

CCXCII.—*Physiologically Active Constituents of the Yew, Taxus baccata. Part II. Ephedrine.*

By JOHN MASSON GULLAND and CYRIL JOSEPH VIRDEN.

THE method employed by us and other workers for the isolation of taxine, the poisonous alkaloid present in the leaves of the yew, is percolation with 1% sulphuric acid, liberation of the base with alkali, and repeated extraction with ether (see Callow, Gulland, and Virden, preceding paper). Though quite suitable for small-scale experiments, this procedure is both tedious and costly when employed with large volumes of solutions, and at the suggestion of Messrs. T. and H. Smith of Edinburgh, to whom we are greatly indebted for carrying out large extractions, an alternative method was investigated. An intimate mixture of dried leaves, moist calcium hydroxide, and benzene was kept for one day. The benzene contained much non-basic material but only a small amount of taxine, and this process is useless for the preparation of the alkaloid, a conclusion also reached by Winterstein and Iatrides (*Z. physiol. Chem.*, 1921, **117**, 240). Nevertheless, a small quantity of ephedrine was isolated as the hydrochloride, and identified by analysis and specific rotation, by conversion into *p*-nitrobenzoyl*ephedrine*, and by the absence of depression of the m. p.'s of mixtures of the hydrochlorides and *p*-nitrobenzoyl derivatives of the isolated base and an authentic specimen.

It is interesting to note that *Taxus baccata* and the Chinese and

Indian *Ephedra* species, which are the source of ephedrine, are related botanically, both belonging to families of the Gymnosperms.

It is doubtful if the yew could form a readily accessible source of ephedrine for medical and pharmacological purposes, since the yield of pure material in the present experiment was only 0.0017%. Nevertheless, it is possible that larger amounts might be obtained, and that the season of picking, the locality, and the age and sex of the tree are important factors in determining the content of the leaves. The authors are unable to continue this investigation, but make this publication in the hope that others may do so.

#### EXPERIMENTAL.

In a large-scale extraction carried out by Messrs. T. and H. Smith, yew leaves, gathered in Edinburgh in May, were dried by exposure to the air in a warm room, stripped from the branches, and freed from all but the smallest twigs. This dried material (45 kg.) was mixed to a paste with benzene and moist calcium hydroxide and kept for 24 hours with occasional stirring. The benzene was separated, dried, and concentrated, finally under reduced pressure, and the residue (35 g.) was a dark-coloured resin, quite unlike the almost colourless, friable glassy material obtained at this stage in an acid extraction of the leaves. It did not harden after being exposed for 6 weeks in a vacuum drying apparatus; and having been dissolved in chloroform in order to simplify further treatment, it was sent to us by Messrs. T. and H. Smith.

The residue from the evaporation of a small portion of the chloroform solution was only partly soluble in dilute mineral acids, and did not contain much taxine. It is our experience that the lime-benzene method of extraction never yields as much taxine as the sulphuric acid-ether process, but in addition, it is probable that considerable decomposition occurred during the prolonged attempts to harden the resin in the drying apparatus, since we have observed that even the purest sample of taxine yet obtained slowly decomposes into non-basic substances when kept in a closed specimen tube.

In the first experiment, the resin, freed from chloroform by distillation, was heated with 5% sulphuric acid on the water-bath. Later, however, when the nature of the products was realised, the following procedure was found to be simpler and equally effective.

The chloroform solution, corresponding to 1.5 g. of resin, was extracted with a small quantity of cold *N*-sulphuric acid in order to separate the basic constituents; the chloroform layer was examined separately (see X, below). An excess of phosphotungstic acid (20% solution in 5% sulphuric acid) was added to the acid extract, and the precipitated phosphotungstate was collected, washed, dissolved

in 60% aqueous acetone, and decomposed with a slight excess of aqueous baryta. The precipitate was removed, and the solution was freed from barium by passage of carbon dioxide, and from acetone by drawing a current of air through it, and was then acidified with hydrochloric acid, filtered, made alkaline with ammonia, and extracted thoroughly with chloroform. The extract, when dried and evaporated, yielded a colourless, uncrystallisable oil, which was converted into moderately pure ephedrine hydrochloride (0.1 g.) by evaporation in a vacuum of its solution in alcoholic hydrochloric acid. After being stirred with acetone and crystallised by addition of ether to an alcoholic solution, it formed colourless plates, m. p. 216° after softening at 212.5° (Found: C, 59.7; H, 7.9; N, 7.0; Cl, 18.0. Calc. for  $C_{10}H_{15}ON, HCl$ : C, 59.6; H, 7.8; N, 7.0; Cl, 17.6%). In aqueous solution,  $[\alpha]_D - 32.6^\circ$  ( $\alpha = -1.04^\circ$ ,  $l = 1$ ,  $c = 3.124$ ). Authentic ephedrine hydrochloride has  $[\alpha]_D = -36^\circ$ . There was no depression in a mixed m. p. determination with authentic ephedrine hydrochloride, m. p. 216° after softening at 212.5°. The yield of hydrochloride was 0.75 g. from 35 g. of resin, but the actual content was estimated at about 1.5 g.; there was considerable loss in earlier purifications before the value of treatment with acetone was realised. Unsuccessful attempts were made to isolate ephedrine by the lime-benzene method from small quantities of leaves (125 g.) gathered in May in the Forest of Dean and at Oxford.

N-p-Nitrobenzoyl*ephedrine* was prepared from an authentic specimen and from the material from yew. When a mixture of ephedrine hydrochloride (0.31 g.) in water (2 c.c.), p-nitrobenzoyl chloride (0.62 g.) in ether (5 c.c.), and sodium hydroxide solution (5 c.c. of 20%) was shaken, the required compound separated in colourless needles, m. p. 186—187° after being recrystallised from alcohol (Found: C, 65.2; H, 5.8.  $C_{17}H_{18}O_4N_2$  requires C, 65.0; H, 5.7%). It did not dissolve in dilute hydrochloric acid. There was no depression in the m. p. of mixtures of the derivatives from both sources.

*Examination of the Chloroform Solution of Non-basic Material (X).*  
—The solution was extracted successively with sodium hydroxide solution, dilute sulphuric acid, and water, dried and distilled. The resulting gum solidified to a colourless powder, m. p. 90—91° with effervescence after softening at 83°, when stirred with light petroleum (b. p. 100—120°). Although readily soluble in most organic solvents, it was divided by treatment with ether into a soluble and an insoluble fraction, and these melted at 40—65° after stirring with light petroleum (b. p. 40—60°). Neither contained nitrogen nor was attacked by semicarbazide, and their investigation was aban-

done as their " melting points " depended on the boiling point of the solvent employed.

THE DYSON PERRINS LABORATORY AND  
THE DEPARTMENT OF PHARMACOLOGY,  
OXFORD.

[Received, July 17th, 1931.]

---