homogeneous and had the same m. p. as lupeol, but a mixed m. p. showed a depression of about 40°. The methylated spirit extract was evaporated to dryness, the residue treated with sufficient 0·25% sulphuric acid to remove the alkaloid, and the acid liquor extracted with ether. It was then treated with 25% sodium hydroxide solution and shaken with chloroform. From this solution, the crude alkaloid was obtained as sulphate by extraction with *N*-sulphuric acid and evaporation to dryness (yield 9·12 g.). This contained a little alkaloid which could be liberated from its salts by sodium carbonate; it was, therefore, dissolved in water, made alkaline with sodium carbonate, and extracted with chloroform. This gave 0·6 g. of dark-coloured varnish, from which nothing crystalline could be obtained and which corresponds with Jobst and Hesse's ditamine from *A. scholaris*. The aqueous liquor was then treated with sodium hydroxide and chloroform, the chloroform concentrated to a small volume, mixed with alcohol, and acidified to methyl-red with 10% hydrochloric acid. Almost at once, the solution gave a crystalline crop of echitamine hydrochloride (4·7 g.).

Villalstonine.—The *oxalate* was purified by crystallisation from alcohol, separating in colourless leaflets, m. p. 235° * (decomp.). The salt from *A. villosa* had $[\alpha]_D$ + 31·2°, that from *A. macrophylla* $[\alpha]_D$ + 32·1° (*c* = 0·56 in acetone), † $[\alpha]_D$ + 55·6° (*c* = 0·5 in water) [Found, on dried material, (*a*) from *A. macrophylla*: C, 67·8, 67·7; H, 6·95, 6·9; N, 7·8, 7·7; OMe, 4·2; NMe, 6·3; (*b*) from *A. villosa*: C, 67·8, 67·8; H, 7·1, 7·0; N, 7·6, 7·7; OMe, 4·2; NMe, 6·4. $C_{40}H_{50}O_4N_4,C_2H_2O_4$ requires C, 68·1; H, 7·1; N, 7·6; OMe, 4·2; 2NMe, 7·8%]. The *hydrochloride*, prepared by the addition of freshly prepared alcoholic hydrogen chloride to dry alcoholic solution of the base, formed colourless needles, m. p. 270° (decomp.), $[\alpha]_D$ + 56·3° from *A. villosa*, + 56·1° from *A. somersetensis* (*c* = 0·5 in water) (Found: loss at 120° in a vacuum, 9·8. $C_{40}H_{50}O_4N_4,2HCl,4H_2O$ requires $4H_2O$, 9·1. Found, on dried salt: C, 66·2, 66·2; H, 7·4, 7·35; N, 7·5, 7·5; Cl, 9·7, 9·7; OMe, 4·2, 4·5; NMe, 6·9, 8·1. $C_{40}H_{50}O_4N_4,2HCl$ requires C, 66·4; H, 7·25; N, 7·75; Cl, 9·8; OMe, 4·3; 2NMe, 8·0%). The dried salt rapidly absorbs moisture from the air (Found: gain on exposure to air, 10·35. Calc. for $4H_2O$: 10·0%).

An aqueous solution of the hydrochloride or other salt of villalstonine slowly becomes pink on keeping. The *sulphate* does not crystallise easily. It is rather sparingly soluble in alcohol and crystallises only after concentration, forming small prismatic rods, which do not melt at 310°, $[\alpha]_D$ + 52·94° (*c* = 1·02 in water) (Found: loss at 110° in a vacuum, 12·7. $C_{40}H_{50}O_4N_4,H_2SO_4,6H_2O$ requires $6H_2O$, 12·6%. Found on dry salt: C, 63·3, 63·2; H, 6·85, 6·95; N, 7·7, 7·55; S, 4·3, 4·3; OMe, 4·1, 4·1; NMe, 6·3, 6·35. $C_{40}H_{50}O_4N_4,H_2SO_4$ requires C, 64·1; H, 7·0; N, 7·5; S, 4·3; OMe, 4·1; 2NMe, 7·8%). On exposure to air the dry salt absorbs 13·4% of its weight (Calc. for $6H_2O$: 14·4%). The *hydrobromide*, prepared by precipitation, crystallised from alcohol in colourless needles, m. p. 293° (decomp.) (Found: loss at 110° in a vacuum, 8·0. $C_{40}H_{50}O_4N_4,2HBr,4H_2O$ requires $4H_2O$, 8·15%. Found, on dry salt: C, 59·4, 59·5; H, 6·3, 6·3; N, 7·1, 7·0; Br, 19·2, 19·3; OMe, 4·0, 3·8; NMe, 7·3, 6·8. $C_{40}H_{50}O_4N_4,2HBr$ requires C, 59·1; H, 6·5; N, 6·9; Br, 19·7; OMe, 3·8; 2NMe, 7·2%). On exposure to air the dry salt absorbed $4H_2O$ (Found: gain on exposure, 8·8. Calc.: 8·9%). The *hydriodide*, colourless balls of needles from methyl alcohol, m. p. 286° (decomp.), showed a tendency to become yellow on recrystallisation and failed to give satisfactory analytical figures (Found, on salt dried at 110° in a vacuum: C, 54·2; H, 5·8; N, 6·2; I, 26·7; OMe, 3·4; NMe, 5·7. $C_{40}H_{50}O_4N_4,2HI$ requires C, 53·0; H, 5·8; N, 6·2; I, 28·0; OMe, 3·4; 2NMe, 6·4%). The *base* was obtained as a colourless granular powder on the addition of sodium carbonate or hydroxide to an aqueous solution of the pure hydrochloride. It was very soluble in most organic solvents and was not obtained in a crystalline condition. For analysis it was triturated with many changes of water, and dried at 100° in a vacuum. It sintered at 218° and slowly melted up to 260° [Found: C, 73·5, 73·7; H, 7·6, 7·6; N, 8·6, 8·4; OMe, 4·8, 4·6; NMe, 7·9, 8·1; *M*, cryoscopic in benzene, using alumina as drying agent (Roberts and Bury, J., 1923, **123**, 2037; Brown and Bury, J., 1924, **125**, 2219), 657, 645, 651. $C_{40}H_{50}O_4N_4$ requires C, 73·8; H, 7·75; N, 8·6; OMe, 4·8; 2NMe, 8·9%; *M*, 650·4). The *dimethiodide* was prepared by

* All m. p.'s are corrected. † All the rotations were done on the dry salts.

When the acid (VI*a*) (0·5 g.) was boiled with potassium hydroxide (1·5 g. in 8 c.c. water) for an hour, it was recovered unchanged on acidification.

Action of Ammonia on Ethyl β-Phenyl-α-1-p-toluenesulphonyloxyhydrindene-2-propionate (VIII).—Ethyl β-phenyl-α-1-hydroxyhydrindene-2-propionate (3 g.), prepared in the usual way, was mixed at 0—10° with *p*-toluenesulphonyl chloride (1·5 g.) and pyridine (1·1 g.) and left overnight. Next day the product was poured into water, extracted with benzene, the extract washed, and the benzene distilled off. The ester (VIII) (4 g.) was a viscous oil. It was dissolved in alcohol (50 c.c.) and saturated with ammonia at 0°. The solution was kept at room temperature for 43 hours and then heated for 5 hours at 100°. The alcohol was distilled off, and the residue dissolved in benzene and washed with dilute hydrochloric acid. Neutralisation of this extract gave no amino-acid or amino-ester. On removal of the benzene, a residue was left consisting of the original acid (m. p. 164°) and a neutral product, m. p. 102° (Found : equiv. by titration, 271·2; C, 81·7; H, 6·05. $C_{18}H_{16}O_2$ requires equiv., 264; C, 81·8; H, 6·06%); this *lactone* (VII*b*; R = CH_2Ph) was insoluble in sodium bicarbonate, but soluble in caustic soda on warming, being reprecipitated on acidification.

Action of Sodium Hydroxide on (VIII).—1 G. of the ester (VIII) was boiled with 10 c.c. of 2*N*-sodium hydroxide; the solution was acidified, extracted with benzene, and the extract washed with sodium bicarbonate solution. From the benzene solution the lactone (VII*b*), m. p. 102°, was obtained.

Conversion of Lactone (VII*a*) *into the Lactone* (VII*b*).—The lactone (1 g.) was boiled under reflux for 2 hours with potassium hydroxide (1 g.) in rectified spirit (5 c.c.), the alcohol removed, water added, the solution acidified, and extracted with ether. The extract was washed with sodium bicarbonate solution and then gave 0·75 g. of the lactone (VII*b*), m. p. 102°. Sodium ethoxide solution acted similarly.

When, however, a solution of the lactone (VII*a*) (7 g.) in absolute alcohol (100 c.c.) was saturated at 0° with hydrogen bromide, left over-night, and then heated under reflux on a boiling water-bath in a stream of hydrogen bromide, the lactone was subsequently recovered unchanged, m. p. 84°.

Condensation of 2-Bromo-1-hydrindone with Ethyl Benzylacetoacetate and with Ethyl Benzylmalonate.—2-Bromo-1-hydrindone (10 g.), prepared as described by Ishiwara (*J. pr. Chem.*, 1924, **108**, 194), was dissolved in absolute alcohol (40 c.c.) and added to a solution prepared by addition of ethyl benzylacetoacetate (11·0 g.) to a solution of sodium (1·15 g.) in absolute alcohol (20 c.c.) cooled by ice. Colourless needles at once began to separate. Next day the solution had turned black. It was boiled under reflux for one hour, the alcohol distilled off, water added, and the oil extracted with ether. On removal of the ether, the residue partly crystallised. Alcohol was added, and the crystals (3·8 g.), m. p. 158—176°, removed. The oil on hydrolysis with alcoholic caustic potash gave only a black tar. Condensation of bromohydrindone with ethyl benzylmalonate gave the same crystalline solid, and an oil which on hydrolysis gave a tar, from which a small quantity of benzylmalonic acid was isolated. The solid product was bromo-hydrindonylhydrindone (Kipping and Revis, J., 1897, **71**, 243) (Found : Br, 22·98. Calc. for $C_{18}H_{13}O_2Br$: Br, 23·4%).

Action of Ammonia on Ethyl β-Phenyl-α-1-bromohydrindene-2-propionate.—The acid (VI*a*; R = CH_2Ph) (5 g.) was dissolved in absolute alcohol (50 c.c.) and a stream of dry hydrogen bromide at room temperature passed through the solution, which was then boiled for an hour in a current of hydrogen bromide; the bromo-ester was worked up in the usual way; yield, 5·5 g. (Found : Br, 15·47%, corresponding to about 70% of the bromo-ester). This ester (5·1 g.) was added to alcoholic ammonia (6*N*, 70 c.c.) and kept at 10° for 144 hours. The alcohol and ammonia were then distilled off from a water-bath, and the residue extracted with ether. An oil (4·4 g.) which contained bromine but no nitrogen was obtained. This was heated for 6 hours with alcoholic ammonia (6*N*, 70 c.c.) at 100°. The product when worked up as before gave 1·5 g. of the lactone (VII*b*), m. p. 102°, and a neutral oil (probably a mixture of the lactones). The action of potassium phthalimide on this bromo-ester gave phthalimide, phthalic acid, the acid (VI*a*), and the lactone (VII*b*), m. p. 102°. The action of sodium *p*-toluenesulphonamide also gave this lactone, m. p. 102°, but no amino-derivative. This lactone was recovered unchanged after 2 hours' boiling with aqueous hydrogen bromide (*d* 1·78) or with an acetic acid solution of hydrogen bromide.

Acetoxy-acid (IX*b*; R = CH_2Ph).—The oil (10 g.) obtained from the mother-liquors from the crystallisation of the acid (VI*a*) was boiled for 2 hours with acetic anhydride (50 c.c.), the product poured into alcohol (50 c.c.), and left at room temperature for 2 hours. The ethyl acetate, etc., were then removed by distillation under reduced pressure, and the residue dissolved

in benzene. The benzene solution was extracted with aqueous sodium bicarbonate, and the extract on acidification gave an *acid* (7·7 g.), m. p. 121° from light petroleum–chloroform (Found: equiv., for saponification of acetyl group, 181; equiv., by direct titration, 309·8; C, 73·7; H, 6·4. $C_{20}H_{20}O_4$ requires equivs., 162, 324; C, 74·1; H, 6·2%). The acid (1 g.) was dissolved in caustic soda (2*N*, 10 c.c.) and left at room temperature for 5 hours. On acidification, the acid (VI*a*) m. p. 164°, was obtained. The acetoxy-acid (1 g.) was heated for 2 hours with an acetic acid solution of hydrogen bromide (15 c.c.), and after the usual procedure afforded the lactone (VII*b*) (0·65 g.), m. p. 102°.

Acetoxy-acid (IX*a*; R = CH_2Ph).—By a procedure similar to the foregoing, the acid (VI*a*) gave an *acetoxy-acid*, m. p. 147°, from light petroleum–chloroform (Found: equiv., by back titration 181, by direct titration 313; C, 73·8; H, 6·7%). On treatment with hydrogen bromide as above this acid (1 g.) gave 0·60 g. of the lactone (VII*a*), m. p. 84°, identical with that similarly obtained from the acid (VI*a*). The acid (IX*a*) (0·5 g.) was heated with sodium hydroxide solution; acidification gave the acid (VI*a*), m. p. 164° (0·40 g.).

trans-α-1-*Hydroxyhydrindene*-2-n-*hexoic Acid* (VI*a*; R = *n*-Bu).—Ethyl *n*-butylacetoacetate (46·5 g.) was added to a solution of sodium (5·75 g.) in absolute alcohol (125 c.c.), and bromohydroxyhydrindene (53·25 g.) dissolved in absolute alcohol (100 c.c.) added. Next day the solution was boiled until neutral (4 hours). The sodium bromide was filtered off, and the ester worked up in the usual way and saponified by addition to a solution of potassium hydroxide (45 g.) in alcohol (150 c.c.). Next day the solution was boiled under reflux for 4 hours (blackening), poured into water (1 l.), filtered from tar, and acidified. The resulting oil was dissolved in benzene, and the solution shaken with ammonia. The calcium salt was then precipitated by the addition of calcium chloride solution, collected, freed from tar by extraction with boiling rectified spirit, and decomposed with hydrochloric acid. The solid *acid* which separated was crystallised from benzene, m. p. 122°, yield 4·0 g. (Found: C, 72·32; H, 8·56. $C_{15}H_{20}O_3$ requires C, 72·57; H, 8·06%). This acid was recovered unchanged after 40 mins.' heating with quinoline at 140°.

cis-*Lactone* (VII*a*; R = *n*-Bu).—The acid (2 g.) was dissolved in an acetic acid solution (20 c.c.) of hydrogen bromide and heated for 2 hours under reflux on a water-bath. The solution when poured into water gave a crystalline product, which was washed with sodium bicarbonate solution and recrystallised from light petroleum or ethyl alcohol; yield 1·3 g., m. p. 105° (Found: C, 78·00; H, 8·20. $C_{15}H_{18}O_2$ requires C, 78·26; H, 7·83%). The *lactone* was recovered unchanged after 2 hours' boiling with alcoholic caustic potash and also after 2 hours' heating at 150° in a sealed tube with the same reagent.

trans-α-1-*Hydroxyhydrindene*-2-*propionic Acid* (VI*a*; R = Me).—The ester was prepared in the usual way from bromohydroxyhydrindene (53·25 g.) and ethyl methylacetoacetate (35·75 g.). The product was worked up as in the preceding case, and the crude acid thus obtained in benzene solution; this solution was extracted with aqueous sodium bicarbonate, the extract filtered and acidified, and the acid again taken up in benzene. The calcium salt, prepared as in the preceding case, was similarly converted into the *acid* (VI*a*; R = Me), which crystallised from benzene–acetone; yield 1·1 g., m. p. 131°, mixed m. p. with (I) 115—120° (Found: C, 69·98; H, 6·80. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·80%).

cis-*Lactone* (VII*a*; R = Me).—The above acid (1 g.) was dissolved in an acetic acid solution (10 c.c.) of hydrogen bromide and heated for 2 hours under reflux on a water-bath. The acetic acid and hydrogen bromide were distilled off under reduced pressure, and the residue dissolved in ether and extracted with aqueous sodium bicarbonate. The solid residue obtained on removal of ether was crystallised from light petroleum–benzene; m. p. 102° (0·68 g.) [Found: C, 76·42; H, 6·36; *M* (Rast's method), 184·5. $C_{12}H_{12}O_2$ requires C, 76·60; H, 6·38%; *M*, 188]. The *lactone* (0·2 g.) was recovered unchanged when heated for 2 hours on a water-bath with caustic potash (0·2 g.) in rectified spirit (2 c.c.).

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