ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

***Cryptocarya pleurosperma*, Alkaloids of.** I. S. de la Lande. (*Austral. J. exp. Biol.*, 1948, **26**, 181). This paper deals with an investigation of the bark of *Cryptocarya pleurosperma* (Fam. Lauraceæ), which is indigenous to Australia. A new alkaloid, cryptopleurine, has been isolated which separates from acetone, methyl alcohol or ethyl alcohol in clusters of white needle-like prisms; m. pt. 195° to 196°C.; it is practically insoluble in water, but very soluble in chloroform and less soluble in ether; formula $C_{24}H_{29}O_3N$ with three methoxy groups. The hydrochloride, hydriodide and picrate are described. The bulk of the alkaloid of the bark is water-soluble and has been isolated in a pure condition. Cryptopleurine is extremely toxic, the LD50 of intravenous doses in rabbits being about 1·5 mg./kg. It is a powerful skin irritant and vesicant. Rubber gloves are essential when handling the alkaloid, with additional precautions, such as a gas mask, when handling the finely-ground bark. In all experimental animals the action of cryptopleurine was slow, usually not being manifest before 12 hours, death usually occurring within 24 to 48 hours. Lethal oral and intravenous doses in rabbits invariably produced marked diarrhœa within 12 hours. Apart from its irritant action it does not possess any other marked physiological activity and has no curare-like action. The water-soluble alkaloid fraction is physiologically relatively inert: it is non-toxic, non-irritant to the skin and has no curare activity. S. L. W.

ANALYTICAL

Amidone and other compounds, Microscopical Identification of. J. A. Schuldiner. (*Anal. Chem.*, 1949, **21**, 298.) The microcrystalline forms produced with solutions of zinc chloroiodide, potassium bromobromide, potassium iodoiodide, mercuric bromide, cadmium iodide and Marmé's reagent are described, and detailed exact procedures necessary to obtain reproducible crystals are given. The precipitation reactions of amidone, pethidine, morphine sulphate, codeine sulphate, diamorphine hydrochloride, cocaine hydrochloride, procaine, dionine, and narceine hydrochloride with the above reagents and with bromine water, ammonium hydroxide solution, Mayer's reagent, 1 per cent. sodium hydroxide solution, lime water and a 2 per cent. solution of cobalt thiocyanate are recorded. In these reactions the reagent was added to 5 ml. of an approximately 0·1 per cent. solution of the compound under test. R. E. S.

Digitalis, Colorimetric Estimation of. Orlo F. Swoap (*J. Amer. pharm. Ass., Sci. Ed.*, 1948, **37**, 268.) The colorimetric method for standardising digitalis due to Knudson and Dresbach (*J. Pharmacol.*, 1922, **19**, 268, and **20**, 205) has been used by the author for a number of years, and results, covering a four-year period, are published. The colorimetric results obtained on 20 tinctures of digitalis and 37 samples of purified digitalis glycoside preparations are compared with the results obtained using the U.S.P. XII cat assay method. The work was carried out before the U.S.P. Reference Standard Digitalis was

available, and values are expressed in terms of ouabain for the colorimetric method, and in cat units for the biological assay. The results indicate that a different standard amount of ouabain is required for each type of digitalis preparation tested colorimetrically if a conversion is to be made for the estimation of biological cat units. L. H. P.

Morphine, Colorimetric Determination of. J. S. N. Cramer and J. G. Voerman. (*Pharm. Weekbl.*, 1949, **84**, 129.) In a method recently given by Guarino, morphine, after oxidation with iodic acid, is treated with ferric chloride. This reaction is unsatisfactory for colorimetric use in several respects, but may be greatly improved by using a nickel salt in place of ferric chloride. Details are as follows. A solution, containing up to 8 mg. of morphine in 15 ml., is treated with 15 ml. of N/10 hydrochloric acid, and 2 ml. of 5 per cent. iodic acid; after 2 minutes 5 ml. of a saturated solution of ammonium carbonate is added, and the mixture is made up to 50 ml. with 5 per cent. ammonium carbonate solution. After 30 minutes, 1 ml. of 1 per cent. solution of nickel sulphate is added, and, after 90 minutes, the colour is determined photometrically, using a suitable (red) filter, and comparing against a blank solution prepared as above with the omission of the iodic acid. No colour is given by meconic acid, or by the five principal other alkaloids of opium. G. M.

Phosphates, Alkalimetric Titration of. J. C. W. Dijksman. (*Rec. Trav. chim. Pays-Bas.*, 1949, **68**, 57.) From the results of titrations it has been suggested that, in purified disodium phosphate, the Na_2O and P_2O_5 are not in exact stoichiometric proportions. Analyses by the author show that, in fact, this is incorrect, and that the misleading results were due to carbonate in the alkali used and alkali phosphate in the phosphoric acid. The two inflection points in the titration curve for phosphoric acid occur at the correct equivalent points, corresponding to *p*H values of 4·5 (0·05 M solution) or 4·3 (0·34 M solution), and 9·1 (at both concentrations) respectively. In presence of an amount of sodium chloride equivalent to the phosphate, the second point is depressed by 0·2. Thus dimethyl yellow and methyl orange are suitable indicators for the first end-point, and thymolphthalein for the second one, but it is necessary to compare against a suitable buffer or, better, against a pure phosphate solution containing any other salts which may be present in the titration liquid. For the second point, phenolphthalein may be used if 16 per cent. of sodium chloride is added to the solution being titrated, and the end-point is compared with a buffer solution of *p*H 8·3. In order to determine phosphates in presence of calcium, iron and aluminium, the latter may be removed by passing through a base-exchange column ("dusarit"). Technical phosphates often contain fluorides or silicofluorides, which interfere with the alkalimetric titration. The accuracy of the titration may be affected by the presence of impurities, especially carbon dioxide and ammonia, present in distilled water, and this is especially important when titrating in dilute solution. The standard alkali, and N/100 acid, should also be free from carbon dioxide. G. M.

Tartrazine in Titration of Chlorides by Volhard's Method. A. J. Berry. (*Analyst*, 1948, **73**, 505.) The use of tartrazine as an adsorption indictaor in the determination of chlorides by Volhard's method without the necessity of removing the silver chloride is recommended. Experiments showed that in chloride determinations in acid solution in which the excess of silver ion is titrated in the presence of silver chloride using tartrazine

as indicator, the same final titration value was obtained whether the titration was completed with standard hydrochloric acid or standard ammonium thiocyanate solutions. The results of a number of titrations are recorded, using 3 drops of a 0.5 per cent. tartrazine solution, and taking the end-point at the stage when the dye was removed from the precipitate and the supernatant liquid assumed a rich lemon colour: agreement with the theoretical value was of the order of 1 in 3,000.

R. E. S.

PLANT ANALYSIS

***Courbonia Virgata*, Chemical Composition and Basic Constituents of.** A. J. Henry and D. N. Grindley. (*J. Soc. chem. Ind., Lond.*, 1949, **68**, 9.) The chemical composition of the air-dry root of *Courbonia virgata* A. Brongn. (Capparidaceae) is:—moisture, 5·90 per cent., ash 7·47 per cent., protein 17·41 per cent., crude fibre 5·78 per cent., sucrose 33·53 per cent., pentosan (araban) 11·17 per cent., fat (soluble in light petroleum) 3·37 per cent., fats (soluble in chloroform but insoluble in light petroleum) 0·81 per cent., tetramethylammonium hydroxide 0·93 per cent., other non-volatile bases, about 0·03 per cent., and some dimethylamine and trimethylamine. The bases probably occur as chlorides. The composition of the ash, and the characteristics of the root fat have been determined. The seeds contain smaller quantities of fat, ash, protein and crude fibre, and the main carbohydrate is starch (64·86 per cent.) The principal basic constituent (tetramethylammonium hydroxide) is present in the proportion of 0·93 per cent. in roots, 0·78 per cent. in aerial stems, 0·70 per cent. in leaves, 0·65 per cent. in thick scaly shoots and 0·15 per cent. in seeds. The method for the isolation of tetramethylammonium hydroxide from the air-dry material is as follows. Percolate with alcohol, evaporate, extract with water, and filter to remove oily matter. Treat the filtrate with basic lead acetate, remove the excess with hydrogen sulphide, evaporate to small bulk, warm with water to 55° to 60°C., add iodine-potassium iodide solution, cool overnight and collect the precipitate on a sintered glass filter. Expel the free iodine by prolonged treatment with hot water, evaporate the solution, dry at 110°C, extract with cold water and filter. Evaporate the filtrate to dryness and wash with dehydrated alcohol until no more colour is extracted. Recrystallise from hot water and wash with dehydrated alchohol. Dimethylamine, trimethylamine and non-volatile bases can be extracted from the alcoholic washings. G. B.

***Dichroa febrifuga* Lour, Antimalarial Constituents of Chinese Drug Ch'ang Shan.** T. Q. Chou, F. Y. Fu and Y. S. Kao. (*J. Amer. chem. Soc.*, 1948, **70**, 1765.) Extraction of the powdered root yielded extracts which were found to contain umbelliferone, 4-quinazolone, a base with the composition $C_{18}H_{23}O_3N_3$ and a water-soluble alkaloid named dichroine. This had the composition $C_{16}H_{21}O_3N_3$ and isomerised readily under suitable conditions to three isomerides α-, β- and γ-dichroines. When oxidised with potassium permanganate, dichroine yielded 4-quinazolone among other products; hydrolysis with sodium hydroxide gave the decomposition products anthranilic acid, formic acid, and ammonia, together with a compound which behaved like a pyrrole derivative. Benzoylation gave a tribenzoyl derivative. Neither carboxyl-, methyl-, nor methylenedioxy-groups were detected. Dichroine formed both normal and acid salts and a nitroso compound. Regarding the antimalarial activity of dichroines, the

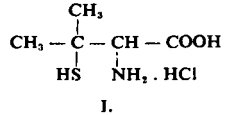
α-isomeride showed the greatest, and the γ-isomeride the least, the curative dose for chicken malaria being found to be 4 mg. of γ-isomer per kg.

R. E. S

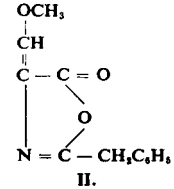
BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Benzylpenillic Acid, Synthesis of. R. W. Holley, F. H. Carpenter, A. H. Livermore, and V. du Vigneaud. (*Science*, 1948, **108**, 136.) The condensation of D-penicillamine hydrochloride (I) with 2-benzyl-4-methoxymethylene-5(4)-oxazolone (II) in pyridine containing triethylamine and subsequent treatment of the crude condensation product, gave needles of D-benzylpenillic acid (III) (micro m.pt., 180° to 182°C. (in 19 per cent. yield), optical rotation $[\alpha]_D^{20°C.}$ + 471° (0·1 per cent. in methyl alcohol); the benzylpenillic acid isolated was the same isomer as that obtained from



I.



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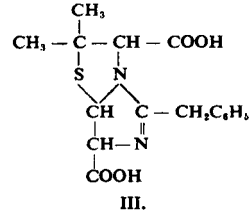
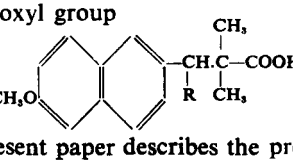


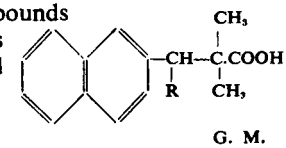
III.

natural benzylpenicillin. When L-penicillamine hydrochloride was substituted for D-penicillamine hydrochloride in the procedure, L-benzylpenillic acid was obtained, identical with D-benzylpenillic acid in all respects, except for its opposite optical rotation, $[\alpha]_D^{21°C.}$ −476° (0·09 per cent in methyl alcohol). When DL-penicillamine hydrochloride was used, optically inactive benzylpenillic acid was obtained (micro m.pt., 177°C. to 179°C). Reference is made to a small antibiotic activity found after the condensation of I and II in pyridine (containing no triethylamine) and to other data published in *The Chemistry of Penicillin*, Princeton Univ. Press, 1948. R. E. S.

β-Naphthylpropionic Acid, Substituted, Œstrogenic activity of. A. Horeau, J. Jacques and S. Julia. (*C. R. Acad. Sci., Paris*, 1948, **227**, 1278.) The suppression of a phenolic hydroxyl group generally results in a considerable diminution of the physiological activity of œstrogens. Substituted (methyl or ethyl)-naphthylpropionic acids (allenolic acids) of the type



are known to be powerfully œstrogenic. The present paper describes the preparation of the corresponding non-phenolic compounds



These acids were found to be about 10 times less active than the methoxy compounds. Detailed biological results are to be published later.

G. M.

Suramin, Studies on. H. M. Dewey and A. Wormall. (*Biochem. J.*, 1948, **43**, 24.) Experiments were carried out to determine whether any simple antiseptic could be added to blood serum or plasma to preserve it for subsequent suramin determinations without interfering with the colour reaction; at the same time an investigation into the reliability of suramin determinations on whole blood samples was made. Throughout the work the suramin was determined by hydrolysis, diazotisation and coupling with methyl-α-naphthylamine, the pink colour produced being matched against a standard Tintometer disc. In a number of determinations in which suramin was added to whole blood (ox, rabbit, and human) the recovery ranged from 60 to 97 per cent.: it was considered that this was due to constituents of the blood cells which inhibited diazotisation or coupling. Quantitative recoveries were obtained when differing amounts of suramin were added to hydrochloric acid-hydrolysed blood. When suramin was added to a sample of whole blood it gave 64 to 69 per cent. recovery in straight determinations but recovery values of 92 and 97 per cent. were obtained from the separated plasma and the red cells. The suramin was almost completely confined to the plasma. The addition of ether, chloroform, toluene (0·3, 0·2 and 0·2 ml. respectively per 2 ml. of serum); phenol and merthiolate (to give concentrations of 0·2 to 0·4 and 0·018 per cent. respectively) and 10·3N HCl (3 ml./2 ml. serum) to serum from rabbits injected with suramin, showed that ether, chloroform, toluene, and hydrochloric acid were not completely satisfactory as preservatives. Serum preserved with phenol or merthiolate gave satisfactory results over periods of 1 to 5 weeks. R. E. S.

BIOCHEMICAL ANALYSIS

Bismuth in Biological Material, Determination of. E. P. Laug. (*Anal. Chem.*, 1949, **21**, 188.) The direct extraction of bismuth with dithizone from aqueous solutions at *p*H 2 cannot be applied satisfactorily to acidified digests of biological material owing to the serious interference of halides and phosphates. It was found that in the presence of 20 per cent. acetic acid with carbon tetrachloride substituted for chloroform as the solvent for dithizone, quantitative extraction of bismuth could be made in the presence of phosphates and halides at *p*H 2·5; simultaneously a separation from lead was effected. Details of the method given involve dry-ashing of the sample at 500°C. followed by solution in concentrated nitric acid. To the diluted solution glacial acetic acid is added to *p*H 2·5 and bismuth is extracted with successive portions of dithizone in carbon tetrachloride; under these conditions some copper and zinc but no lead are extracted. The metal dithizonates are washed with dilute nitric acid and then with dilute nitric acid containing potassium bromide. By this means, bismuth dithizonate is decomposed and the bismuth reverts to the aqueous phase as a complex bromide salt. When the aqueous phase is adjusted to *p*H 9·5, this complex is again decomposed. Bismuth is then extracted with dithizone in chloroform and the density of the coloured solution is determined in a spectrophotometer at 490μ. Results are given for the recovery of bismuth added to rat tissue. R. E. S.

Cadmium in Biological Materials and Foods, Estimation of. R. L. Shirley, E. J. Benne and E. J. Miller. (*Anal. Chem.*, 1949, **21**, 300.) A procedure for estimating small amounts of cadmium is given. The sample is first evaporated to dryness with 2N sulphuric acid and ashed at

550°C.; the residue is then extracted with N/1 hydrochloric acid, the resulting extract being diluted, neutralised, and adjusted to *p*H 2·0 to 2·3. The adjusted acid extract is then treated as follows:—(1) an aliquot portion is extracted with a carbon tetrachloride solution of dithizone to remove the interfering ions of copper and mercury and most of the cobalt and nickel, (2) the aqueous phase is adjusted to *p*H 8·5 to 9·0 with an ammonium hydroxide-ammonium citrate buffer solution containing Rochelle salt, dimethylglyoxime is added, and the solution is extracted with chloroform to remove cobalt and nickel not extracted previously, (3) sodium hydroxide is added to make an approximately 5 per cent. solution followed by extraction with a carbon tetrachloride solution of dithizone to remove the cadmium. The extracted cadmium dithizonate was determined photometrically, the maximum absorption occurring at 515 mμ. The use of amber glassware was found to give protection from light, particularly in the case of the blank solution. Results of the sensitivity of the procedure compared favourably with those published previously. Amounts of magnesium or calcium phosphate greater than 100 mg. may interfere. R. E. S.

Pregnandiol, New Colorimetric Determination of. J. W. Goldzieher. (*J. Lab. clin. Med.*, 1948, **33**, 251.) An aliquot portion, containing about 0·1 to 1 mg. of pregnandiol, of a solution of the sample in a suitable solvent such as ether-alcohol is evaporated to dryness in a 10-ml. graduated flask, and about 6 ml. of zinc chloride reagent (38 per cent. in glacial acetic acid) and exactly 2·5 ml. of acetyl chloride added. The flask is warmed in a water-bath at 50°C. for 30 minutes, cooled in ice to room temperature, allowed to stand for 20 minutes, and the volume adjusted to 10 ml. with zinc chloride reagent. The intensity of the colour is compared with that of a standard prepared in the same manner using 0·5 mg. of pregnandiol. The method was found to be accurate to within 4 per cent. G. R. K.

PHARMACY

DISPENSING

Pectin of *Opuntia vulgaris*, Penicillin delay action of. H. Diacono and V. Massa. (*Ann. pharm. Franc.*, 1949, **6**, 461.) The addition of the pectin of *Opuntia vulgaris* to penicillin solution gives a delaying effect comparable to that of Subtosan (which contains polyvinylpyrrolidone). The formula used was as follows. Calcium magnesium pectate from *Opuntia vulgaris*, 10 g.; sodium chloride, 8·5 g.; potassium chloride, 0·5 g.; calcium chloride cryst., 0·5 g.; magnesium chloride cryst., 0·005 g.; N/1 hydrochloric acid, 17·1 ml.; sodium bicarbonate, 1·68 g.; water, to 1 l. Repeated intramuscular administration of 0·1 g. of this pectin to guinea-pigs did not produce any harmful effects. G. M.

Procaine and Procaine-Adrenaline, Stability of Solutions of. F. Gélébart. (*Ann. pharm. Franc.*, 1949, **6**, 439.) Solutions of procaine may become discoloured on storage, owing to oxidation. This may be prevented by the addition of sodium bisulphite. When adrenaline is also present, the procaine appears to catalyse the oxidation of the adrenaline, and discoloration is much more rapid. In such solutions the physiological action of the adrenaline is reversed, the action being hypotensive, while the procaine, in addition to losing its anæsthetic action, acquires an increased toxicity while

sensitising the patient to the toxic action of the changed or unchanged adrenaline. Impurities in the procaine are an important factor in producing this decomposition, and ampoules prepared with pure procaine and distilled water free from traces of metals may be kept for several months, even without the addition of sulphite. G. M.

PHARMACOGNOSY

Colchicum Seeds, Colchicine Content of. F. Santavý and J. Buchníček. (*Pharm. Acta Helvet.*, 1949, **24**, 20.) The colchicine content was determined in 111 samples of the seeds of *Colchicum autumnale* Linn. from Moravia and Silesia. It was found to vary from 0·60 to 1·23 per cent.; the mean value being 0·81 per cent. The weight of the seeds varied from 183 to 406/g., the mean value being 262. The colchicine content reached a maximum (1·2 per cent) with seeds corresponding to 350/g.: with larger or smaller seeds the percentage was less. G. M.

***Datura*, Effect of Cultural Conditions on Alkaloidal Content of.** R. Hegnauer and H. Flück. (*Pharm. Acta Helvet.*, 1949, **24**, 1.) Two kinds of *Datura* grow well in Switzerland, and these have been regarded as separate species, the white flowered form being *D. stramonium* Linn. and the violet flowered one as *D. tatula* Linn. A detailed description is given of the morphology and biology of the former species. There is a considerable difference in the alkaloidal content of individual plants, even though all are seedlings of a single mother plant. The alkaloidal content also varies with the variety, e.g., *D. stramonium* " Zurich " contained, in the leaf, from 0·128 to 0·235 per cent. of alkaloid; while *D. stramonium inermis* " Dordrecht " had from 0·335 to 0·578 per cent. The mean alkaloidal content of seedlings varied in the same way as that of the mother plants, indicating that yields can be improved by selection. Removal of the capsules or, even more, of the flowers, leads to a greater vegetative development with, at the same time, an increase in the percentage of alkaloids. The attempt to produce the same effect by spraying the plants with growth hormones resulted in a considerable disturbance in the growth of the young flowers and leaves. The vegetative period of the treated plants was considerably lengthened, and the autumnal drop in alkaloidal content of the leaves was retarded.

G. M.

Psyllium Seeds and Their Mucilages, A Quantitative and Qualitative Evaluation of Official and Unofficial Species. D. Greenberg. (*J. Amer. pharm. Ass., Sci. Ed.*, 1948, **37**, 139.) A convenient means for the quantitative determination of the mucilage separated from psyllium seeds has been described. This involves soaking the seeds for 20 hours, at first with vigorous agitation, in 20 ml. of water per g. of seeds and subsequent expression of the mucilage by hand press; the mucilage is dried at 95° to 100° C., and weighed. The swelling factor of psyllium seeds is not indicative of their mucilage content, but depends on the viscosity of the mucilage formed, and other related factors. The viscosity, the swelling factor, and the proportion of mucilage obtained show no direct relationship between the many possible swelling factors obtainable for any given lot of seeds and the proportion of mucilage yielded by the seeds, nor is the proportion of mucilage obtainable from the seeds an indication of the viscosity of that mucilage; it is therefore suggested that more exacting standards than now required by the N.F. VIII

for the evaluation of psyllium seeds be considered. Two unofficial seeds have been described and assayed. *Plantago rhodosperma* grows on sandy soil from Missouri and Oklahoma to Louisiana, Texas and Arizona; the seeds yield 16 to 20 per cent. of a very thick and viscous mucilage, 150 mg. of which diluted to 20 ml. with water yields a semi-solid mass, resembling closely the consistency of "set" gelatin. *P. wrightiana* grows in dry sandy soil and is a native of Texas and Arizona; the seeds compare favourably in all respects with the official seeds, and yield about 20 per cent. of a viscous mucilage. These seeds of *P. wrightiana* can resist fermentation for several weeks, before yeast colonies begin to develop; they even resist transplants of mycelial mats of *Aspergillus niger*. This seems to indicate that there is present in *P. wrightiana* a substance which prevents or retards the growth of bacteria and fungi. The seeds of other species ferment within 24 to 48 hours after adding water, and become covered with moulds. L. H. P.

PHARMACOLOGY AND THERAPEUTICS

Antacid Buffers, A Study of, II. Prolonged Neutralisation. J. M. Holbert, N. Noble, and I. W. Grote. (*J. Amer. pharm. Ass., Sci. Ed.*, 1948, **37**, 292.) An efficient antacid should neutralise the gastric acidity rapidly to *p*H 3.5 to 4, thus performing a double role in the prompt relief of pain and in the inactivation of pepsin, and should not cause reflex secretion of further hydrochloric acid by the gastric mucosa. In the evaluation of antacids the length of time required for neutralisation, the change in *p*H, and the length of time a given quantity of antacid is effective in neutralising acidity, must be considered. This length of time during which various antacids were effective in neutralising artificial gastric juice was studied *in vitro* under conditions resembling those in the stomach, the acid reaction mixture was removed from time to time, and an equivalent volume of fresh and artificial gastric juice was added. The efficiency of the antacid was followed by *p*H determinations. This method is a modification of the procedure due to Johnson and Duncan (*Quart. J. Pharm. Pharmacol.*, 1945, **18**, 251.); 10 commonly used antacid powders were compared, they included 2 preparations of aluminium hydroxide, aluminium dihydroxyaminoacetate, magnesium trisilicate, magnesium hydroxide, sodium bicarbonate, and several compound powders; the aluminium preparations appeared to be the antacids of choice, according to the above criteria. L. H. P.

Caronamide, Absorption and Elimination of. K. H. Beyer, E. K. Tillson, H. F. Russo, G. S. Schuchardt and S. R. Gass. (*J. Pharmacol.*, 1948, **94**, 167.) Caronamide is rapidly and completely absorbed when administered orally to dogs, as judged by the plasma levels and the overall urinary recovery of the drug and its metabolite(s). Some 43 per cent. of a given dose of caronamide is excreted within 4 hours after its administration, and urinary recovery is essentially complete within 24 hours. After oral or intravenous administration of caronamide to normal dogs, or intravenous administration to bilaterally nephrectomised dogs, a portion of the drug is metabolised. About 60 per cent. of a dose of the drug administered to normal dogs is excreted as such, the remaining 40 per cent. being excreted in the form of an unknown metabolite or metabolites more soluble than the parent compound. The distribution of caronamide in the body is of the same order as, but greater than, that for mannitol, the volume distribution approximating extracellular water. S. L. W.

Diatrin, Toxicologic and Antihistaminic Properties of. N. Ercoli, R. J. Schachter, W. C. Hueper and M. H. Lewis. (*J. Pharmacol.*, 1948, **93**, 210.) N.N'dimethyl-N'phenyl-N'2(thienylmethyl)ethylenediamine hydrochloride (W-50) is an analogue of antergan and of W-53, another thienyl derivative, which have already been reported to possess definite antihistamine properties. The authors found it to be better tolerated in mice, rats, rabbits, guinea pigs, cats and dogs than pyribenzamine, neoantergan, benadryl, antergan, and W-53. Depending on the route of administration, its average lethal dose is $1\frac{1}{2}$ to 4 times higher than that of the others. Its comparative tolerance is even greater on the basis of convulsive dose. The normal weight gains, and the absence of pathological findings in the organs of animals treated for long periods with diatrin, are further indications of the relative non-toxicity of the drug. The pharmacological action of diatrin (toxic symptoms, lowering of blood pressure, increase of respiratory rate) is similar to that of other ethylenediamine derivatives. Its therapeutic index is high, particularly by the oral route (300-1200); by subcutaneous administration the index is 40 to 80 in anaphylactic shock, and 800 in histamine asthma. S. L. W.

Methyl Fluoroacetate (M.F.A.), Toxicity and Pharmacology of. G. L. Foss. (*Brit. J. Pharmacol.*, 1948, **3**, 118.) The toxicity by mouth and subcutaneous injection has been determined for a variety of animals. There is considerable variation of dosage from 0·1 mg./kg. in the dog to 10 to 12 mg./kg. in the monkey, and the order of decreasing susceptibility is: dog, guinea-pig, cat, rabbit, goat, and probably horse, rat, mouse and monkey. It is thus more toxic than strychnine or nicotine, and is one of the most poisonous substances known. Lethal concentrations in food, water or milk were not detected either by smell or taste, even by animals such as the cat or dog. In most animals it acts as a convulsant poison and causes progressive depression of respiration. It is toxic by mouth, by injection, and by inhalation, but not when applied to the skin. The convulsive pattern is considered similar to that of leptazol; like leptazol, it acts on the whole central nervous system, but the higher centres are more sensitive than the lower. It stimulates the rate and volume of respiration, and then causes failure of respiration, probably central in origin. Blood pressure is little affected by small doses, but very large doses have a nicotine-like action. It presents a serious hazard as a food and water contaminant if used as a poison for rodents and other vermin. The author suggests the following lines of treatment for poisoning in man: early intravenous injection of a rapidly-acting barbiturate such as pentothal sodium, intramuscular injection of a more prolonged acting cortical depressant such as phenobarbitone sodium, careful supervision of respiration supplemented by oxygen therapy and/or artificial respiration, the possible use of intravenous hypertonic glucose as in status epilepticus, and careful use of tubocurarine to control convulsions. S. L. W.

Miracil D. Toxicology, Absorption and Excretion. F. Hawking and W. F. Ross. (*Brit. J. Pharmacol.*, 1948, **3**, 167.) Miracil D is the hydrochloride of 1-methyl-4-β-diethylaminoethylaminothioxanthone, and has been devised for the treatment of schistosomiasis (bilharziasis). It is a crystalline, orange-yellow powder, soluble up to 1 to 2 per cent. in water at room temperature. It has an irritant action when applied locally to the tissues, and subcutaneous or intramuscular injection causes considerable inflammation and some necrosis. Intravenously it is much more toxic than when given by

mouth and it tends to cause thrombosis of the vein. Oral administration is therefore preferred. Rabbits tolerate repeated daily doses of 50 mg./kg. by mouth, and monkeys tolerate 200 mg./kg. 4 times a week. Its behaviour after oral administration was examined in 6 volunteers. It appears to be rapidly absorbed from the alimentary canal, and after single doses of 0·2 g. the concentration in the blood rises to about 1 mg./litre at 2¼ hours. Over 90 per cent. of the drug absorbed is broken down in the body and only about 7 per cent. is excreted in the urine. There is little tendency for the drug to accumulate in the body. When the drug is stopped it disappears from the blood in 2 or 3 days and ceases to appear in the urine after 3 days. In animals prolonged overdosage may produce degenerative changes in the liver and the renal tubules, but these are often only slight. In volunteers, the maximum tolerated dose for repeated administration was about 0·2 g. per day. Overdosage produced nausea, prostration, tiredness and headache; insomnia, and yellow discoloration of the skin and sclerotics also occurred, and the urine was bright yellow. The symptoms, which are unpleasant rather than dangerous, do not appear until after a latent period of 18 to 24 hours. It was later found that patients can tolerate 0·6 g. or more daily without severe ill-effects. S. L. W.

Penicillin: Suspension with Adrenaline. N. Ercoli, W. C. Hueper, L. Landis, M. M. Lewis and B. S. Schwartz. (*Amer. J. med. Sci.*, 1948, **215**, 498.) A notable increase in penicillin blood level duration occurs on the addition of small doses of adrenaline to an oily suspension. The preparation suggested for human use consists of a suspension of 300,000 units of crystalline potassium penicillin in 1 ml. of vegetable oil containing 0·3 mg. of adrenaline. The suspension can be injected with a 20 or 21 gauge needle. The systemic vasopressor activity of adrenaline is diminished by the oil, so that only one-twentieth to one-fortieth of the therapeutic dose is necessary to prolong penicillin levels. Observations are detailed of numerous experiments on dogs, man, rabbits and rats. Blood-level curves indicated that following administration of penicillin in oil containing vasoconstrictor the duration of the blood-level increases proportionately up to only a certain penicillin dosage. This ceiling dosage is approximately 200,000 units for the dog and 300,000 units for man, and in both cases gives a one-day level. It was noted that compared with one-day duration of blood-levels the urine of subjects treated contained penicillin up to 2½ to 3 days. In experimental animals it was found that administration of this preparation gives considerably longer durations in the organs than in the blood. It is assumed that the improved therapeutic activity depends on the prolongation of the penicillin content in the organs and on the initial levels in the blood. Mice infected intraperitoneally with 1000 lethal doses of pneumococcus were almost all protected by prophylactic treatment with 500 units/20g. injected subcutaneously in 0·5 ml. of oil containing 0·06 mg. of adrenaline 3 hours earlier. An aqueous solution of penicillin gives no protection in doses of 2000 units/20 g. H. T. B.