ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

***Erythrina thollonia*, a Curare-like Compound from.** C. Lapière and G. Coppée. (*Experientia*, 1948, **4**, 387.) From *Erythrina thollonia* (from the Belgian Congo) one of the authors succeeded in isolating an alkaloid, $C_{16}H_{19}NO_3$, with a powerful curare-like action on the frog. At a concentration of less than 1 in 10^6, it produces a complete neuro-muscular block; and on electrical stimulation of the motor nerve, there is no contraction but the muscle reacts by giving an electrical wave having exactly the same characteristics as those of a similar preparation made with curare or with quaternary ammonium derivatives, while a similar parellelism is found in the decurarisation by means of veratrine. The alkaloid has little curariform activity on mammals; with the isolated phrenic diaphragm preparation of the rat, incomplete block was produced at a concentration of 1 in 5000.

G. M.

Quinine, Extraction from Cinchona Barks. N. B. Bhunvara and M. L. Khorana. (*Indian J. Pharm.*, 1949, **11**, 148, 152.) Alkaloids may be extracted from cinchona bark by the use of dilute acid. A suitable method is: 30 g. of bark in No. 60 powder is stirred for 40 minutes with 400 ml. of 0·5 per cent. hydrochloric acid, filtered with suction and the residue washed with hot water. About 85 per cent. of the total alkaloidal content of the bark is removed by the first extraction, and the residue is treated with a further 200 ml. of the acid for 20 minutes to give a total extraction of 94·2 per cent. The acid solution is made just alkaline to phenolphthalein. For this purpose, slaked lime is preferable to sodium hydroxide, which yields too fine a precipitate. The alkaline mother liquor contains a little of the alkaloids, and may be acidified, filtered and used to extract a further quantity of bark, enabling 93 per cent. of the total alkaloids of the bark to be recovered at this stage. The precipitate can be treated by 4 hot extractions with alcohol. Alternatively, 4 cold extractions with turpentine can be used and in this case it is not necessary to evaporate the solvent, as the alkaloids can be removed by shaking with dilute sulphuric acid. Using either alcohol or turpentine, about 91 to 93 per cent. of the total alkaloids of the bark is extracted. Turpentine can also replace benzene or mineral oils in the processes of extraction already in use, and extraction of a mixture of powdered bark and soda lime can be carried out at room temperature instead of the higher temperatures usually used when benzene or mineral oil is employed. The ratio of total solids to alkaloids in the extract is lower for turpentine than for benzene. The alkaloid is removed from the solvent by shaking with 0·5 per cent. sulphuric acid. The powdered drug, after treatment with soda lime, may be packed into a percolator and immediately percolated with turpentine, the bark usually being exhausted when 10 ml. of percolate has been collected for each g. of drug. Some of the solvent retained by the drug may be recovered by pressing the marc.

and a further quantity by warming the marc with water, although a better yield is obtained by distillation, and solvent recovered in this way is cleaner

G. B.

ANALYTICAL

Amidone, Microchemical Identification of. R. C. Watson and M. I. Bowman. (*J. Amer. pharm. Ass. Sci. Ed.*, 1949, **38**, 369.) The reactions of amidone (6-dimethylamino-4:4-diphenyl-3-heptanone) with 197 reagents including many of the common so-called "alkaloidal reagents" were examined. Of these, 43 gave crystals, the remainder giving only amorphous precipitates or none at all. Only 3 reagents, palladium chloride, potassium ferrocyanide, and bromine water yielded crystals which gave a positive identification of amidone; these reagents give relatively few crystalline precipitates with other common alkaloids and synthetic drugs. The tests were made by placing the reagent drop on a microscope slide adjacent to the sample drop and allowing the two drops to flow together; the slide was allowed to stand for a short time and was then examined under a microscope (magnification × 100) for crystal formation. The slides were not scratched to aid crystallisation and cover glasses were not used. Photomicrographs are given of the crystals obtained with palladium chloride solution (approximately 1 per cent. in dilute hydrochloric acid), with potassium ferrocyanide solution (approximately 5 per cent. in water) and with a dilute solution of bromine water (3·5 ml. of saturated bromine water in 100 ml. of water).

R. E. S.

Antihistamines, Identification of. T. J. Haley and G. L. Keenan. (*J. Amer. pharm. Ass. Sci. Ed.*, 1949, **38**, 384.) Methods have been investigated for the identification and differentiation of 7 new anti-histamines namely : neoantergan (N′-*p*-methoxybenzyl-N′-2-pyridyl-N-dimethylethylenediamine), neohetramine (N′-*p*-methoxybenzyl-N-2-pyrimidyl-N′-dimethylethylenediamine), linadryl (β-morpholinoethylbenzhydryl ether hydrochloride), decapryn (α-[2-dimethylaminœthoxy]α[methylbenzyl]-pyridine, No. 204 (2-imidazoline-2-methyl benzhydryl ether), antistine (N′-phenyl-N′-benzylaminomethyl imidazoline), and dramamine, (Sc. 1694, N-dimethylethylbenzhydryl ether-8-chlorotheophyllinate). Tables of the melting points of the compounds and of their salts are given. The reactions obtained with concentrated sulphuric acid, concentrated nitric acid, Mandelin's reagent, Marquis' reagent, Frohde's reagent, Buckingham's reagent, chloroplatinic acid, chloroauric acid and picric acid solution are also listed. The precipitation reagents used were of little value due to the formation of amorphous precipitates, although decapryn succinate formed a crystalline precipitate with chloroplatinic acid. The colorimetric tests can be regarded as useful in any general classification, but a melting-point determination is necessary for an accurate identification.

R. E. S.

Benzene in Presence of Homologues, Polarographic Determination of. A. S. Landry. (*Anal. Chem.*, 1949, **21**, 674.) The determination is accomplished by nitration of the aromatic compounds present in the atmosphere by aspirating the air for 10 minutes through a U.S. Bureau of Mines type of bubbler for nitrating benzene. The toluene and xylene nitration products are then selectively oxidised with chromium trioxide and the dinitrobenzene is isolated using the differential solubility in light petroleum. Details of procedure for the nitration and extraction are given and polarograph curves, under varying conditions, are included. The

curves for dinitrobenzene, dinitrotoluene and dinitroxylene show the effect of the selective oxidation procedure, as the treated compound produces a curve that has a very small step in comparison to the untreated nitrated compound. Calibration curves are given and it can be deduced that concentrations of toluene above a certain amount will introduce an error: such an error is not large but further work is in progress to establish a correction factor. A colorimetric method based on the selective oxidation-differential solubility procedure is also being developed. R. E. S.

Benzoic, Salicylic and Acetylsalicylic Acids, Colorimetric Determination of. C. Lapière. (*J. Pharm. Belg.*, 1948, **3**, 123.) The method is based on the colouration given by these acids with copper sulphate and pyridine. Five ml. of a solution of 2·5 to 20 mg. of the acid in pyridine (10 per cent.) is placed in a separating funnel, and exactly 5 ml. of chloroform, and 1 ml. of a solution of 0·5 ml. of pyridine and 0·4 g. of copper sulphate in 5 ml. of water are added. After shaking, the chloroformic solution is run off into a stoppered tube, dehydrated with sodium sulphate, and transferred to a 1 cm. cell. The colour is determined using filter S66·6. The quantity of the acid, in mg., is given by the formula E/0·048 (for benzoic acid), E/0·064 (for salicylic acid), or E/0·033 (for acetylsalicylic acid). The colour may also be measured in ammoniacal solution, by shaking 4 ml. of the chloroformic solution with 5 ml. of a solution of 50 g. of ammonium sulphate in 100 ml. of 2 per cent. ammonia. In this case filter S61 is used, and the factors are E/0·026 (for benzoic acid), E/0·0275 (for salicylic acid) or E/0·0185 (for acetylsalicylic acid). The latter method is sometimes of advantage when it is necessary to eliminate the effect of coloured substances which are soluble in chloroform.

G. M.

Bromine, Iodimetric Microdetermination of. J. F. Alicino, A. Crickenberger and B. Reynolds. (*Anal. Chem.*, 1949, **21**, 755.) A sample of 3 to 6 mg. was analysed by the catalytic combustion method of Pregl with certain modifications. A combustion time of 20 to 30 minutes was necessary and the contents of the absorbing spiral (N sodium hydroxide solution) were transferred to a flask with water. After the addition of 5 ml. of a 20 per cent. sodium dihydrogen phosphate solution, 5 ml. of a commercial sodium hypochlorite solution (approximately 5 per cent.) was added and the solution was heated just to boiling; 5 ml. of a 50 per cent. sodium formate solution was added (with accompanying vigorous effervescence), and after cooling to room temperature 10 ml. of sulphuric acid (9N), 1 drop of ammonium molybdate solution (0·5N) and potassium iodide (approximately 1 g.) were added, the liberated iodine being titrated within 1 to 2 minutes. A blank determination on the complete procedure was necessary with each new sample of bleaching solution, the blank ranging from about 0·2 to 0·4 ml. of sodium thiosulphate solution. Satisfactory agreement with the calculated values was obtained with a wide variety of bromine compounds and although no improvement in accuracy and precision over existing methods was claimed, the method was quick and an average analysis required only 1 hour. R. E. S.

Camphor, in Galenical Preparations, Determination of. J. Julien. (*Trav. Lab. Mat. Med.*, 1943-5, **32**, Part 5.) Although a large number of methods have been suggested for the determination of camphor in galenical preparations, few are satisfactory. Polarimetry cannot be used for the determination of synthetic camphor. Other physical methods lack specificity, they are dependent on the alcohol concentration, or are insufficiently delicate.

Colorimetric methods are not considered on account of the special apparatus required. Volumetric methods, dependent on the formation of oximes, are numerous, but do not give satisfactory results. The best methods are those based on weighing camphor as the 2:4-dinitrophenylhydrazone. For tincture of camphor the process of Janot and Mouton (*J. Pharm. Chim.*, 1936, **23,** 547) is recommended: for other preparations (including camphorated oil and ammoniacal camphorated liniment that of Leonard and Smith (*Analyst.*, 1898, **23,** 281). No satisfactory methods were found for paregoric elixir and for compound ammoniacal camphorated liniment. G. M.

Cyanides, Argentometric Determination of. N. Serries. (*Trav. Soc. Pharm. Montpellier*, 1948, **8,** 71.) For accurate determination of cyanides by the method of Denigès it is essential to avoid too high a concentration of ammonia, to use sufficient iodide, and not to dilute too much. When the conditions described below are observed, the volume of silver nitrate solution is proportional to the quantity of cyanide at any concentration. Ten ml. of a solution containing 10 ml. of ammonia, 6 g. of potassium iodide, and water to 100 ml., is mixed with the solution of cyanide or of hydrocyanic acid, and the volume is made up to about 100 ml. The mixture is then titrated with 0·02N or 0·05N silver nitrate until there is a slight permanent turbidity. In order to allow for the amount of silver nitrate required to produce the turbidity, 0·05 ml. is subtracted from the reading. G. M.

GLYCOSIDES, FERMENTS AND CARBOHYDRATES

Ouabain, Microscopical Characterisation of the Polymorphic Forms of. G. L. Keenan. (*J. Amer. pharm. Ass., Sci. Ed.*, 1949, **38,** 355.) Ouabain crystallises in two forms. (1) Quadrilateral plates, obtained by crystallisation from water at room temperature. The crystals show very weak refraction in polarised light (crossed Nicol prisms) and apparently belong to the tetragonal system. The refractive indices ($\omega = 1{\cdot}525$; $\epsilon = 1{\cdot}523$) are similar to those of immersion fluids, and consequently the borders of the plates are almost invisible in ordinary light. (2) Rod form, obtained by crystallisation from alcohol (95 per cent.). The crystals show strong double refraction with parallel extinction and positive elongation, when viewed with crossed Nicol prisms supplemented by the selenite plate. The refractive indices are $\alpha = 1{\cdot}533$, $\beta = 1{\cdot}547$, $\gamma = 1{\cdot}580$. G. B.

Rutin, Occurrence of, in *Sambucus canadensis*. B. C. King and A. E. Schwarting. (*J. Amer. pharm. Ass., Sci. Ed.*, 1949, **38,** 531.) Rutin was isolated from the leaves and flowers. Extraction studies did not reveal its presence in the stem, nor in the immature or mature fruit. Leaves were collected at 1-week to 10-day intervals from the time of early leaf development until after fruiting. Flowers were collected at immature and mature stages; a commercial sample of elder flowers was also used in the study. The material was extracted with ethyl alcohol in a Soxhlet extractor, the extract concentrated under reduced pressure and allowed to crystallise after addition of water. The rutin was identified by the melting-point, 186° to 192°C., by spectrophotometric examination, and by chemical tests. The purified aglycone obtained melted at 313°C. and an acetyl derivative melted at 196°C. These figures corresponded with quercetin. Phenylosazones fractionated with acetone gave soluble and insoluble fractions with m.pts. corresponding to those of rhamnosazone and glucosazone respectively. Results showed that rutin occurs in amounts up to 0·52 per cent. and that there is

variation in the amount in plants growing under different conditions. A progressive rise in content during the growing season until the fruiting stage was shown. G. R. K.

PLANT ANALYSIS

***Digitalis purpurea*, Chromatographic Examination of.** F. Ulrix. (*J. Pharm Belg.*, 1948, **3**, 2.) Chromotography of a solution of digitalis extract in a mixture of (exactly) 1 part of methyl alcohol and 15 parts of chloroform, on alumina, gave a column showing three definite zones. Of these the lower zone (III) may be separated by washing through the tube; zone II is eluted by absolute alcohol and zone I with dilute alcohol. Purification of these zones was then continued as follows. Zone II: by dilution with water and partial evaporation of the alcohol a precipitate was formed which, after washing with methyl alcohol to remove pigments, was identified as gitoxin. Zone III: chromatography from ethyl acetate gave three zones containing respectively digitoxin, gitoxigenin and digitoxigenin. Zone I: it was not found possible to identify the third heteroside, gitalin, in this fraction, which appeared to contain the two purpurea glucosides described by Stoll. Chromatography from ethyl alcohol of various strengths gave six distinct zones giving, with Kiliani's reagent, alternatively purple and brown colorations. Two of these appear to be due to the purpurea glucosides A and B of Stoll, the others to four heterosides not previously described—purpurea glucosides A_2, B_2, A_3 and B_3. The experiments thus fail to confirm the presence of gitalin or of the hypothetical purpurea glucoside C, while the compounds actually identified were gitoxigenin, digitoxigenin, gitoxin, digitoxin, the purpurea glucosides A and B, and the four new glucosides. When chromatography is applied to commercial preparations of digitalin and digitoxin, they are found to be mixtures. G. M.

Ergothioneine Content of Ergots from Different Plant Hosts. G. Hunter, S. G. Fushtey and D. W. Gee. (*Canad. J. Res.* (*E*), 1949 **27**, 240.) The ergothioneine content was determined as follows. 30 to 50 mg. of sample was placed in a 15-ml. centrifuge tube with 4 ml. of water and 1 drop of 2 N acetic acid, and the tube put in boiling water for 10 minutes. The contents of the tube were transferred to a mortar, the ergot finely ground, and the mixture returned to the tube with the aid of 5 to 6 ml. of water. The tube was replaced in boiling water for 5 minutes and then centrifuged. The supernatant liquid was treated with a slight excess of uranium acetate and again centrifuged. The excess of uranium was removed with sodium dihydrogen phosphate and the supernatant liquid decanted. Aliquot portions of this solution were assayed by the diazo method of Hunter (*Canad. J. Res.* (*E*), 1949, **27**, 230); at least two aliquots should show strict linear transmittance. The analyses were carried out usually on a single sclerotium in triplicate and the results expressed as percentage of air-dried material. Five specimens of ergot of barley showed an overall average of 376 mg. of ergothioneine per 100 g., with a range of 231 to 531 mg. For 5 specimens of ergot of rye, the average was 336 mg./100 g.,.and the range, 183 to 474 mg. Ergots from *Bromus* and *Agropyron* contained about the same concentration as barley and rye ergots. The lowest values were obtained from ergots from *Calamagrostis*, but the sample may have contained extraneous material.

G. R. K.

Plant Constituents, a Proposed Method of Isolating. G. D. Curtis and L. E. Harris. (*J. Amer. pharm. Ass., Sci. Ed.*, 1949, **38**, 468.) Ethoxyethanol

(Cellosolve) will extract all plant constituents that are normally extracted by the use of light petroleum, ether, chloroform, and alcohol. A scheme of isolating plant constituents is presented involving their extraction with ethoxyethanol and fractional separation by the addition of water. It is estimated that the extraction and separation of plant constituents by this method can be accomplished in about one-third the time required for the traditional four-solvent method, at only about half the cost. S. L. W.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Heparin, Notes on Fractionation and Colorimetric Assay of. O. Snellman, R. Jensen and B. Sylven. (*Acta chem. scand.*, 1949, **3**, 589.) By means of electrophoresis, commercial heparin was separated by these authors into two distinct fractions, both of which exerted anticoagulant and metachromatic activities (*J. biol. Chem.*, 1948, **174**, 265). This paper is a report of attempts made to separate heparin by means of serial precipitation, using the organic precipitants acetone, alcohol and dioxane. The experiment was unsuccessful, both components precipitating concurrently in a characteristic two-step fashion. No reasonable explanation of this fact can so far be advanced. During the first phase of precipitation a remarkable discrepancy was observed between the anticoagulant and metachromatic activity of the remaining solute material. This may be due to the possible precipitation of some impurity which might hamper the metachromatic reaction. This unexplained phenomenon constitutes a source of error in colorimetric assay of heparin. S. L. W.

Salicylic Acid, Metabolism and Toxicity of, in Combination with Various Drugs. G. Cranheim, J. Wiland and M. Ehrlich. (*J. Amer. pharm. Ass., Sci. Ed.*, 1949, **38**, 451.) Combinations of sodium salicylate with various antacids (sodium bicarbonate, aluminium hydroxide gel, and magnesium trisilicate) and with sodium or calcium ascorbate were investigated for toxicity and salicylate absorption and excretion. The drugs were administered to rabbits and dogs, in water (10 to 15 ml. respectively) by stomach tube, followed by 5 and 10 ml., respectively, of plain water. The results of acute toxicity tests while not very definite on the basis of a statistical analysis, seemed to indicate that both sodium bicarbonate and ascorbic acid reduce to some extent the acute toxicity of salicylic acid, while magnesium trisilicate is without any effect. An investigation of blood levels in rabbits after single doses showed that, except for large doses of sodium salicylate, all the antacids used reduce the concentration of salicylic acid in the blood. With repeated doses of sodium salicylate the addition of magnesium trisilicate has no effect on the salicylate blood level while sodium bicarbonate reduces it. Data are presented showing the urinary excretion of free and conjugated salicylic acid in dogs and free salicylic acid in rabbits. No salicyluric acid could be detected in rabbit urine. S. L. W.

Vitamin A, Examination of Indian Shark Liver Oils for. S. M. Bose and V. Subrahmanyan. (*Ind J. med. Res.*, 1949, **37**, 1.) The analytical characteristics of a number of commercial shark liver oils obtained from Madras, Travancore and Bombay were determined using standard methods. For 26 representative samples the saponification values varied from 140 to 190, the acid values from 0·46 to 26·05, the acetyl values from 12·1 to 38·2, the iodine values from 140 to 163, the unsaponifiable matter from 1·55 to 13·27 per cent., the iodine values of the unsaponifiable matter from

132 to 192, the peroxide number from 0 to 6·2, the induction period at 65°C. from 3·5 to 8·8 hours, the moisture content from 0·26 to 2·09, and the iodine values (calculated) of the glycerides from 141 to 161. The vitamin A potency of 35 samples varied from 656 to 21,984 I.U. per g. of oil; values were determined by the Lovibond Tintometer method, the Pulfrich photometric method using filter S.61 ($B_{1\text{ cm.}}^{1\text{ per cent.}}$), and by $E_{1\text{ cm.}}^{1\text{ per cent.}}$ 328 mμ determination. The $B_{1\text{ cm.}}^{1\text{ per cent.}}$ values for the unsaponifiable fractions were invariably found to be higher than those for the whole oils. The ratio, $B_{1\text{ cm.}}^{1\text{ per cent.}}$ value (unsap. matter)/$B_{1\text{ cm.}}^{1\text{ per cent.}}$ value (whole oil), ranged between 1·02 and 1·72 for 28 samples analysed, the average being 1·34; the ratio tended to be lower for the richer oils and higher for the poorer oils, suggesting the presence of some saponifiable substance in the oil which inhibited the development of maximum blue colour. The $E_{1\text{ cm.}}^{1\text{ per cent.}}$, 328 mμ values, however, were found to be lower for the unsaponifiable portions than for the whole oils. The ratio, E (whole oil)/$E_{1\text{ cm.}}^{1\text{ per cent.}}$ (unsap. matter), was found to range between 1·03 and 1·34, the average being 1·17, this ratio being lower for the high potency oils than for the low potency oils. The ratio, $B_{1\text{ cm.}}^{1\text{ per cent.}}$ $E_{1\text{ cm.}}^{1\text{ per cent.}}$ for the unsaponifiable portion of the oil, was found to vary from 1·84 to 2·68 (neglecting only one lowest value 1·22 and one highest value 2·97), the average being 2·31 for 28 samples. The factor for converting $B_{1\text{ cm.}}^{1\text{ per cent.}}$ into I.U./g. varied from 763 to 1616, the average being 945 for 28 samples; the range of variation was, however, narrower when the unsaponifiable fractions were used and was found to be between 597 and 870, the average being 713. R. E. S.

BIOCHEMICAL ANALYSIS

Benzylpenicillin, Infra-red Assay of Procaine Salt of. N. H. Coy, C. W. Sabo and B. T. Keeler. (*Anal. Chem.*, 1949, **21**, 669.) Infra-red spectra studies showed that all the different types of penicillin possessed a characteristic band at 5·6μ which was not present in any degradation product of penicillin, the band being attributed to the presence in the molecule of the β-lactam carbonyl group. Chloroform, which is transparent in the region 5·0 to 5·2μ, was found to dissolve sufficient benzylpenicillin to produce a strong absorption band at 5·6μ; the procaine moiety of the penicillin salt did not interfere with the strength of the 5·6μ band. There was a straight line relationship between optical density and concentration over a range of concentrations from 0·2 to 0·8 per cent. Fourteen commercial samples of procaine penicillin were examined and the results are given, together with the biological values; the test was further applied to miscellaneous samples of the procaine salt of benzylpenicillin, including aqueous suspensions and also mixtures in oil with aluminium stearate. In the case of the aqueous suspension, the water was first removed by spreading the sample on a watch glass and drying in a vacuum desiccator. For samples containing oil, those compounds which interfered with the infra-red absorption at 5·6μ were removed by treating the sample with light petroleum and centrifuging. The solvent was decanted and the residue taken up in chloroform and tested. Results indicated that various procaine penicillins, including those which had deteriorated on storage, could be tested with accuracy by the infra-red method. R. E. S.

Lactose in Urine, Detection of. A. A. Ormsby and S. Johnson. (*J. Lab. clin. Med.*, 1949, **34**, 562.) Mix 5 ml. of urine with 1 ml. of a 0·2 per cent. aqueous solution of methylamine hydrochloride and 0·2 ml. of a

10 per cent. aqueous solution of sodium hydroxide, cover the tubes with glass bulbs or marbles and heat on a water-bath at 56°C. Urine containing 0·5 per cent. of lactose produces a red colour after heating for 20 minutes, and 0·05 per cent. of lactose can be detected after heating for 30 minutes and allowing to stand at room temperature for 30 minutes. Maltose gives the same colour, but other sugars give no reaction or only a yellow colour. Higher temperatures cannot be used on account of caramelisation, and violent shaking or exposure to air during the test should be avoided. The sensitivity of the test decreases if the quantity of sodium hydroxide used is outside the limits of 0·2 to 0·4 ml. of 10 per cent. solution. Ammonia in quantities up to 10 mg. of nitrogen increases the sensitivity of the test, but greater amounts inhibit the formation of the colour. For quantitative work, the temperature and alkalinity must be carefully controlled. The absorption is measured using a filter having its maximum transmission at 540 mμ and a cell containing urine as a blank to compensate for the colour of the urine. An allowance has to be made for the concentration of ammonia present, unless the ammonia is first completely removed with permutit and then 5 mg. of N ammonia is added to increase the sensitivity of the test. G. B.

Vitamin B_{12}: Microbiological Assay using *Lactobacillus leichmannii*, H. T. Peeler, H. Yacowitz and L. C. Norris. (*Proc. Soc. exp. Biol. N.Y.*; 1949, **72**, 515.) The organism used is *Lactobacillus leichmannii* ATCC 4797, but ATCC 7830 has also been used successfully. It is grown in a synthetic medium containing nearly 50 ingredients including numerous amino acids, with mineral salts, canned tomato juice and vitamins, and 0·3 unit of 15 unit U.S.P. injectable liver extract per 10 ml., and adjusted to *p*H 5·5. The optimum concentrations of several of the constituents for growth of the organism were worked out in numerous trials. Inoculation and incubation are in accordance with the technique of Daniel *et al.* (*J. biol. Chem.*, 1948, **174**, 71). Five ml. of double strength medium and the sample to be assayed are placed in the assay tubes and inoculated with the organism, and the tubes are then incubated at 37°C. for 16 hours, or until the tube containing 0·1 mg. of vitamin B_{12} gives a reading of 30 on the galvanometer scale of a Coleman spectrophotometer at wave-length 650 mμ. The turbidity of the unknown is read by placing the blanks at 100 on the galvanometer scale. A standard curve is prepared from known amounts of vitamin B_{12}, from which quantities can be read off according to the galvanometer reading. Vitamin B_{12} was found to have 24,000 times the activity of thymidine, and the latter can therefore be ignored. When the method was applied to U.S.P. liver extracts, ranges 87·1 to 2170 mμg. were found to correspond to 1 so-called U.S.P. unit. The method was also applied to the determination of B_{12} in various substances used in chick diets. Wilson's liver L (389 mμg., crude casein (104 mμg.), white fish meal (98·3 mμg.), condensed fish solubles (92 mμg.) and red fish meal (111 mμg.) were found to be particularly rich in B_{12}. H. T. B.

PHARMACY

DISPENSING

Ascorbic Acid Solutions, Deterioration and Stabilisation. S. K. Ganguly. (*Indian J. Pharm.*, 1949, **11**, 145.) Ascorbic acid solutions deteriorate rapidly at a low *p*H in the presence of air and copper. Stabilisation of the solutions may be achieved by buffering to about

*p*H 6 and storing under carbon dioxide or nitrogen. It is an advantage if the solutions are prepared free from copper. The following method is given. Dissolve 60 g. of trisodium phosphate ($Na_3PO_4,12H_2O$ of reagent purity) and 1 g. of chlorocresol in 100 ml. of freshly distilled, pyrogen-free water, add 15 ml. of pure calcium carbonate and place in a 2-l. pyrex flask closed with a cotton plug wrapped with cellophane paper freed from soluble electrolytes and copper by repeated boiling with water. Shake thoroughly and autoclave at 15 lb. for 20 minutes, cool and filter through sintered glass into a sterilised pyrex flask. Heat to boiling, pass nitrogen through the solution and saturate with nitrogen at 0°C. The removal of copper should be confirmed by the dithizone test. To the buffer solution add 55 g. of ascorbic acid, saturate with nitrogen at 0°C., filter through sintered glass into resistant glass containers and seal under nitrogen. The *p*H of the resulting solution is 6·0 to 7·0, and deterioration on storage of the sealed containers at 25° to 30°C. for 3 months is of the order of 4 per cent. G. B.

NOTES AND FORMULÆ

Methapyrilene Hydrochloride (Thenylene Hydrochloride). (*New and Non-official Remedies; J. Amer. med. Ass.*, 1949, **140,** 1097.) Methapyrilene hydrochloride is N, N-dimethyl-N′(α-pyridyl)-N′-(α-thenyl)-ethylenediamine hydrochloride $(CH_3)_2N.CH_2.CH_2N(C_5H_4N)(C_5H_5S)$, HCl. It is a white crystalline powder with a faint odour, m.pt. 159° to 162°C., soluble in water, alcohol and chloroform, and slightly soluble in ether and benzene; a 5 per cent. aqueous solution has a *p*H of 5·9 to 6·4 Addition of alkali to an aqueous solution liberates the base as an oil. With sulphuric acid it gives an orange-red solution, which becomes reddish brown (distinction from pyribenzamine hydrochloride). Methapyrilene hydrochloride gives a pink precipitate with Reinecke's salt and in alcoholic solution a yellow precipitate with trinitrophenol. It is assayed for chloride content, and also for base by liberation with alkali, extraction with ether, shaking the ether with a known excess of hydrochloric acid, extracting with water and titrating the excess of acid. It contains 12·1 to 12·4 per cent. of hydrogen chloride and 87·0 to 88·5 per cent. of base. A 0·001 per cent. alcoholic solution exhibits ultra-violet absorption maxima at 2400 and 3050 Å and a minimum at 2740 Å. Methapyrilene hydrochloride is an antihistamine substance with a moderate tendency to gastrointestinal irritation. The average adult dose is 50 to 100 mg. G. R. K.

Thonzylamine Hydrochloride (Neo-hetramine). (*New and Nonofficial Remedies; J. Amer. med. Ass.*, 1949, **139,** 1148.) Thonzylamine hydrochloride is N, N-dimethyl-N′-(*p*-methoxybenzyl)-N′-(2-pyrimidyl)-ethylenediamine hydrochloride, $(CH_3)_2N.CH_2.CH_2.N(C_4H_3N_2)(CH_2.C_6H_4.OCH_3)$,HCl. It is a white, crystalline powder with a faint odour, m.pt. 173° to 176°C., soluble in water, alcohol and chloroform, and almost insoluble in ether. A 2 per cent. aqueous solution has *p*H 5·1 to 5·7, and addition of alkali liberates the base as an oil. It gives a pink precipitate with Reinecke's salt, a yellow dipicrate which melts at 141° to 145°C. and with sulphuric acid a pink colour which becomes red. A 0·001 per cent. alcoholic solution exhibits an ultra-violet absorption maximum at 2440 Å. It contains 17·0 to 17·6 per cent. of nitrogen and 98·5 to 101·5 per cent. of thonzylamine hydrochloride, determined by extracting the free base from alkaline solution with ether, recombining with hydrochloric acid and titrating the excess of

acid. Thonzylamine hydrochloride is an antihistaminic substance less efficacious than most of the other members of the group, but much better tolerated. The average adult dose is 100 mg. G. R. K.

Zincundecate (Desenex). (*New and Nonofficial Remedies; J. Amer. med. Ass.*, 1949, **140,** 21.) Zincundecate is a preparation containing undecylenic acid and zinc undecylenate and used as powder or ointment in the treatment of fungal infections of the skin. Undecylenic acid, 10-hendecenoic acid, or 10-undecenoic acid (CH_2:$CH.(CH_2)_8.CO_2H$) is a yellow liquid soluble in alcohol but almost insoluble in water. It has a refractive index at 25°C. of about 1·4486, a specific gravity at 25°C. of about 0·911, and an iodine value of 131 to 138, and contains 95 to 108 per cent. of undecylenic acid when titrated with potassium hydroxide. Zinc undecylenate, $(C_{10}H_{19}CO_2)_2Zn$, is a very fine white powder insoluble in water and alcohol. The content of zinc undecylenate, determined by ashing, is 98 to 102 per cent., calculated on the dried material; the loss on drying at 105°C. for 2 hours is not more than 1·25 per cent. Desenex is supplied as a powder containing zinc undecylenate 20 per cent., and undecylenic acid, 2 per cent., in talc, and as an ointment containing zinc undecylenate, 20 per cent., and undecylenic acid, 2 per cent., in a water-miscible base. G. R. K.

PHARMACOGNOSY

Fluorescence of Vegetable Drugs. C. R. Chase, Jr., and R. Pratt. (*J. Amer. pharm. Ass., Sci. Ed.*, 1949, **38,** 324.) Powdered drugs (a) mounted in a solution of nitrocellulose in amyl acetate (b) treated with methyl alcoholic N sodium hydroxide, dried and mounted in solution of nitrocellulose in amyl acetate, and (c) treated with methyl alcoholic N sodium hydroxide and used while still wet, were examined by radiation from a mercury arc with a filter passing the 365 mμ band. 93 per cent. of the drugs examined showed fluorescence after treatment by at least one of these methods. An identification key based on the colour of the fluorescence has been worked out for 151 drugs and some further distinctions can be made by comparison of the intensities. For example, China and Saigon cinnamon do not fluoresce when mounted by methods (a) and (b), and may be distinguished from the Ceylon variety which shows fluorescent spots. Treatment (c) gives a blue colour with Ceylon cinnamon; China and Saigon give a green colour, but these varieties can be distinguished by the intensity of the fluorescence. In order to identify certain leaves (e.g. belladonna, hyoscyamus and stramonium) which are not readily distinguished by the above treatment, further tests have been devised which also serve to distinguish the different varieties of certain drugs. Alcoholic extracts of the drugs are treated (1) with silver nitrate, followed by 0·1 N sodium hydroxide and (2) with 0·1 N sodium hydroxide followed by mercuric chloride. The different varieties of benzoin or cinchona, for example, can be distinguished by the colour of the fluorescence produced by this treatment. The colour of the fluorescence of an alcoholic extract is sufficient to distinguish long buchu from short buchu. G. B.

Gum Arabic from Tanganyika. H. E. Coomber and F. J. Coomes. (*Bull. imp. Inst.*, 1948, **46,** 231.) Three samples of gum collected in September, 1947, have been examined and compared with samples of *Acacia senegal* gum from Tanganyika, and Kordofan cleaned gum. The results were considered encouraging since figures for ash, matter insoluble in cold water, colour and acidity were rather better than those of a sample of

commercial Kordofan cleaned gum previously examined. On the other hand the solutions were much less viscous than that of the Kordofan gum, a fact which may limit the value of the Tanganyika product.

	Samples			*Acacia senegal* from Tanganyika	Kordofan cleaned
	1	2	3		
Moisture, per cent.	14·4	14·6	14·5	15·9	14·0
Ash, per cent.	1·3	1·2	1·1	2·3	3·0
Acid value, mg. KOH/g. gum	1·6	1·8	1·6	2·5	2·9
Matter insoluble in cold water	0·24	0·13	0·04	0·11	0·24
Viscosity of 10 per cent. w/w solution at 20°C. relative to water	4·35	4·0	4·3	5·21	13·50
Dynamic centipoises pH (50 per cent. w/v solution)	4·78	4·39	4·72	—	—
Colour (50 per cent. w/v solution)					
Lovibond scale :—	4·43	4·27	4·31	—	—
Yellow	1·3	2·0	1·0	—	6·7
Red	0·5	0·8	0·5	—	1·7
Black	Nil	Nil	Nil	—	1·3

G. R. A. S.

Opium Poppy, Dutch Culture of. W. R. Becker and A. W. M. Indemans. (*Pharm. Weekbl.*, 1949, **84**, 669.) The investigations, previously reported, of the alkaloidal content of a number of varieties of the opium poppy, grown in Holland, were continued during 1948. The wet season resulted in a considerable drop in alkaloidal content, and this was most marked with the foreign varieties. Since the capsule is only a by-product in the production of poppy seed, it would hardly be profitable for the Dutch grower to attempt to develop varieties rich in morphine and suitable for the climate. Moreover the result of such attempts is problematic, since it is just those varieties with a high morphine content which, in a normal wet summer, show the greatest drop in content to a level comparable with that of the native varieties. The same considerations apply to German and French varieties, Dutch poppy seed is of very good quality, and the introduction of foreign strains would probably lead to a reduction in quality. G. M.

Pyrethrum Flowers from Ceylon. A. E. Chittenden and H. E. Coomber. (*Bull. imp. Inst.*, 1948, **46**, 230.) Chemical examination of a sample of Ceylon flowers, which was of very good appearance, showed that it was similar in total pyrethrin content to Kenya-grown flowers.

	Ceylon Sample per cent.	Kenya Sample per cent.
Pyrethrin I	0·74	0·89
Pyrethrin II	0·70	0·64
Total Pyrethrins	1·44	1·53

G. R. A. S.

PHARMACOLOGY AND THERAPEUTICS

***nor*Adrenaline, Liberation from the Suprarenal Gland.** E. Bulbring and J. H. Burn. (*Brit. J. Pharmacol.*, 1949, **4**, 202.) The object of this investigation was to discover what substance was released by the normal suprarenal gland during splanchnic stimulation. In the spinal cat the ratio of contraction of the denervated nictitating membrane to that of the normal membrane is very much greater when noradrenaline is injected than when adrenaline is injected. If the cat is eviscerated and the splanchnic fibres to one suprarenal gland stimulated, the effect on the membranes is inter-

mediate between that of adrenaline and that of noradrenaline, and can be matched by infusing a mixture of the two. Such a match cannot be made with a mixture of adrenaline and dehydroxynorephedrine (corbasil) and other reasons exclude epinine or hydroxytyramine as substances which might be released. If the splanchnic is stimulated repeatedly a gradual decline in the proportion of adrenaline secreted was observed in normal cats, but this decline seemed absent in cats fed on a diet rich in methionine. The authors conclude that the evidence indicates the lease of noradrenaline as well as of adrenaline from the suprarenal gland in amounts varying from 20 to 80 per cent. of the total. S. L. W.

***p*-Aminosalicylic Acid, Increase in Resistance of Tubercle Bacilli to.** A. Delaude, A. G. Karlson, D. T. Carr, W. H. Feldman and K. H. Pfuetze. (*Proc. Mayo Clin.*, 1949, **24,** 341.) Cultures from 71 patients who had not been treated with *p*-aminosalicylic acid, including 10 cultures which were resistant to streptomycin, were found to be resistant to only 0·006 or 0·012 mg. of the sodium salt per 100 ml. of egg-yolk agar medium. Eighteen of these patients were treated with *p*-aminosalicylic acid alone for 94 days or less and at the end of therapy cultures were still resistant to these concentrations. Cultures isolated from 4 of 5 patients treated with *p*-aminosalicylic acid for periods of 157 to 251 days were able to grow in concentrations of the sodium salt of 1·6 to 6·4 mg. per 100 ml. of medium, but cultures from 4 patients who received approximately the same amount of *p*-aminosalicylic acid therapy in combination with promin and streptomycin did not show this resistance to the sodium salt *in vitro*. S. L. W.

Ammonium Compounds: Intravenous Toxicity. N. W. Karr and E. L. Hendricks. (*Amer. J. med. Sci.*, 1949, **218,** 302.) The toxicity of ammonium chloride solution when administered intravenously in the treatment of alkalosis is dependent mainly on the rate of administration and is virtually independent of the total amount given. The clinical effect is dependent mainly on the amount given. Toxic effects are due to the ammonium ion and not to the acidifying action of the compound. H. T. B.

Antabuse: Formation of Acetaldehyde in Relation to Dosage and to Alcohol Concentration in Blood. J. Hald, E. Jacobsen and V. Larsen. (*Acta Pharmacol. Toxicol.*, 1949, **5,** 179.) An increased amount of acetaldehyde has been identified in the expired air of rabbits treated with antabuse and alcohol. Increasing doses of absorbed antabuse, up to 1 g. result in increasing amounts of acetaldehyde in the blood of rabbits when the alcohol concentration in the blood is kept constant. When this saturation limit is reached the absorption of more antabuse has no further effect on the acetaldehyde level. On the other hand, in animals saturated with antabuse, increasing concentrations of alcohol in the blood result in increasing concentrations of acetaldehyde. While the reason for this is not clear it is of great importance in connection with the clinical use of antabuse, since it means that higher doses of alcohol will give more marked symptoms and that a single heavy dose may perhaps result in alarming symptoms. It is highly advisable therefore to observe caution in respect of the alcohol dosage to antabuse-treated patients. S. L. W.

Antabuse, Sensitising Effect to Ethyl Alcohol. J. Hald, E. Jacobsen and V. Larsen. (*Acta . Pharmacol. Toxicol.*, 1948, **4,** 285.) The toxicology and pharmacology is reviewed and a study of its absorption and elimination rate in man is reported. The ingestion of even moderate amounts of alcohol on the day following oral administration of 1 g. gives

rise to the following symptoms. Within 5 to 15 minutes after taking the alcohol there is a feeling of heat in the face, followed a few minutes later by vasodilation, which reaches its maximum intensity within about 30 minutes, by which time the face is scarlet with a slight tinge of blue. The sclerae are also involved, causing a "bull eyed" appearance, and there is slight oedema in the loose tissue under the lower eyelids. Simultaneously with the flushing, palpitations start, with a feeling of intense pulsation in the lower neck, sometimes accompanied with a pulsating headache. The pulse is accelerated but at this stage the blood pressure is generally unaltered. There may be a feeling of constriction in the neck, with a sensation of dyspnœa; more frequently there is mild irritation in the throat, causing coughing. After larger doses of alcohol, 40 to 50 g. or more, especially when taken with food, nausea may occur, beginning 30 to 60 minutes after the onset of the cardiovascular symptoms; when nausea is felt the intense flushing disappears and a considerable fall in blood pressure takes place. After a shorter or longer time the nausea results in copious vomiting. The intensity and duration of the symptoms varies with the individual and with the dose of alcohol; about 5 g. will produce mild symptoms in sensitive individuals and after 10 g. symptoms always occur. The symptoms last from 30 to 60 minutes in slight cases to several hours in more pronounced ones. When the symptoms fade the patient feels exhausted but feels completely well after a few hours' sleep. No signs of habituation have been observed; indeed, it seems that the tolerance for alcohol is often lowered in repeated experiments. S. L. W.

Anthisan and Phenergan, Comparison of as Histamine Antagonists. W. H. Bain, J. L. Broadbent and R. P. Warin. (*Lancet*, 1949, **257**, 47.) These two histamine antagonists were compared quantitatively as regards their weight-for-weight potencies, durations of action and therapeutic efficacies in chronic urticaria. The relative potencies were compared by estimating the oral doses of each required to produce the same degree of reduction of the intradermal histamine weal response. Phenergan was shown to be about 7 times as potent as anthisan. The relative durations of action were estimated from the times taken for the maximum effect of approximately equipotent doses of the drugs to be reduced by half. The mean half-action time for phenergan was $19\frac{1}{2}$ and for anthisan $5\frac{1}{8}$ hours. The two drugs were compared therapeutically in 20 cases of chronic urticaria, anthisan being given at the usual intervals but phenergan, because of its long duration, in a single dose at night. Of the 20 patients 14 preferred phenergan because of the fewer side-effects. The relative therapeutic potencies were estimated from the individual ratios between the daily dose of anthisan and the daily dose of phenergan required to produce the same therapeutic effect. Phenergan was found to be, on an average, 14 times as potent as anthisan. Thus, a patient with chronic urticaria whose condition was controlled by 350 mg. of anthisan a day, is likely to show a similar clinical response to a single daily dose of 25 mg. of phenergan.

S. L. W.

Atropine, Pethidine, Procaine and Quinidine; Common Pharmacological Properties. N. K. Dutta. (*Brit. J. Pharmacol.*, 1949, **4**, 197). This paper describes the action of these substances on the perfused superior cervical ganglion of the cat, on the phrenic nerve-diaphragm preparation of the rat, and on the bronchioles of the guinea-pig. Thus they were examined for curariform activity, both in the ganglion and at the motor end-plate, and also for antihistamine activity. The experiements provided further evidence that no sharp line of distinction is possible between the actions of these four

substances though they are classified quite differently for medical purposes. All of them depress the response of the perfused cervical ganglion to preganglionic stimulation, acting in this way like *d*-tubocurarine. They all augment the contractions of the isolated rat diaphragm, both when stimulated through the nerve and when stimulated directly after curarisation; very high concentrations depress the contractions. They all depress the bronchoconstrictor action of histamine in the guinea-pig; atropine and pethidine have about one-tenth, procaine about one-hundredth, and quinidine about one four-hundredth the potency of antistin. S. L. W.

Aureomycin in the Treatment of Penicillin-resistant Staphylococcal Bacteræmia. D. R. Nichols. (*Proc. Mayo. Clin.*, 1949, **24,** 309.) Of 50 strains of *Staphylococcus aureus* recently isolated from various clinical materials 34 were penicillin-resistant, and of 15 strains isolated from patients with bacteræmia 12 were penicillin-resistant. Growth of all the strains of staphylococci isolated was inhibited by aureomycin, and 4 of 6 patients suffering from penicillin-resistant staphylococcal bacteræmia recovered when treated with aureomycin. In 4 of the patients the drug was given by intermittent intravenous administration, a dose of 200 to 500 mg. in 250 ml. of normal saline solution being administered 4-hourly every 6 or 12 hours, 10 to 15 minutes being allowed for injection. The drug was given orally in 2 cases and to complete the course of treatment in the other 4 a dose of 500 mg., 750 mg., or 1 g. was given every 4 or 6 hours. Vitamin supplements were given either orally or intravenously with prolonged aureomycin therapy. Of the 2 patients who died one had received oral therapy only and the other the combined intravenous and oral therapy. Use of aureomycin is not advocated as a routine in the treatment of staphylococcal bacteræmia but it would appear to be the drug of choice in penicillin-resistant cases. S. L. W.

Cinchona Alkaloids, Toxicity of. C. C. Johnson and C. F. Poe. (*Acta Pharmacol. Toxicol.*, 1948, **4,** 265.) The toxicity of quinine, quinidine, cinchonine and cinchonidine, for white rats (injected intraperitoneally) and for micro-organisms has been studied. The study of the effect on micro-organisms was divided into two parts: (1) an investigation of the effect of the alkaloids on the normal fermentative action of bacteria of the genus *Escherichia* and of the genus *Aerobacter;* (2) a comparison of the germicidal and antiseptic values of the alkaloids with phenol, using *Eberthella typhi* and *Staphylococcus aureus* as the test organisms. In general, the experimental results with cinchonine and cinchonidine showed the *d*-isomer to be more toxic for white rats and for bacteria than the *l*-isomer; quinine on the other hand was found to be more toxic than quinidine. Quinine, quinidine and cinchonidine showed greater toxicity for *Aerobacter,* whereas cinchonine showed slightly greater toxicity for *Escherichia.* Slight antiseptic or germicidal action was shown by the alkaloids on *E. typhi* (a phenol co-efficient of 0·03 for cinchonidine and of about 0·10 for quinine), but little action was shown against *S. aureus.* The relative degree of toxicity of alkaloids for animals and bacteria correlated fairly well. S. L. W.

Compound E, Effects of on the Acute Phase of Rheumatic Fever. P. S. Hench, C. H. Slocumb, A. R. Barnes, H. L. Smith, H. F Polley, and E. C. Kendall. (*Proc. Mayo. Clin.*, 1949, **24,** 277.) In each of 3 patients with acute rheumatic fever the intragluteal administration of 17-hydroxy-11-dehydro-corticosterone (compound E) was followed by the rapid disappearance not only of the fever, tachycardia and polyarthritis but also the elevated sedimentation rates and abnormal electrocardiographic

changes. The compound E acetate was administered in the form of a suspension, in solution of sodium chloride, of finely ground crystals in a concentration of 25 mg./ml. The total daily doses generally were 200 mg. (100 mg. twice daily) at first for several days, and 100 mg. (50 mg. twice daily) for a few more days. No definite toxicity or mental depression was encountered. It is not yet possible to draw conclusions as to the effect of compound E on the rheumatic hearts of these 3 patients, but in view of the markedly beneficial effect which this compound has on the skeletal muscles and fibrous tissues of patients with rheumatoid arthritis, it is hoped that it will exert a similar effect on the cardiac muscle. S. L. W.

Decamethonium Iodide as a Muscle Relaxant in Anæsthesia. A. J. H. Hewer, B. G. B. Lucas, F. Prescott and E. S. Rowbotham. (*Lancet*, 1949, **256**, 817.) The effect of decamethonium iodide as a muscle relaxant in surgical anæsthesia was investigated in a series of 85 unselected patients, whose ages ranged from 13 to 79 years. The surgical procedures varied from simple orthopædic manipulations to major thoracic surgery. All patients were induced with thiopentone, and the majority were anæsthetised with intermittent thiopentone-nitrous oxide-oxygen. The total dose of decamethonium iodide varied from 3 to 15 mg., given intravenously. The onset of curarisation began after 2 to 3 minutes and reached a peak within 4 to 8 minutes, the duration of relaxation being 15 to 25 minutes. Relaxation comparable to that obtained with *d*-tubocurarine could only be obtained with doses which paralysed the muscles of respiration, though very adequate operating conditions were present during the phase of respiratory recovery. In some cases this state of muscular relaxation with respiratory paralysis was obtained with the initial dose of 3 mg. Complete curarisation was produced by a dose little above the sub-threshold one. The return of muscular tone and respiration was equally abrupt, the tidal air returning to normal within 3 minutes of the onset of recovery. Repeated doses produced no cumulative effect even when given to maintain relaxation for as long as 3 hours. No significant side-effects were noted and bronchial or laryngeal spasm was not observed in any case. In none of the 85 cases was there sufficient respiratory depression to cause alarm. The authors conclude that decamethonium iodide is a satisfactory relaxing agent with a wide margin of safety, provided adequate pulmonary ventilation is maintained, and that the antagonist, pentamethonium iodide, has no useful place in anæsthetic practice because of its autonomic blocking effect, which might be a contributory factor in operative shock. S. L. W.

Dibromoprocaine Hydrochloride, Radioactive, as Spinal Anæsthetic, Tissue Distribution of. F. Howard. (*Nature*, 1949, **163**, 679.) In the first series of experiments doses of the anæsthetic varying from between 0·007 and 0·03 g. were given to cats, by lumbar puncture. Autopsies were performed at periods of 1 to 39 hr. after administration of the anæsthetic and specimens taken from the organs, the sample being broken down in lithium hydroxide solution under reflux and the resulting fine suspensions estimated by means of scaling unit and "liquid" counter. In a second series the anæsthetic was given intravenously, in order to study the effects on tissue concentration of higher blood levels. In the intrathecal series the blood levels were between 5·4 and 1·3 μg. per ml. as against levels of 44 μg. per ml. in the intravenous series. Apart from spinal cord and spinal root only the kidney and liver showed a concentration above that obtaining in the blood, namely, 9 times and 3 times the concentration respectively, while their secretions,

urine and bile, showed maximal concentrations of 133 times and 27 times that of the blood respectively; the concentration in the duodenal contents followed that of the bile. Of the remaining tissues, the lung showed the highest drug concentration (0·8) and muscle tissue the lowest (0·1). With increased time between administration and autopsy a slight increase in the blood-tissue ratios was observed, the effect being maximal about 20 hours after administration. When the drug was given intravenously the cerebrospinal fluid in the lumbar theca showed a barely estimable amount of tracer, while the cord showed 0·05 to 0·1 times, and the roots 0·3 to 0·4 times, blood concentration. At high blood levels the concentrating activity of liver and kidney appeared to decrease, but variations in blood levels had little effect on the blood-tissue ratios elsewhere. S. L. W.

Diethyl nitrophenylthiophosphate (DPTF), Poisoning by. A. H Anderson and T. Jersild. (*Acta Pharmacol. Toxicol.*, 1949, **5**, 129.) This is one of a new group of insecticides, the so-called alkylpolyphosphates and their related compounds, which are being used in horticulture and are particularly effective against aphides; other members of the group are hexathyltetraphosphate (HTF) and tetrathylpyrophosphate (TPF). They were originally believed to be almost non-toxic to man and animals but it is now known that DPTF is absorbed through the skin, as well as through the lungs and after subcutaneous injection. The effect is qualitatively the same for all alkyl phosphates and depends on the fact that these substances inhibit cholinesterase. Hence the signs of poisoning resemble those following injection of large doses of acetylcholine, namely fibrillar contractions of the striated muscles, convulsions, pilomotor contractions, increased salivation, peristalsis, bronchial secretion and miosis. Treatment is mainly focused on the pulmonary œdema and cessation of respiration. Atropine is the rational antidote. S. L. W.

Emetine, Distribution of in Tissues. L. G. Parmer and C. W. Cottrill. (*J. Lab. clin. Med.*, 1949, **34**, 818.) The tissue distribution of emetine in rabbits after a single injection was determined. Within half an hour the highest concentrations of drug were found in the lung, kidney and spleen. The liver and heart contained much less, and the intestinal level was relatively very low. In striated muscle of the leg it was found in very low amounts up to 2 hours after injection. Significant amounts of the drug were not detectable in the brain. In most organs the maximum concentration of drug occurred within 12 to 24 hours after injection, this level persisting with slight change through the second day and then gradually declining, so that by the fourth day the concentration in the major organs was about half what it was at the maximum. Some organs were free of emetine after 2 weeks, but lymph node and kidney contained significant quantities for as long as 4 weeks, and the spleen did not become free of the drug for between 6 and 9 weeks. The authors note that while almost all toxic symptoms from emetine in man and animals are associated with the heart, muscles and intestine, it was in just these organs that the lowest concentrations of the drug were found. In other words only those organs having contractability as their most important function are adversely affected even though the concentration in these organs is not very high. They suggest as a possible explanation that emetine interferes with a chemical function of the cell which converts glycogen into contractile energy. S. L. W.

***l*-N-Ethylephedrine and *l*-Ephedrine: Comparison of Pharmacological Actions.** A. Åström. (*Acta Pharmacol. Toxicol.*, 1948, **4**, 53.) *l*-N-ethyl-

ephedrine and *l*-ephedrine seem to have the same qualitative effect, the differences observed being mainly quantitative. The pressor effect of *l*-ephedrine was some 10 to 15 times stronger than that of *l*-N-ethylephedrine when doses of 0·5 to 1 mg./kg. were used. The effect of adrenaline on the blood pressure was not diminished by the two amines in chloralosed cats; cocaine depressed the effect of both substances. The effect of small doses on normal rabbit intestine is often a stimulation, and of larger ones always an inhibition, of the rhythmic contractions, the effect on the tone being very slight. After increasing the tone with acetylcholine or other compounds an inhibitory action was observed. The spasmolytic action of *l*-N-ethylephedrine was about twice that of *l*-ephedrine. Small doses of the ephedrines abolished the usual inhibitory effect of adrenaline on isolated strips of rabbit intestine and the action of electrical stimulation of the periarterial nerves to the intestine. Non-pregnant uterus of rabbit and cat were stimulated by the two amines, but the rhythmic contractions were diminished at the same time; in this respect *l*-N-ethylephedrine was somewhat more active than *l*-ephedrine. S. L. W.

Norisodrine Sulphate Dust, Inhalation of in Asthma. L. R. Krasno, M. J. Grossman and A. C. Ivy. (*J. Allergy*, 1949, **20,** 111.) A group of 24 asthmatic patients with symptoms ranging from 3 to 28 years, and not satisfactorily controlled with the usual drugs, were treated by the inhalation of norisodrine dust. The dose consisted of the amount of drug (3 to 5 mg.) released by one inspiration from an inhaler, the patient being instructed to take one inhalation of the dust during an impending attack of asthma and to repeat this within half to one hour as necessary. Nineteen of the patients responded satisfactorily and were brought completely under control with this treatment, 4 showed a good response and 1 was uninfluenced. Sixteen patients were controlled by the inhalation of norisodrine dust alone, 8 required norisodrine plus aminophylline and iodides, and/or an antihistamine, a combination of drugs appearing to be effective when each drug by itself was ineffective. In asthma with bronchitis a combination of penicillin dust and norisodrine dust therapy appears very effective. The inhalation of norisodrine dust is a safe procedure, no serious side-reactions being observed. Transitory palpitation and/or dizziness were noted in only 4 of 30 subjects. Continued use of the dust does not give rise to diminution in its effect. S. L. W.

Piperidine, Pyrrolidine and Pressor Concentrates from Dog Urine, Pharmacology of. M. J. Lockett. (*Brit. J. Pharmacol.*, 1949, **4,** 111.) Pressor concentrates from both normal dog and normal human urine were prepared by the author (*J. Physiol.*, 1944, **103,** 185; 1946, **105,** 138) and were referred to as base B concentrates. After incomplete oxidation of these concentrates with potassium permanganate the following substances can be identified in pharmacologically significant amounts: piperidine, pyrrolidine, dimethylamine and ammonia. These four bases were absent in the original concentrates but can be obtained as degradation products from base B concentrates. This paper is concerned with a comparison of the pharmacological action of base B concentrates with that of suspected degradation products. Of the four degradation products piperidine and pyrrolidine exhibited approximately equal pressor activity. The amounts of piperidine and pyrrolidine derived from base B concentrates might account for rather less than half the pressor action of the original base B concentrates, but for the dissimilarity in the actions of the base B concentrates and these two bases. The main features of this dissimilarity are that the pressor action of base B concentrates is not reversed by tetraethylammonium chloride, and is only very slightly reduced

after acute sympathectomy, denervation, or removal of the suprarenal glands. Piperidine and pyrrolidine cause the liberation of acetylcholine into the effluent perfusate from the superior cervical ganglion and of a pressor compound into the adrenal venous blood; base B concentrates do not. These dissimilarities indicate that piperidine and pyrrolidine were not present as such in the original base B concentrates, though they can be obtained from these concentrates by oxidative degradation, and that the pressor activity of these concentrates is due to some compound other than piperidine or pyrrolidine.

S. L. W.

Streptomycin and *p*-Aminosalicylic Acid, Additive Effect of, in Experimental Tuberculosis Infection. R. J. W. Rees and J. M. Robson. (*Nature*, 1949, **164**, 351.) By using the cornea of the rabbit as the site of infection it has been found possible by a method based on that described by Robson (*Brit. J. Ophthal.*, 1944, **28**, 15) to produce a standard tuberculous lesion reliable enough for studying the effect of anti-tuberculous substances *in vivo*. Twelve rabbits were used ; in one group of 6 both eyes, and in the others the right eyes only, were infected, by intracorneal injections, with approximately 300 tubercle bacilli. After a mean incubation period of 8 days all infected eyes developed early small tuberculous lesions. The animals were then divided into three groups and treated as shown in the table.

Group	No. of Rabbits	Right Eye	Left Eye
A	6	Streptomycin and *p*-aminosalicylic acid ...	Streptomycin
B	3	*p*-aminosalicylic acid	Streptomycin
C	3	Untreated controls	Streptomycin

Treatment by intravitreous injections was started on the 9th day after inoculation, streptomycin being given in 10 mg. doses twice weekly and *p*-aminosalicylic acid in 10 mg. doses three times weekly. Group C all developed rapidly progressive tuberculous lesions. In group B, while the lesions were active and progressive, those treated with *p*-aminosalicylic acid were smaller than in the control group. In group A, after 4 weeks' treatment, the left eyes all showed very small but active lesions whereas the right eyes, on combined therapy, all appeared inactive and showed fading lesions, and when therapy was stopped all the lesions in both eyes rapidly spread. The additive effect with streptomycin and *p*-aminosalicylic acid demonstrated in this experiment was striking enough to suggest that, if confirmed in man, it might add considerably to the chemotherapy of acute tuberculosis, particularly in reducing the tuberculous flora before resistance to streptomycin developed. S. L. W.

Thiomerin: A New Diuretic. A. R. Feinberg, J. H. Isaacs and W. S. Boikan. (*Amer. J. med. Sci.*, 1949, **218**, 298.) Thiomerin is the disodium salt of N(γ-carboxymethylmercaptomercuri-δ-methoxy)propylcamphoramic acid and is a mercurial diuretic which is active when given subcutaneously. In an investigation on 409 patients, receiving a total of 2069 injections, it was found that thiomerin is virtually non-toxic, painless when given subcutaneously and equally or more effective than other mercurial diuretics. The usual dose was 0·14 to 0·3 dissolved in 1 to 2 ml. of water.

H. T. B.

Trichloroethylene, Toxicity of. A. R. Hunter. (*Brit. J. Pharmacol.*, 1949, **4**, 177.) A batch of 10 mice was exposed for 1 hour to 1 per cent.

[*Continued on page* 198