XXXI.—*A Synthesis of Hydrastine. Part I.*

By EDWARD HOPE, FRANK LEE PYMAN, FREDERICK GEORGE PERCY REMFRY, and ROBERT ROBINSON.

THE experiments described in the present communication were carried out from 1910 * and gave results which were somewhat difficult to understand at that time. As shown below, two optically inactive stereoisomerides having the constitution assigned to hydr-

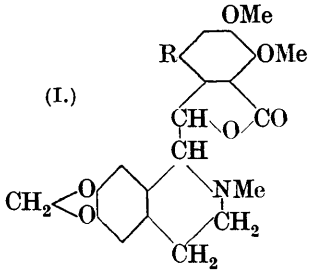
* A note on "Anhydrohydrastininemeconine" was published (P., 1912, **28**, 17).

astine were isolated and neither was identical with an isomeride, m. p. 162°, obtained by the prolonged action of alcoholic potassium hydroxide on the natural *l*-base. A description of the hydrastine isomeride, m. p. 162°, will be included in Part II of this series. It may be recalled that the two best syntheses of α-gnoscopine (*dl*-narcotine) are the following (Hope and Robinson, J., 1914, **105**, 2086) :— (1) Condensation of cotarnine and nitromeconine to nitro-β-gnoscopine, followed by elimination of the nitroxyl through the related amino- and hydrazino-β-gnoscopines and finally by the isomerisation of β-gnoscopine with formation of α-gnoscopine. (2) Condensation of cotarnine with iodomeconine to iodo-α-gnoscopine and reduction of this base by means of amalgamated aluminium in boiling alcoholic solution.

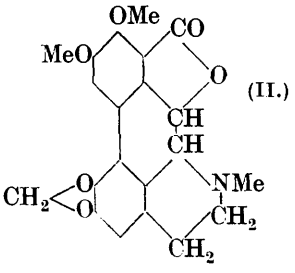
In the hydrastine case the results were not quite parallel, since the main products isolated by the nitromeconine and iodomeconine routes were identical, but mixtures were obtained in both cases.

Hydrastinine and nitromeconine in boiling alcoholic solution furnish a mixture of *anhydrohydrastininenitromeconines* (I; R = NO_2) in excellent yield. Separation of the components at this stage was impracticable, but on reduction with stannous chloride and hydrochloric acid the amino-*r*-hydrastines (I; R = NH_2) were obtained and by taking advantage of the more sparing solubility of one of the bases and of its dihydrochloride, the mixture was resolved into dl-*aminohydrastine*-a, m. p. 216—217° (corr.), and dl-*aminohydrastine*-b, m. p. 196—197° (corr.).

(I.)



(II.)



On reduction of the related diazonium chlorides by means of stannous chloride in concentrated hydrochloric acid solution these bases yielded the isomeric hydrazinohydrastines (I; R = $NH{\cdot}NH_2$), but on oxidation with cupric salts the latter stereoisomerides behaved differently. dl-*Hydrazinohydrastine*-a afforded dl-*hydrastine*-a (I; R = H) in good yield, whereas dl-*hydrazinohydrastine*-b under similar conditions gave dl-*hydrastine*-b in poor yield, the main product being in this case dl-*dedihydrohydrastine* (II).

The phenanthrene constitution suggested for this interesting base

has not been rigorously proved to be correct, but it is very probably so in view of the method of preparation and the facts that the substance does not yield hydrastinine on oxidation and was recovered unchanged after an attempt had been made to reduce it by means of hydrogen and palladinised charcoal.

The inactive hydrastines exhibited the behaviour of lactones and afforded hydrastinine on oxidation.

We have no precise information in regard to the relation of the inactive isomerides to the natural *l*-hydrastine or to the parallel gnoscopine-narcotine series and these matters can be more conveniently discussed at a later stage.

Experimental.

Anhydrohydrastininenitromeconine (I; R = NO_2).—More than fifty preparations of this substance were made and the yields varied from 80—90%. Hydrastinine (20·7 g.) was added to a boiling solution of nitromeconine (23·9 g.) in 95% alcohol (700 c.c.): orange crystals began to separate in 2 minutes and after 15 minutes the mixture was filtered hot, giving nitrohydrastine (*a* and *b*?) (30·0 g., m. p. 167°) and a mother-liquor from which, on concentration and cooling, two further crops could be obtained (2·0 g., m. p. 164°; 5·5 g., m. p. 155°). In a similar experiment a suspension and solution of nitromeconine (24·0 g.) in boiling absolute alcohol (500 c.c.) became clear on the addition of hydrastinine (20·0 g.); the mixture was boiled for 5 minutes, cooled, and filtered after 2 hours (37·0 g., m. p. 159—165°). Analyses were made of a specimen, m. p. 167—168° (Found: C, 58·7; H, 4·7; N, 6·4%), and of one of m. p. 173° (decomp. a few degrees higher) which separated from trichloroethylene in orange-yellow prisms (Found: C, 58·8; H, 4·7. $C_{21}H_{20}O_8N_2$ requires C, 58·9; H, 4·7; N, 6·5%). The base is relatively stable in solutions of strong acids, but is decomposed with formation of its generators by means of acetic acid, slowly in the cold and very rapidly on heating. The *hydrochloride*, prepared from the crude base by trituration with 10% hydrochloric acid, is sparingly soluble and crystallises in yellow prisms, m. p. 137—138° (Found: Cl, 7·4. $C_{21}H_{20}O_8N_2$,HCl requires Cl, 7·6%); when heated in aqueous solution, it also breaks down into nitromeconine and hydrastininium chloride (recognised as cyanohydrohydrastinine). Separation of the nitrohydrastines *a* and *b* by means of the hydrochloride was attempted but without success.

The orange base dissolved in concentrated hydrochloric acid to a yellow solution; on dilution the hydrochloride separated and on further dilution a clear colourless solution was obtained; addition of platinic chloride to this gave no precipitate, but auric chloride,

mercuric chloride, and picric acid gave rise, respectively, to amorphous, nearly colourless flocks, a colourless crystalline precipitate, and a yellow precipitate.

The Aminohydrastines a *and* b (I; R = NH_2).—The results obtained in numerous reductions of anhydrohydrastininenitromeconine were much affected by slight variations of the conditions and afforded some evidence that one or other of the isomerides was produced in the process of reduction or alternatively was transformed in the working-up—in one series of reproducible experiments an almost homogeneous product (aminohydrastine-*a*) was obtained.

Anhydrohydrastininenitromeconine (10 g.) was dissolved in cold acetic acid (40 c.c.), and a solution of hydrated stannous chloride (25 g.) in concentrated hydrochloric acid (40 c.c.) and granulated tin (5 g.) were added with cooling to below 7°. After 3 hours a salt of the aminohydrastine separated and after 6 hours the whole was dissolved in water (1500 c.c.), mixed with fresh 50% potassium hydroxide solution (250 c.c.), and at once extracted several times with chloroform. The combined chloroform solutions were dried with potassium carbonate and concentrated; when nearly all the solvent had been removed, crystallisation commenced from the boiling liquid; methyl alcohol was then added and after cooling the base was collected (17·0 g. from two operations, m. p. 212—213°). Practically nothing was obtained from the mother-liquor.

In a long series of other experiments, however, mixtures were obtained (except in one instance and in that case the yield was inferior) and the following is typical.

Anhydrohydrastininenitromeconine (20 g.) was stirred with cold acetic acid (90 c.c.) and, when solution occurred, granulated tin (10 g.), cut in small pieces, and a solution of hydrated stannous chloride (44 g.) in concentrated hydrochloric acid (80 c.c.) were quickly added. The mixture was cooled by means of running water, but the temperature rapidly rose to 25° and then fell slowly to 15°. After 20 minutes' stirring, the flask was kept in running water for 4 hours; the temperature during this period was 12—15°. The sparingly soluble double tin salt was worked up separately in one experiment and then furnished only aminohydrastine-*b*. Usually, however, the whole was dissolved in water (1000 c.c.), mixed with aqueous potassium hydroxide (400 c.c., 7 : 10), and the warm solution shaken with chloroform (2000 c.c.); the extract was dried and concentrated to 75—100 c.c., and alcohol (150 c.c. S.V.M.) added. Aminohydrastine (8·2 g., m. p. 208—209°) separated and successive concentrations to half the volume afforded further crops (6·35 g., m. p. 174—175° with softening from 170°, and 1·3 g.,

m. p. 172—173° with softening from 166°; total yield, 16·35 g. or 88%).

Other experiments in which the quantities of the reagents used were varied gave similar but not identical results. The total yield was reduced when the operations were conducted on a larger scale, doubtless as the result of hydrolysis of the nitrohydrastine due to the rise of temperature (to 30—40°) that could not be avoided even by cooling in running water. Again, when a weaker potash solution was employed, the product was not all obtained in the chloroform extract. Addition of more potash and a second extraction afforded a further quantity of the base and comparison of the results with those obtained in an experiment in which concentrated aqueous potash was used, but in which the conditions were otherwise identical, suggested that the more concentrated alkaline solution actually transformed the *a*-base into *b*-base.

Separation of the Aminohydrastines-a *and* -b.—The product melting above 200°, for example, that mentioned above, m. p. 208°, is nearly pure aminohydrastine-*a*; specimens of lower melting point were treated as follows.

The mixture (41·4 g.) was finely ground and shaken with 5% hydrochloric acid (175 c.c.) at 95°. After several hours the liquor was separated from aminohydrastine-*a* dihydrochloride (19·2 g., m. p. 267—268°) and concentrated to half bulk; a further crop (0·8 g., m. p. 264°) of the same salt was then obtained (the total yield corresponded to 17·0 g. of the *a*-base). The mother-liquors afforded a chalky precipitate on basification and this became crystalline when triturated with a little hot alcohol and was then recrystallised from that solvent (yield, 20·6 g., m. p. 189°).

The total yields obtained varied somewhat: in a typical early experiment they were, aminohydrastine-*a*, 40·4%, and aminohydrastine-*b*, 31·3%; in later experiments they were more of the order, aminohydrastine-*a*, 61·2%, and aminohydrastine-*b*, 27·3%.

Aminohydrastine-a crystallised from chloroform–methyl alcohol in rosette-shaped aggregates of colourless needles, m. p. 216—217° (corr.) with decomposition a few degrees higher (Found: C, 63·0, 63·2; H, 5·5, 5·7; N, 7·1. $C_{21}H_{22}O_6N_2$ requires C, 63·3; H, 5·6; N, 7·0%). This base is sparingly soluble in alcohol and ether, in which it exhibits an intense blue fluorescence. It forms sparingly soluble crystalline salts such as the hydrochloride, m. p. 267—268°, the hydrobromide, sulphate, nitrate, and phosphate. The neutral tartrate, m. p. 201—203° (corr.), crystallised from water in short prismatic needles without resolution.

Acetamidohydrastine-a, prepared by the action of cold acetic anhydride on the amine, crystallised from hot alcohol in fern-like

groups of needles, m. p. 208—211° (Found: C, 62·6; H, 5·6. $C_{23}H_{24}O_7N_2$ requires C, 62·7; H, 5·5%).

Aminohydrastine-b was more readily soluble in most solvents than its isomeride and crystallised from alcohol in colourless plates, m. p. 196—197° (corr.) (Found: C, 63·1; H, 5·5. $C_{21}H_{22}O_6N_2$ requires C, 63·3; H, 5·6%). Crystalline salts of this isomeride could not be obtained. A mixture of equal parts of the bases *a* and *b* had m. p. about 178—182°.

Hydrazinohydrastine-a (I; R = $NH{\cdot}NH_2$).—A mixture of aminohydrastine-*a* (5·0 g.) and concentrated hydrochloric acid (60 c.c.) was diazotised at − 5° with 6 c.c. of a solution of 56 g. of sodium nitrite in 100 c.c. of water, and after 1½ hours a solution of hydrated stannous chloride (20 g.) in concentrated hydrochloric acid (30 c.c.) was added in one portion. The mixture was stirred and water (500 c.c.) and a solution of pure potassium hydroxide (120 g. in 200 c.c. of water) were successively added. The amorphous precipitate produced soon crystallised; on recrystallisation from alcohol (50 c.c.), the first crop of felted needles obtained weighed 3·3 g., and concentration of the mother-liquor afforded a further 0·4 g. Hot alcohol changed the needles to prisms, and the pure *base* separated from alcohol in well-shaped hexagonal prisms, m. p. 175° (corr.) (Found: C, 60·9, 61·0; H, 5·6, 5·7; N, 9·7. $C_{21}H_{23}O_6N_3$ requires C, 61·0; H, 5·6; N, 10·2%). The acid oxalate separated from water in microscopic crystals, m. p. 225° (decomp.), and is a very sparingly soluble salt.

*iso*Propylidenehydrazinohydrastine-*a* separated in a crystalline form, m. p. 190°, when the base was warmed with acetone.

Hydrazinohydrastine-b.—Aminohydrastine-*b* (15 g., m. p. 189°) was dissolved in concentrated hydrochloric acid (150 c.c.), cooled to 5°, and diazotised below 8° by the slow addition of sodium nitrite (2·7 g.) in water (27 c.c.); a crystalline powder, presumably hydrastinediazonium chloride, may separate from the solution at this stage.

Reduction was effected by means of crystallised stannous chloride (45 g.) in concentrated hydrochloric acid (90 c.c.) and after 5 minutes the mixture was diluted with 1800 c.c. of water and made alkaline by the addition of saturated aqueous sodium carbonate (900 c.c.). The precipitate and the filtrate were extracted separately with chloroform. The combined extracts were dried with potassium carbonate and concentrated to about 30 c.c., and the remainder of the solvent was allowed to evaporate at room temperature. The residue, mixed with benzene, afforded crystals of hydrazinohydrastine-*b* (8·1 g., m. p. 178°) and the filtrate, mixed with acetone and concentrated, gave 3·2 g. of *iso*propylidenehydrazinohydrastine-*b*,

m. p. 204°. This derivative was decomposed by boiling for 10 minutes with 10% sulphuric acid (20 c.c.), a further 2·2 g. of hydrazinohydrastine-*b*, m. p. 178°, thus being isolated (total yield, 10·3 g. or 66%).

Hydrazinohydrastine-b crystallised from chloroform in almost colourless, lozenge-shaped plates containing $1CHCl_3$. A partly effloresced sample lost 18·2% at 100° (calc., 22·4%). Dried at a low temperature and finally at 100°, the base had m. p. 183—184° (corr.) (Found : C, 60·7; H, 5·7. $C_{21}H_{23}O_6N_3$ requires C, 61·0; H, 5·6%).

The iso*propylidene* derivative was readily soluble in hot acetone and sparingly soluble in the cold; it crystallised from acetone in large prisms, m. p. 217—218° (corr.) (Found : C, 64·0; H, 6·1; N, 8·8. $C_{24}H_{27}O_6N_3$ requires C, 63·5; H, 6·0; N, 9·3%).

Hydrastine-a (I; R = H).—Hydrazinohydrastine-*a* (2·5 g.) was dissolved in acetic acid (5 c.c.) and water (50 c.c.) and oxidised by the slow addition of cold saturated aqueous cupric acetate (60 c.c.). The resulting hydrastine partly separated along with a little cuprous oxide, and this was isolated by means of ether. A further quantity was extracted from the solution after addition of ammonia (total yield, excellent). The *base* was crystallised from methyl alcohol (m. p. 134—135°), ethyl alcohol (rectangular prisms, m. p. 135°), and finally from ethyl acetate in more compact, colourless prisms, m. p. 137° (Found : C, 65·7; H, 5·5; N, 3·7. $C_{21}H_{21}O_6N$ requires C, 65·8; H, 5·5; N, 3·7%). Another specimen crystallised from alcohol in almost rectangular, quadrilateral plates, m. p. 137—138° (corr.) (Found : C, 65·6; H, 5·5; N, 3·8%). This base is sparingly soluble in ether or cold alcohol but is freely soluble in chloroform. The hydrochloride crystallised from water in diamond-shaped plates (decomp. above 165°). The hydrogen oxalate is sparingly soluble in cold water.

The *picrate* crystallised from methyl ethyl ketone in tiny, bright yellow prisms, m. p. 219° (decomp.) (Found : N, 8·3. $C_{27}H_{24}O_{13}N_4$ requires N, 8·1%). It is very sparingly soluble in hot alcohol and acetone and may be obtained conveniently by boiling a solution of the hydrazine in methyl alcohol with copper sulphate, filtering the liquid, and adding methyl-alcoholic picric acid. The derivative separated in good yield and afforded hydrastine-*a*, m. p. 137°, on decomposition with methyl alcohol and ammonia. l-*Hydrastine picrate*, prepared for comparison, crystallised from methyl ethyl ketone in bright yellow needles, m. p. 184° (Found : N, 8·2%). It was sparingly soluble in boiling alcohol and on decomposition in methyl-alcoholic ammonia *l*-hydrastine, m. p. 132—133°, was regenerated. The *hydrogen* d-*tartrate* crystallised from water in

colourless silky needles, m. p. 108—110° (corr.) (decomp.) (Found in air-dried material: loss at 100°, 9·4. Found in material dried at 100°: C, 54·9, 54·9; H, 5·2, 5·2. $C_{21}H_{21}O_6N,C_4H_6O_6,3{\cdot}5H_2O$ requires H_2O, 9·1%. $C_{21}H_{21}O_6N,C_4H_6O_6,0{\cdot}5H_2O$ requires C, 55·3; H, 5·2%). A specimen dried at 100° was dissolved in hot absolute alcohol; on cooling, an amorphous solid, changing to warty crystals, separated. These had m. p. 160°, but on crystallisation from water they gave the characteristic silky needles, m. p. 104°, of the hydrated salt. Evidently resolution was not effected.

A mixture of hydrastine-*a* (3·8 g., purified through the tartrate) and *d*-camphorsulphonic acid (2·3 g.) was dissolved in water (70 c.c.) and kept. After inoculation the d-*camphorsulphonate* (4·2 g.) separated in plates and a further crop (1·3 g.) was obtained by concentration of the mother-liquor. Both specimens or the white prisms obtained by crystallisation from alcohol sintered at 135° and melted and decomposed at 145° (corr.) (Found in an air-dried specimen: loss at 100°, 1·6. Found in material dried at 100°: C, 60·2, 60·3; H, 6·1, 6·1. $C_{21}H_{21}O_6N,C_{10}H_{16}O_4S,0{\cdot}5H_2O$ requires H_2O, 1·4%. $C_{21}H_{21}O_6N,C_{10}H_{16}O_4S$ requires C, 60·5; H, 6·1%).

Hydrastine-b.—A solution of hydrazinohydrastine-*b* (9·5 g.) in 50% aqueous acetic acid (50 c.c.) was diluted with water (100 c.c.) and shaken with 10% aqueous copper acetate (200 c.c.). When the copious effervescence ceased, 10% sulphuric acid (50 c.c.) was added and the copper eliminated as sulphide. The filtered solution was rendered alkaline by means of sodium carbonate and extracted with chloroform. The extract was concentrated to a syrup, which was gently warmed with alcohol (20 c.c.); on keeping, dedihydrohydrastine (5·0 g., m. p. 178°) separated. The mother-liquor, which contained more of this base mixed with hydrastine-*b*, was evaporated to dryness and the residual gum (3·0 g.) was dissolved in a little dilute hydrochloric acid and shaken with chloroform. The chloroform solution, treated with sodium carbonate, dried, and evaporated, gave 1·4 g. of a base which yielded crude hydrastine-*b* (0·6 g., m. p. 135°) on crystallisation from alcohol. Repetition of this process gave a further quantity (0·4 g., m. p. 138°). Fractional crystallisation from alcohol eventually gave pure *hydrastine*-b in splendid, colourless, quadrilateral prisms, m. p. 150—151° (corr.) (Found: C, 65·0, 65·1; H, 5·4, 5·8. $C_{21}H_{21}O_6N$ requires C, 65·7; H, 5·5%).

A tartrate, m. p. about 65—70°, was obtained in a crystalline form, but the properties of this salt and of the base itself have not yet been adequately studied.

Dedihydrohydrastine (II).—This *base*, obtained as described above, crystallised from alcohol in colourless matted needles, m. p. 183°

(corr.) (Found : C, 65·9, 65·9; H, 5·0, 5·2. $C_{21}H_{19}O_6N$ requires C, 66·1; H, 5·0%). The salts with mineral acids were crystalline and sparingly soluble in water; the oxalate was rather readily soluble in water. A trace of the base dissolved in sulphuric acid to a colourless solution that became successively yellow, orange, reddish-brown, greenish-brown, slaty blue, and violet when heated. Under similar conditions, *l*-hydrastine gave a cherry-red solution changing to brown and both hydrastine-*a* and -*b* gave the same reaction as the natural base.

Comparison of the Behaviour of l-*Hydrastine*, *Hydrastine*-a, *Hydrastine*-b, *and Dedihydrohydrastine on Oxidation.*—The base (0·05 g.) was dissolved in 15% sulphuric acid (2 c.c.), and the solution warmed with manganese dioxide (0·02 g.). *l*-Hydrastine and hydrastines -*a* and -*b* each gave a pale greenish-brown fluorescent solution, which was treated with sodium carbonate and filtered; addition of potassium cyanide then afforded cyanodihydrohydrastinine. Dedihydrohydrastine gave an intense cherry-red solution which became pale brown on the addition of sodium carbonate and yielded no cyanodihydrohydrastinine. Hydrastine-*a* and *l*-hydrastine gave identical results in the following experiment. The base (1·0 g.) was dissolved in a mixture of nitric acid (2 c.c., *d* 1·42) and water (8 c.c.), and the solution maintained at 75° for 20 minutes. The cold solution was basified by means of potassium hydroxide; hydrastinine then separated in the crystalline condition (0·4 g.). The substance was identified by condensation with nitromethane (0·5 g.), yielding anhydrohydrastininenitromethane, which formed colourless needles, m. p. 122°, from ethyl alcohol (Hope and Robinson, J., 1911, **99**, 2136). The mother-liquor was acidified and extracted with ether and the residue after removal of the solvent was boiled for 3 hours with alcohol (10 c.c.) and hydroxylamine hydrochloride (0·5 g.). The precipitate obtained on the addition of water crystallised from alcohol in colourless slender needles, m. p. 230° alone or mixed with authentic hemipinimide.

Hydrastine-*b* was not obtained in sufficient quantity to enable us to repeat the experiment with that base, but qualitative tests showed that hydrastinine and opianic acid resulted in this case also. On the other hand, no indications of the formation of hydrastinine or opianic acid were obtained as the result of the action of hot dilute nitric acid on dedihydrohydrastine.

Chlorohydrastine-a (I; R = Cl).—A solution of cupric chloride (5·0 g.) in hot water (30 c.c.) was added to one of hydrazinohydrastine-*a* (1·0 g.) in 1% hydrochloric acid (30 c.c.). After the evolution of nitrogen ceased, the precipitate was collected and dissolved in hot water, and copper eliminated by means of hydrogen

sulphide. The filtrate was concentrated and extracted with chloroform, and the extract shaken with aqueous sodium carbonate and dried with potassium carbonate. After removal of the solvent the residue crystallised from alcohol in colourless prisms, m. p. 152° (Found: C, 60·1; H, 5·0; Cl, 8·4. $C_{21}H_{20}O_6NCl$ requires C, 60·4; H, 4·8; Cl, 8·5%). The hydrochloride of this base crystallised from dilute hydrochloric acid in colourless prismatic needles. On prolonged treatment of a boiling alcoholic solution with amalgamated aluminium strips a rather poor yield of hydrastine-*a*, m. p. 136°, was obtained. It is better to employ the iodo-derivative.

Iodohydrastine-a (I; R = I).—Aminohydrastine-*a* (3 g.) was diazotised as described above under hydrazinohydrastine-*a* and the solution was added to one of potassium iodide (30 g.) in water (500 c.c.). When effervescence ceased, iodine was destroyed by means of sulphur dioxide and the base was precipitated by ammonia, collected, and crystallised from methyl alcohol (yield, 2·0 g.). It separated from ethyl alcohol in colourless leaflets, m. p. 172°; recrystallisations from benzene and from ethyl acetate did not raise the melting point (Found: C, 49·4; H, 4·0. $C_{21}H_{20}O_6NI$ requires C, 49·5; H, 4·0%).

Condensation of Hydrastinine and Iodomeconine.—The chief product of this reaction was iodohydrastine-*a*, but an isomeride, doubtless iodohydrastine-*b*, was also obtained. The use of condensing agents, for example, potassium carbonate, was not found to improve the yield.

A solution of iodomeconine (15 g.) and hydrastinine (10 g.) in methyl alcohol (40 c.c.) was boiled for 3 hours under reflux and, after removal of the solvent, the residue was extracted with 10% hydrochloric acid. The extract was filtered and shaken with benzene to remove neutral substances and then with chloroform. The latter extract, which contained iodohydrastine hydrochloride, was shaken with aqueous sodium carbonate to liberate the base, dried, and evaporated. The oily residue (19·2 g.) gave 6·2 g. of crystalline material on sludging with alcohol and a further quantity was recovered from the mother-liquor as the hydrobromide. The crystals were found to be a mixture of two iodohydrastines and these were separated by slow fractional crystallisation from alcohol. The first crop, m. p. about 158° but not clear till about 190°, consisted of diamond-shaped and hexagonal plates; the second crop contained two forms which could be separated by hand, namely, (1) fern-shaped, dull crystals, m. p. 194—195° (corr.), and (2) massive, clear amber blocks, m. p. 172—173° (corr.). A mixture of these had m. p. 140—150° and the subsequent crops were mixtures

having various melting points. The product, m. p. 193—195°, is regarded as *iodohydrastine*-b (Found : C, 49·7; H, 4·3. $C_{21}H_{20}O_6NI$ requires C, 49·5; H, 4·0%).

In another experiment iodomeconine (9·0 g.) and hydrastinine (5·0 g.) were condensed in boiling methyl alcohol (75 c.c.) during 2 hours. A certain amount of the product crystallised from the hot solution and practically pure iodohydrastine (7·5 g.) was readily isolated by solution in dilute hydrochloric acid, filtration, basification with ammonia, and crystallisation from methyl alcohol. This specimen had m. p. 155—160°, raised to 170° by repeated crystallisation from methyl alcohol and not depressed on admixture with iodohydrastine-*a* from aminohydrastine-*a*.

The hydrochlorides of iodohydrastines-*a* and -*b* and of the mixture, m. p. 157°, or a mixture of any of them all melt and decompose at 222—223° (corr.). They form microscopic, elongated, hexagonal plates and are sparingly soluble in water. The hydrobromides behave similarly, forming colourless prisms, m. p. 205—206° (corr.) (decomp.), that are more sparingly soluble than the hydrochlorides.

On reduction by means of 6% sodium amalgam in hot aqueous alcohol or by means of amalgamated aluminium in boiling alcohol, iodohydrastine-*a* gave hydrastine-*a*, m. p. 137—138°. The product was purified in the latter series of experiments through the picrate and the yield was 80% from material of m. p. 172°, but much less from a base of m. p. 160° owing to the serious loss in the processes of crystallisation.

A bromohydrastine, m. p. 170—171° (corr.), was prepared in small relative yield by the condensation of hydrastinine and bromomeconine; it separated from alcohol in colourless diamond-shaped crystals and gave a hydrobromide that crystallised in prisms, m. p. 287—288° (decomp.).

4-*Acetoxy*-3-*methoxyphthalide*.—Normeconine methyl ether (Mathiessen and Foster, J., 1867, **20**, 519) was acetylated by means of boiling acetic anhydride in the presence of sodium acetate (yield, 90%). The derivative crystallised from alcohol in colourless prismatic needles, m. p. 127—128° (corr.) (Found : C, 59·0; H, 4·3. $C_{11}H_{10}O_5$ requires C, 59·4; H, 4·6%).

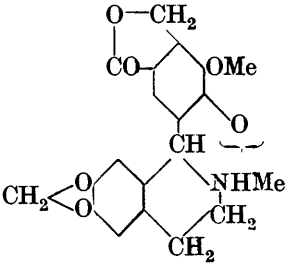
4-*Benzoyloxy*-3-*methoxyphthalide*, obtained by applying the pyridine–benzoyl chloride method, crystallised in colourless prisms, m. p. 135—136° (corr.) (Found : C, 65·3; H, 4·0. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·3%).

m-*Nitrobenzoyloxy*-3-*methoxyphthalide* crystallised from acetone in hexagonal plates, m. p. 192—193° (corr.) (Found : C, 58·7; H, 3·5. $C_{16}H_{11}O_7N$ requires C, 58·3; H, 3·4%). In this case the sodium

salt of normeconine methyl ether in aqueous solution was brought into reaction with *m*-nitrobenzoyl chloride at 100°.

p-Nitrobenzoyloxy-3-methoxyphthalide was similarly obtained; it crystallised from aqueous acetone in colourless prismatic needles, m. p. 202—203°.

Hydrastininium Salt of Normeconine Methyl Ether (?).—The acyl derivatives of normeconine methyl ether did not condense with hydrastinine under any conditions which we tried and the phenol itself gave rise to a salt (?). A solution of hydrastinine (0·63 g.) and normeconine methyl ether (0·55 g.) in ethyl alcohol (1·5 c.c.) was boiled; separation of colourless crystals began after 5 minutes. After 15 minutes the solid was collected and crystallised from hot water, in which it was sparingly soluble. The colourless needles (0·28 g.), m. p. 334° (corr.) (Found: C, 65·0; H, 5·3. $C_{20}H_{19}O_6N$ requires C, 65·0; H, 5·2%), gave no coloration with ferric chloride in aqueous solution, but after warming with dilute acid or alkali the blue coloration characteristic of normeconine methyl ether could be obtained. If this substance were of the hydrastine type, it would be more stable than it is towards acids and alkalis, but, on the other hand, if it were merely a salt there seems to be no reason why the ferric chloride reaction should not be exhibited as the result of hydrolytic processes setting free the phenol in aqueous solution. Probably it is a phenoxide in which some unsuspected co-ordinate link is present and confers exceptional stability, although the possibility that it is a phenol-betaine of the following constitution is not excluded.



THE UNIVERSITIES OF MANCHESTER AND OXFORD.
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