ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

Achilleine, Alkaloid of *Achillea millefolium* L. F. M. Miller and L. M. Chow. (*J. Amer. chem. Soc.*, 1954, **76**, 1353.) From the yarrow plant, *Achillea millefolium* L., a crystalline alkaloid, achilleine, $C_{14}H_{26}N_2O_6$, m.pt. 247 to 248° C., $[\alpha]_D$−14·3° (water, *c* 10) was isolated. It is weakly basic, gives positive, but non-reproducible, results in the *N*-methyl determination, and contains no methoxyl group. It is very soluble in water, slightly soluble in ethanol, but almost completely insoluble in less polar solvents. On the basis of physical data and chemical evidence, achilleine is tentatively formulated as a glyco-alkaloid containing a pyrrolidine or piperidine nucleus bearing an *N*-methyl group and a carboxamide function. It was found to reduce the clotting time of blood in rabbits as determined by the Sabraze method. A. H. B.

***Rauwolfia serpentina*, A Preliminary Chemical Examination of.** W. L. Holt and C. H. Costello. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 144.) Extracts were prepared by percolation with a mixture of 10 parts of acetone and 90 of ethanol, 2 per cent. of strong solution of ammonia being added for the preliminary maceration, since this increased the potency of the extracts. Of 9 samples tested, Dehra Dun and Himalayan materials generally showed the greatest hypotensive action, Coastal Plain and Bihar being about half and Malabar 1/5th as potent. Coastal Plain and Malabar varieties were adulterated with another species of *Rauwolfia*. The total alkaloidal content as determined by the B.P.C. 1949 method did not run parallel with hypotensive activity, because of variations in the proportions of the different alkaloids present. The best solvents for extraction of total alkaloids and hypotensive principles were found to be chloroform, acetone, and ethylene dichloride. A method of extraction of the alkaloids and separating them into main groups is described. G. B.

***Rauwolfia Serpentina* Benth. Isolation of δ-Yohimbine and a New Related Alkaloid from.** F. L. Weisenborn, M. Moore and P. A. Diassi. (*Chem. Ind.*, 1954, 375.) In addition to reserpine, δ-yohimbine (previously encountered only in *Coryanthe yohimbe*) and a hitherto undescribed related alkaloid were isolated from *Rauwolfia serpentina* Benth. After crystallisation of reserpine from a fraction containing the weakly basic constituents of the root, the mother liquors were chromatographed on acid-washed alumina. Elution with 1:9 ether-benzene gave a new alkaloid $C_{22}H_{26}O_4N_2$, m.pt 240 to 241° C. The alkaloid δ-yohimbine, was obtained by further elution of the column with 1:1 ether-benzene, and was shown to be identical with py-tetrahydroserpentine (mixed m.pts., ultra-violet and infra-red spectra). A. H. B.

ANALYTICAL

Gitoxin, Fluorimetric Determination of. J. F. A. Fruytier and J. A. C. van Pinxteren. (*Pharm. Weekbl.*, 1954, **89**, 99.) The method of Jensen (*Acta pharm. tox., Kbh.*, 1952, **8**, 101) for the fluorimetric determination of gitoxin uses as reagent a mixture of hydrochloric acid and glycerol. The method can

not however be applied satisfactorily to a mixture of digitalis glycosides as the material is not sufficiently soluble in the solvent. More satisfactory results are obtained by using a mixture of 5 volumes of hydrochloric acid (38 per cent.), 5 of glycerol and 1 of ethanol. The fluorescence is measured after 1 hour. Digitoxin does not interfere with the determination. By this method it was possible to demonstrate the presence, in commercial digitoxin, of quantities up to 15 per cent. of gitoxin. For determination in digitalis, the drug was first treated by the method of Langejan and van Pinxteren (*Pharm. Weekbl.*, 1953, **88**, 529). Of the mixture of glycosides and genins obtained in this way from 1 g. of leaf, dissolved in 50 ml. of ethanol (24 per cent.), 5 ml. was evaporated cautiously and the residue dissolved in 20 ml. of ethanol (96 per cent.): 1 ml. of this solution was mixed with 10 ml. of hydrochloric acid-glycerol mixture, shaken vigorously for 1 hour, and then compared with a standard gitoxin solution treated in the same way. Three successive determinations showed a content of 0·17, 0·16 and 0·16 per cent. of gitoxin (aglycone + glycoside). The total content of substances giving a colour with dinitrobenzoic acid was 0·24 per cent., calculated as digitoxin. Thus a large proportion of the glycosides belong to the gitoxin group. G. M.

Magnesium, Calcium, Zinc, Cadmium, Titanium and Zirconium, Spectrophotometric Titrations with Ethylenediamine tetra-acetic Acid. P. B. Sweetser and C. E. Bricker. (*Analyt. Chem.*, 1954, **26**, 195.) In an effort to extend the versatility of ethylenediamine tetra-acetic acid (versenate) as a volumetric reagent, the ultra-violet region of the spectrum was studied for use in the spectrophotometric determination of the end-point. A procedure is described for the determination of calcium, magnesium, cadmium and zinc in ammonia-ammonium chloride solutions; calcium in the presence of magnesium and cadmium in the presence of zinc. A method was developed for the determination of zirconium involving the addition of excess of versenate and back-titration of the excess with ferric iron solution. Versenate solutions as dilute as 0·001 M give a very sharp end-point even when the total volume of the solution being titrated exceeds 100 ml. A. H. B.

Morphine, Colorimetric Method for Quantitative Determination of. L. Szabolcs. (*Hungarian J. Chem.*, 1953, **59**, 67, *Through Hungarian Technical Abstracts.*) The reaction of morphine with potassium iodate in acid media serves as a basis for the colorimetric determination of morphine. After rendering the reaction mixture alkaline a stable colour was formed. The amount of morphine salt present can be measured photometrically since a linear relation exists between the colour intensity and concentration. Experimental procedure: to 4 ml. of the solution to be analysed (containing 1 to 4·5 mg. of morphine/ml.) one drop of a 10 per cent. solution of hydrochloric acid and 0·2 ml. of a potassium iodate solution (saturated at room temperature) was added. After 1 minute the colour intensity reaches its maximum, and then 0·2 ml. of a 10 per cent. solution of sodium hydroxide is added. Stand the solution for about 20 minutes, and make up to 25 ml. The colorimetric determination is made using a Pulfrich photometer with an S 50 filter. The extinction of 1 mg. morphine hydrochloride is 0·190 using a 30 mm. cuvette. Apomorphine, pyramidon and acetylsalicylic acid interfere with the determination. They can be eliminated by preparing a stock solution in the presence of bismuth subnitrate and subsequently filtering. J. R. F.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Castle's Intrinsic Factor, Isolation of. A. L. Latner, R. J. Merrills and L. C. D. P. Raine. (*Lancet*, 1954, **266**, 497.) The authors claim to have isolated the intrinsic factor of Castle from the hog gastric mucosa in a satisfactory pure state. It is mucoprotein in nature. The material was tested for activity in man by determining its effect on the fæcal excretion of radio-active vitamin B_{12} given orally. Details of the isolation are to be published shortly. From its behaviour in the ultracentrifuge it is shown to contain 5 per cent. of protein. The remaining 95 per cent. appeared to be homogenous and to have a molecular weight below 20,000. It is similar to a material previously obtained from human gastric juice by paper strip electrophoresis. G. F. S.

Glycyrrhetinic Acid, Metabolism of, in Human Subjects. V. M. v. Katwijk and L. G. Huis In't Veld. (*Nature. Lond.*, 1954, **173**, 733.) Using a method by which the urinary excretion of the acid, in amounts as small as 0·01 mg. per 24 hours, could be determined, none could be detected in the urine of a patient with Addison's disease who was treated with 2·28 g. of the acid orally every 24 hours. The urine of a patient with a jejunal ulcer who received 2·5 g. for 24 hours orally also failed to show a trace of this compound. The detection of possible catabolites of the acid was then considered, and it was found that after administration, extraction of the urine with butanol at 15° C. yielded a substance which gave a red colour with 71 per cent. sulphuric acid in methanol solution. Glycyrrhetinic acid itself does not give a colour. Of 20 samples of urine from patients not being treated with the acid 1 gave a positive result, and of 30 samples collected during treatment with the acid all gave a positive result. The red solution has an absorption maximum lying between 555 and 560 mμ as measured with a Beckman spectrophotometer. Work on the optimum condition for colour development and the isolation and identification of this possible catabolite is in progress. J. R. F.

***Mycobacterium tuberculosis*, Chromatographic Isolation of Polysaccharides from.** B. Siegel, G. A. Candela and R. M. Howard. (*J. Amer. chem. Soc.*, 1954, **76**, 1311.) An electrolytic extraction of the polysaccharides from the tubercle bacillus was devised. By this process, additional polysaccharides not present in the autolysate, were extracted. The polysaccharides were isolated by adsorption on silica gel and then elution with the following sequence of increasing polar solvents: hexane, chloroform, methanol and water. 12 different polysaccharide fractions were isolated from the autolysate from a human strain of *Mycobacterium tuberculosis* and 21 from the electrolytic extraction of the cells. Of these polysaccharide fractions, 19 had the ability to bind antibodies *in vitro*. All the 21 fractions gave typical polysaccharide absorption curves in the ultraviolet. A. H. B.

BIOCHEMICAL ANALYSIS

Chloramphenicol, Comparison of a Microbiological and a Chromatographic Assay Method for. T. Higuchi, A. D. Marcus and C. D. Bias. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 135.) Preparations of chloramphenicol were assayed by chromatographic separation of the antibiotic followed by measurement of the ultra-violet absorption of the chloroform-ethyl acetate solution at

278 mμ. Good recoveries were achieved and the results were in agreement with those of microbiological assays based on the inhibition of the oxygen uptake of *Escherichia coli*. The assay was carried out by dissolving a sample in chloroform containing 10 per cent. of ethyl acetate. 5 ml. was placed on a silicic acid column with water as the internal phase. Chloroform was passed through the column until about 40 ml. of eluate containing impurities less polar than chloramphenicol had been obtained. The solvent was changed to chloroform containing 10 per cent. of ethyl acetate and this fraction, containing chloramphenicol was collected for spectrophotometric analysis. This method is applicable to samples containing a fraction of a mg. of chloramphenicol, but needs modification before it can be used for quantities of a few μg. G. B.

Lead in Blood, Determination of, with Dithizone. M. Mokranjac and S. Radmić. (*Acta Pharm. Jug.*, 1953, **3**, 253.) The determination of small quantities of lead in blood using dithizone is inconvenient because of the presence of iron and the formation of a yellow colour which masks that of the normal colour of lead dithizonate. The following method is suggested. Place 10 ml. of blood in a 150-ml. beaker to which 10 ml. of concentrated nitric acid and 0·25 ml. of concentrated sulphuric acid are added. Heat carefully until nearly all the nitric acid has been driven off. Cool a little, and add 5 ml. of nitric acid and repeat the heating. Then add a further 5 ml. of the acid and heat until sulphur trioxide is formed. Cool, add 1 ml. of 30 per cent. hydrogen peroxide, heat carefully until the peroxide has evaporated, and repeat the addition and evaporation of peroxide 3 or 4 times. A whitish residue is left which is then heated to remove all the sulphur trioxide. Cool, add 1 ml. of a 1 : 1 mixture of hydrochloric and nitric acid, and heat until almost dry. Add 5 ml. of 50 per cent. hydrochloric acid, and to the cooled solution in a separator introduce 10 ml. of ether. Shake well to allow the iron to pass into the ether, separate and then evaporate the solution to dryness. Add 2 ml. of water, heat to boiling, and after the addition of 5 ml. of a 20 per cent. citric acid solution, cool, and introduce 2 to 3 drops of thymol blue (in 0·25 per cent. ethanol) and ammonia to *p*H 9·2 (colour changing to blue). Then add 3 ml. of a 10 per cent. solution of potassium cyanide and 10 ml. of a solution containing: 15 ml. of a 10 per cent. potassium cyanide solution, 5 ml. of concentrated ammonia, 15 ml. of a 20 per cent. citric acid solution, and water to 100 ml. Shake 5 ml. of dithizone solution (5 mg. per cent. in carbon tetrachloride) with the solution in a separator for 5 minutes. Run off the carbon tetrachloride solution into another separator and repeat the extraction using 3 ml. of dithizone solution each time until its green colour changes. Remove excess dithizone from the mixed solutions with 1 in 300 ammonia. Filter into a 10 or 25 ml. graduated flask, and make up to the mark with carbon tetrachloride. This solution is now ready for spectrophotometric or electrophotometric determination. It is necessary to make a calibration curve for the instrument used. The error calculated after many analyses varied between 1·1 and 4·3 per cent. J. R. F.

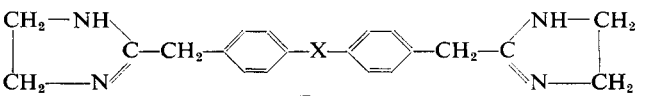
Penicillin in Feeding Stuffs, Assay of. S. A. Price and K. A. Boucher. (*Analyst*, 1954, **79**, 150.) A paper disc plate method, developed from the procedure of Esposito and Williams (*Proc. Soc. Exp. Biol. N.Y.*, 1952, **81**, 660), is described for the assay of penicillin in feeding stuffs, using *Bacillus subtilis* as the test organism. The standard solution is prepared by dilution in methanol of a buffered aqueous solution of sodium benzylpenicillin, final dilutions for assay

being made in an unfortified extract of the feeding stuff under test. Feeding stuffs were extracted with methanol and the solutions were taken up on paper discs, the dried discs being applied to the medium in a randomised Latin square assay design. With the method as described, the limits of error (P = 0·95) were of the order of 90 to 111 per cent. in an 8 × 8 assay of two samples with 8 replicates per dose, or 85 to 117 per cent. if four samples were used and the number of replicates reduced to 4. Both sodium benzylpenicillin and procaine benzylpenicillin were found to be unstable when dissolved in aqueous methanol, unless phosphate was present. R. E. S.

"Strepogenin," Determination of, with *Lactobacillus bifidus*. P. Roine, H. Gyllenberg and V. Salakivi. (*Acta. chem. scand.*, 1954, **8**, 161). An assay process for strepogenin based on the fact that it is an essential growth factor for certain strains of *Lactobacillus bifidus* is described. Its effect on this organism is specific at least in that asparagine and glutamine have no activity. The use of this test organism has the following further advantages: the blank values are always very small, the growth response is pronounced, and the basal medium is very simple. Figures for the strepogenin-activities of 13 different preparations are given, using peptonised milk as the strepogenin standard. A. H. B.

CHEMOTHERAPY

Theophylline Derivatives, Bifunctional, and Corresponding Iminazolines. G. P. Hager and C. Kaiser. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 148.) A series of iminazoline derivatives of type I were prepared (X = –O–, $-CH_2.CH_2-$, $-O(CH_2)_3O-$, and $-O(CH_2)_5O-$) by fusion of the corresponding dinitriles with ethylenediamine *p*-toluenesulphonate. Another bifunctional analogue of tolazoline, 1:5-bis(2-methylene-3-iminazoline) naphthalene, which is also related to naphazoline, was prepared, and appeared to be the most active compound.



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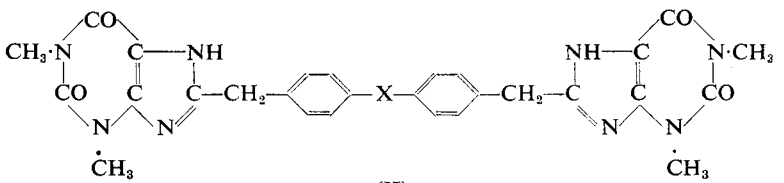

(II)

These substances lowered the blood pressure of dogs, but only when administered in doses which inhibited respiration. Compounds of type II were obtained by fusion of the dicarboxylic acid with 1:3-dimethyl-5:6-diaminouracil and cyclisation with sodium hydroxide, or by refluxing with phosphorus oxychloride. These bifunctional analogues of 8-benzyltheophylline produced an effect on blood pressure similar to that of the parent substance but had the disadvantage of limited solubility in water. G. B.

PHARMACY

GALENICAL PHARMACY

Bacitracin, Stability of Solutions of. V. Würtzen. (*Dansk Tidsskr. Farm.*, 1954, **28**, 34.) Bacitracin, although a polypeptide containing cysteine, does not give any reaction with nitroprusside, with or without the addition of cyanide. Old solutions however react with nitroprusside in presence of cyanide, indicating the presence of a disulphide group. The deterioration of solutions appears to be a process of oxidation initiated by light. Neither nordihydroguaiaretic acid, ascorbic acid nor hydroquinone were effective in preventing the loss of strength of solutions of bacitracin when exposed to diffused daylight. By replacement of the air by nitrogen, a solution may be kept in diffused light for 3 months with a loss in activity not greater than 10 per cent. A certain amount of antioxidant action was shown by *p*-phenylenediamine and *p*-aminophenol. G. M.

Cyanocobalamin and Ascorbic Acid, Stability of, in Liquid Formulations. A. Bartilucci and N. E. Foss. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 159.) The effects of *p*H and of various added chemicals were studied in solutions containing 10 μg. of cyanocobalamin and/or 50 mg. of ascorbic acid per ml., containing 0·05 per cent. of propyl 4-hydroxybenzoate as preservative. The maximum stability of ascorbic acid and ascorbic acid/cyanocobalamin solutions occurred at *p*H 6·0 to 7·0, but solutions of cyanocobalamin alone were most stable at *p*H 4·5 to 5·0. Tetrasodium ethylenediamine tetra-acetate had a stabilising effect on ascorbic acid solutions, and slightly improved the keeping properties of ascorbic acid/cyanocobalamin solutions stored at 40° C. This substance was harmful to cyanocobalamin solutions, unless acidified. Ascorbic acid appeared to be most stable in solutions containing high concentrations of propylene glycol with water, glycerol or D-sorbitol solution. In mixed ascorbic acid/cyanocobalamin solutions, a vehicle consisting of equal quantities of propylene glycol and glycerol gave maximum stability, there being no loss of cyanocobalamin and about 10 per cent. loss of ascorbic acid after 6 months' storage at room temperature. It appears that the products of the decomposition of ascorbic acid play an important part in the destruction of cyanocobalamin. G. B.

NOTES AND FORMULÆ

Nitrofurantoin (Euradantin). (*New and Nonofficial Remedies, J. Amer. med. Ass.*, 1954, **154**, 339.) Nitrofurantoin is *N*-(5-nitro-2-furfurylidene)-1-aminohydantoin and occurs as a yellow bitter powder with a slight odour; it decomposes at 258° to 262° C., and is very slightly soluble in ethanol and almost insoluble in ether and water. It dissolves in sodium hydroxide solution to give an orange-red colour. A 0·0005 per cent. solution prepared with dimethylformamide and water exhibits ultra-violet absorption maxima at about 266 and 368 mμ ($E^{1\text{ per cent.}}_{1\text{ cm.}}$ about 753) and a minimum at about 305 mμ; the ratio of the absorption at 368 mμ to that at 266 mμ is 1·26 to 1·46. When dried at 105° for 5 hours, nitrofurantoin loses not more than 1·0 per cent. of its weight; sulphated ash, not more than 0·05 per cent. It contains 95·0 to 105·0 per cent. of nitrofurantoin and is assayed by measuring the absorption of a 0·0005 per cent. solution at 368 mμ. Nitrofurantoin is useful for the treatment of bacterial infections of the urinary tract. G. R. K.

PHARMACOLOGY AND THERAPEUTICS

Adenosine 5-Monophosphate, Treatment of Calcific Tendinitis with. A. M. Susinno and R. E. Verdon. (*J. Amer. med. Ass.*, 1954, **154**, 239.) A total of 36 patients with chronic calcific tendinitis of the shoulder were treated with intramuscular injections of 20 mg. of adenosine 5-monophosphate given daily or on alternate days in 1 ml. of gelatin solution. Thirteen controls were given 1 ml. of either saline solution or gelatin solution. Results were evaluated on loss of pain and significant improvement in abduction, rotation or elevation of the arm. 31 of the 36 patients gave satisfactory responses with 3 to 14 injections (average 9 injections). There were 6 recurrences in this group; four were given a further course of treatment, with similar results, while in the other two the recrudescence was so mild that further treatment was considered unnecessary. Of the controls, one responded to saline solution. 10 of the others did not respond after an average of 16 injections but responded promptly to adenosine 5-monophosphate. No severe reaction of any kind was encountered with intramuscular administration of the drug. A number of patients reported diuresis, flushing, or a slightly painful site of administration. Almost half the cases exhibited an apparent "flare-up" of symptoms and disability in the fifth to tenth day of treatment, followed in a day or two with a notable overall improvement. An additional 17 patients were similarly treated and 13 of these gave satisfactory results. G. R. K.

Adrenaline and Noradrenaline, Comparative Effects of, in the Dog. R. Ahlquist, J. Taylor, C. Rawson and V. Sydow. (*J. Pharmacol.*, 1954, **110**, 352.) In this paper relative potencies of adrenaline and noradrenaline are determined and the results analysed statistically. The test preparations used are the arterial blood pressure, heart rate, renal and femoral blood flow, splenic contraction and intestinal activity of dogs, anæsthetised with sodium pentobarbitone.

Noradrenaline was found to be significantly more effective than adrenaline as a pressor agent and in producing vagal bradycardia whereas adrenaline was found to be significantly more effective in producing splenic contraction, intestinal relaxation and vasoconstriction in the femoral and renal vascular beds. M. M.

Adrenaline and Noradrenaline in Separate Adrenal Medullary Cells. N. Hillarp and B. Hökfelt. (*Acta. physiol. scand.*, 1953, **30**, 55). A method is described for the cytological differentiation of noradrenaline from adrenaline in the adrenal medulla. Adrenal glands of the rat, guinea-pig, rabbit, cat, dog, cow, sheep, horse and domestic fowl are treated with 2·5 per cent. potassium iodate in acetate buffer at *p*H 6, when the noradrenaline in the gland is converted into insoluble brownish-black granules. Under these conditions adrenaline does not form an insoluble pigment. Both amines can be demonstrated by treatment with 2·5 per cent. potassium bichromate at *p*H 5·6 when adrenaline and noradrenaline give brown pigments. No method has yet been found for the selective cytological demonstration of adrenaline. By these methods it is shown that 5 to 15 per cent. of the medullary cells in the rat, 20 to 50 per cent. in the cat, 15 to 30 per cent. in the cow and 10 to 40 per cent. in the dog, sheep and horse show an intense noradrenaline reaction, while in the guinea-pig and rabbit there is no noradrenaline pigmentation. These figures agree well with biological and chemical estimates of the noradrenaline content of the glands. Noradrenaline is therefore apparently selectively stored in certain specific cells of the adrenal

medulla. This cytological selectivity suggests that noradrenaline is not only a precursor of adrenaline but also an independent hormone. M. M.

Anticholinesterases, Pharmacology of Some New. F. H. Shaw and G. A. Bentley. (*Aust, J. exp. Biol. Med. Sci.*, 1953, **31**, 573.) The anticholinesterase activity of some acridine, pyridine and thiazole derivatives was estimated manometrically. The modifications of the actions of acetylcholine on the isolated frog rectus abdominis, the Straub amphibian heart and isolated mammalian intestine and uterus by the compounds were also determined. There was some correlation of anticholinesterase activity and pharmacological effects in those derivatives showing a high degree of cholinesterase inhibition (e.g., the 2–, 3–, 4– and 5– aminoacridines), but this was not uniform throughout the range of test preparations and on the amphibian hearts especially some of the compounds had an atropine-like action. Also, others of the series having no anticholinesterase activity showed on some preparations a potentiation of the effects of acetylcholine. The significance of these results is discussed. G. P.

Carotid Body and Sinus, Effect of Drugs on. C. Heymans, A. L. Delaunois, L. Martini and P. Janssen. (*Arch. int. Pharmacodyn.*, 1953, **96**, 209). The effects of some cholinomimetic and cholinolytic drugs on the chemoreceptors of the carotid body and on the baroreceptors of the carotid sinus have been reinvestigated by the authors, since much of the work in this field has produced conflicting results. The technique adopted was that of Heymans *et al.* (Heymans *Actualités Pharmacologiques*, 5e serie, 1952, p. 111, Paris) and was conducted on dogs under morphine and chloralosane anæsthesia. Femoral arterial blood pressure, thoracic movements and respiratory volume were recorded. Injections of acetylcholine, lobeline and potassium cyanide were made through the thyroid artery into the common carotid circulation, all efferent branches of the carotid bifurcation except the occipital arteries supplying the carotid bodies being tied off. All other drugs were injected either intravenously or into the conjunctival space surrounding both carotid body and sinus areas. Positive significance to results was attributed only where changing one factor resulted in practically 100 per cent. change in response or where a dose-response relationship was clearly demonstrable. Local application of neostigmine to the carotid body and sinus induced moderate respiratory stimulation whereas eserine had no such action when applied similarly. Both drugs increased the sensitivity of the chemoreceptors to acetylcholine markedly, and sensitivity to lobeline slightly. Eserine also increased slightly the sensitivities of the chemoreceptors to potassium cyanide. Neither drug affected baroreceptor sensitivity to change in blood pressure. Intravenously, large doses of atropine did not affect responses of the chemoreceptors to acetylcholine, lobeline or potassium cyanide, but local application of similar doses to the carotid body, besides causing a rise in blood pressure blocked the action of these drugs on the chemoreceptors. Local application of small doses had no effect on either the chemoreceptor or baroreceptor sensitivity. Intravenous doses of tetraethylammonium, hexamethonium, methantheline, or pendiomide had no significant effect on chemoreceptor stimulation by acetylcholine, lobeline and potassium cyanide. Similarly local application of these ganglion-blocking agents did not modify either chemoreceptor response to the three stimulants or baroreceptor sensitivity to blood pressure variation. Some of the results are therefore at variance with those of other workers and do not support the suggestion that acetylcholine is the chemical mediator of carotid body chemoreceptor or carotid sinus barorec eptor activity G. P.

Demyelination. J. B. Cavanagh and R. H. S. Thompson. (*Brit. med. Bull.*, 1954, **10**, 47.) The series of changes involving the break-up and loss of the myelin sheath of the nerve fibre, either in peripheral nerves or in the central nervous system, constitutes one of the standard reactions to injury exhibited by nervous tissue, and occurs in a wide variety of different types of injury. From a survey of the various means by which demyelination can be brought about experimentally it appears that not only is it not yet possible to reproduce in laboratory animals the true counterpart of the lesions of disseminated sclerosis but that there is so far no clear idea as to the underlying biochemical mechanism in most of the experimental demyelinations. From the biochemical point of view four apparently dissimilar procedures can give rise to these lesions: (1) copper deficiency, (2) intoxication by cyanide, presumably acting by producing cerebral anoxia, (3) intoxication by certain of the anticholinesterases, and (4) deficiency of certain vitamins of the B complex, notably aneurine and cyanocobalamin. A further fact which has emerged from recent isotopic studies is that myelin is in a constant state of "turnover," with new formation balancing its disintegration, and it is possible that the complex set of synthetic reactions involved in this formation of myelin may become deranged. Indeed, it would seem more likely that the demyelination in anoxia or in aneurine deficiency would be due to a failure in endothermic synthetic processes. S. L. W.

Dextromethorphan Hydrobromide and Codeine, Quantitative Comparison of. L. J. Cass, W. S. Frederik and J. B. Andosca. (*Amer. J. Med. Sci.*, 1954, **227**, 291.) A statistical evaluation of the comparative antitussive activities of dextromethorphan hydrobromide, codeine and a placebo was conducted on 69 patients with varying degrees of cough. The dextromethorphan was given at three doses, 6, 12 and 18 mg., and codeine in a dose of 15 mg. The drugs were administered orally three times daily for seven days so that each patient had five drugs in 35 days. The drug sequence was allocated at random. Taking the placebo as being equivalent to zero dose of dextromethorphan, there was a good dose-response relationship for this drug. From this dose-response curve, 15 mg. dextromethorphan hydrobromide had an antitussive effect equal to that of 15 mg. codeine. There was, however, no significant statistical difference between 12 and 18 mg. of dextromethorphan hydrobromide or 15 mg. of codeine. On the other hand, the 6 mg. dose of dextromethorphan was significantly more effective than the placebo, and significantly less effective than 12 mg. dextromethorphan. The most suitable dose of the drug seems to lie between 10 and 15 mg. The incidence of side effects (nausea, vomiting, constipation and drowsiness) was much more marked with 15 mg. codeine than with any of the doses of dextromethorphan. G. P.

Histamine Analogues, Effect of on Cutaneous Pain. S. R. Rosenthal. (*Arch. int. Pharmacodyn.*, 1953, **96**, 220). The local anæsthetic activity of a series of 52 compounds related to histamine, including heterocyclic structures containing pyridine, pyridazine, pyrimidine, pyrazine, quinoxaline, quinoline, pyrazole, thiazole and imidazole nuclei, was determined by a guinea-pig weal method. A two per cent. solution of the drug was injected intradermally into the shaved skin of the guinea-pig to form a weal. The skin over the weal was stimulated electrically to obtain an axon reflex response and the duration of suppression of this reflex by the drug compared with one per cent. procaine solution injected similarly into an adjacent area. Twenty of the compounds showed some degree of local anæsthesia, 3 : 5 diphenyl 1-(β-aminoethyl) pyrazole, in particular, being much more effective than procaine. No strict correlation between local

anæsthetic activity and antihistamine activity was apparent. The pain-producing effect of some of the compounds was compared with that of histamine by intradermal injection in man, but only 2-methyl 4-(β-aminoethyl) imidazole approached the activity of histamine in this respect. The results further support the theory that histamine or a histamine-like substance may be the mediator for cutaneous pain. G. P.

Histamine, 5-Hydroxytryptamine and a Potent, Slow Contracting Substance, Presence of, in Wasp Venom. R. Jaques and M. Schachter. (*Brit. J. Pharmacol.*, 1954, **9**, 53.) Wasp venom contains three highly active smooth muscle stimulants—histamine, 5-hydroxytryptamine and a potent, slow-acting substance as yet unidentified. The presence of histamine was demonstrated chromatographically and by isolation using Code's method. These gave estimates for histamine content of 20 mg. and 16 mg., respectively, per g. of dried venom. 5-Hydroxytryptamine was identified chromatographically and the eluate from the corresponding chromatogram showed a content of 0·32 mg. per g. of dried venom. The third smooth muscle stimulant was demonstrated in presence of atropine and mepyramine on the guinea-pig ileum, after desensitisation of the ileum to tryptamine derivatives. This substance resembled bradykinin in that it withstood boiling at neutral—though not at high—*p*H, for long periods; it contracted the rat colon and was inactivated when the venom was extracted for histamine by Code's method. Also crude untreated wasp venom in a concentration of 3×10^{-7} will contract the guinea-pig ileum rendered unresponsive to histamine, acetylcholine and 5-hydroxytryptamine; bradykinin in similar conditions has a similar degree of activity. Crude wasp venom occasionally released histamine from the isolated perfused cat skin preparation. G. P.

Histamine—Effect of Intravenous Infusions of, on the Urinary Histamine and on Gastric Secretion in Man. H. M. Adam, W. I. Card, M. J. Riddell, M. Roberts and J. A. Strong. (*Brit. J. Pharmacol.*, 1954, **9**, 62.) The appearance of free histamine in the urine was compared with the rate of gastric acid secretion in three healthy male subjects after slow intravenous infusion of histamine acid phosphate. When the rate of infusion was sufficient to cause an increase in the acidity of the gastric juice there was a corresponding rise in urinary histamine. The threshold for the two effects varied from 7·4 to 13·0 ng./kg./min. With further increase in dose, the two secretions rose concomitantly. The proportion of free histamine excreted in the urine during the infusion was approximately one per cent. of the total dose and was independent of the rate of infusion. Free histamine also appeared in the gastric juice, where its concentration was similar to that in the urine, but more variable. Again the amount appearing was independent of the rate of infusion. Whether the histamine in the juice was derived from the plasma or from the gastric mucosa could not be determined from the results. The urinary free histamine would, however, seem from the evidence to be obtained from the plasma, although an increased plasma content could not be detected during the infusion, even when the dose was high. G. P.

4-Hydroxycoumarin, Metabolism of, in the Dog. S. Roseman, C. F. Huebner, R. Pankratz and K. P. Link. (*J. Amer. chem. Soc.*, 1954, **76**, 1650). The study of the fate of dicoumarol *in vivo* is difficult because only small continuous doses can be tolerated and therefore 4-hydroxycoumarin with about 1/20th the activity was chosen for study. When injected into the blood stream of the dog, approximately 75 per cent. appeared in the urine within 24 hours. The fate of the

remainder is unknown. No significant increase in the urinary output of the steam-distillable phenols or the ethereal sulphate fraction occurred and no salicylic acid was found in the urine. Approximately 50 per cent. of the 4-hydroxycoumarin injected appears in the urine in the free state and 25 per cent. as 4-hydroxycoumarin β-D-glucopyranosiduronic acid. Dilute acid hydrolysis of this latter compound formed *o*-hydroxyacetophenone. 4-Hydroxycoumarin underwent a similar degradation under similar conditions.

A. H. B.

Liver Residue, Protective Effect of, on Immature Male Rats Fed Toxic Doses of Acetylsalicylic Acid. B. H. Ershoff, H. B. McWilliams and E. W. Thurston. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 175.) Immature male rats, fed on a diet containing 0·5 per cent. of acetylsalicylic acid showed significant retardation of growth and reduction of the weight of the thymus, prostate and seminal vesicles, as compared with animals from whose diet the acetylsalicylic acid was omitted. These effects were largely counteracted by the administration of liver residue, the coagulated water-insoluble material remaining after the extraction of water-soluble matter. The factor protecting the animals against toxic doses of acetylsalicylic acid did not appear to be any known vitamin of the B group. It was not present in significant amounts in the purified casein which formed part of the diet of the rats. Possibly it is the same substance present in liver residue which has been observed to protect rats against the toxic effects of thyroid, thyroxine, mepacrine, cortisone etc. G. B.

Mercaptoethylamine; Failure to Protect against Mutagenic Effects of Radiation. W. D. Kaplan and M. F. Lyon. (*Science*, 1953, **118**, 777.) It has been shown that β-mercaptoethylamine gives protection against the lethal effects of radiation and produces a marked decrease in mortality when administered intraperitoneally to mice during the half hour preceding whole-body radiation. The object of these experiments, using *Drosophila melanogaster* and mice as test organisms was to determine whether this substance also protects against the mutagenic effects of radiation. The combined studies clearly indicate that mercaptoethylamine has no influence upon the genetic effects of radiation, nor does it protect the male germ cells against radiation death. These findings support those of other workers, suggesting that this substance exerts its protective action through the liver and that the primary effects of radiation on other organs are not prevented. S. L. W.

Nalorphine in the Prevention of Neonatal Asphyxia due to Maternal Sedation with Pethidine. S. J. Paterson and F. Prescott. (*Lancet*, 1954, **266**, 490.) Nalorphine, *n*-allylnormorphine, antagonises the pharmacological actions of morphine. It has been found effective in abolishing respiratory depression in the newborn infant due to the sedation of the mother with pethidine or 'omnopon'. After delivery the cord was not cut until the child had gasped and cried. If the child did not gasp within 10 secs. nalorphine 0·5 mg. in 2 ml. was injected into the umbilical vein. If the child did not cry within two minutes the dose was repeated. In the control series (262 babies), which did not receive nalorphine, 16 per cent. showed respiratory depression and resuscitation was necessary in 91 per cent. of these. In the test series (203 babies) 14 per cent. showed respiratory depression, and 80 per cent. of these gasped within half a minute of receiving an injection of nalorphine. The effects were striking in babies which were limp and asphyxiated before treatment. No ill effects from nalorphine were seen in any of the babies. It is suggested that nalorphine should permit the use of morphine, pethidine and related drugs nearer to the time of delivery. G. F. S.

Plasma Fractions in the Treatment of Injury. M. E. Mackay. (*Brit. med. Bull.*, 1953, **10**, 31.) In the treatment of injury by plasma proteins two groups of proteins are of major importance. These are fibrinogen and thrombin, which bring about coagulation of blood and prevent protein loss; and serum albumin which may be used in the treatment of trauma. The colloid osmotic pressure of serum albumin accounts for 80 per cent. of that of whole blood; 1 g. of albumin will hold 18 ml. of fluid in circulation. On this basis a standard dose of 25 g. of albumin, the considered equivalent of 500 ml. of citrated plasma, has been adopted by American workers. In traumatic shock doses of 25 g. of albumin may be given at 15 to 20 minute intervals. Blood should be given at the same time to correct anæmia, and saline if necessary for the dehydration. The place of albumin in hæmorrhagic shock is to tide the patient over while blood transfusion is arranged. Dramatic improvement has been obtained in patients with burns given albumin. Excessive doses of concentrated albumin may, however, cause pulmonary congestion and œdema, and it should not be given at or above a rate of 25 g./hour. Albumin has a low viscosity compared with plasma, and concentrated solutions are stable in aqueous media. A 25 per cent. w/v solution of albumin in 0·04 M acetyltryptophane may be heated for 10 hours at 60° C. thus destroying the causative agent of serum hepatitis. Fibrinogen and thrombin may be purified and concentrated, and these purified proteins, or materials manufactured from them, are used as hæmostatics. Fibrin clot, pressed into sheets and made plastic by heat or treatment with glycerol, is used in the repair of dural defects. Fibrin foam is made by whipping fibrinogen into a foam which is then converted to fibrin with thrombin, dried from the frozen state, and heated to 130° C. The sponge so formed is especially of value in neurosurgical operations; it is most useful in controlling capillary oozing and is efficacious in free venous bleeding, but less so in arterial bleeding. Mixtures of fibrinogen and thrombin have been used for sealing of small vessels in the cut surface of the lung and to reinforce pleural sutures over bronchial stumps. In skin grafting these mixtures are used as adhesives to hold the skin graft in place; vascularisation occurs in 3 days as compared with a month without the mixture, and there is less pigmentation than with pressure dressings. S. L. W.

Tuberculosis in Man, Chemotherapy of. N. D. D'Esopo. Report to the Council on Pharmacy and Chemistry. (*J. Amer. med. Ass.*, 1954, **154**, 52.) This report covers the 2-year period between January, 1951, and February, 1953; the number of persons reported on was 15,000, and the study was concerned almost exclusively with pulmonary tuberculosis. The use of streptomycin twice weekly and *p*-aminosalicylic acid daily is now considered the treatment of choice by most workers. The use of *p*-aminosalicylic acid alone is uncommon and undesirable. The use of dihydrostreptomycin has been largely discontinued, since experience has shown that it causes appreciably more deafness than the streptomycin. At present it is agreed that isoniazid should not be used alone in the treatment of pulmonary tuberculosis; the combined streptomycin and isoniazid regimen gives promise of being equally effective as streptomycin and *p*-aminosalicylic acid, but this has not yet been clearly established. Except for patients tolerating unusually high dosages, oxytetracycline would appear to be of low efficacy, but it is effective in delaying the emergence of resistance to streptomycin. Clinical trials of viomycin now in progress indicate that it may cause serious reactions and has only limited efficacy in pulmonary tuberculosis. Neomycin, mycomycin and erythromycin all appear to be ineffective.

(ABSTRACTS *continued on p.* 575).

alkaloids provides an excellent example of the use of conformational analysis, though the absence of any mention of these studies in connection with the sterioids is indeed surprising. Notable additions include complete sections on fluorohydrocarbons, the tropolones, penicillin, the chemistry of acetylenic compounds and such newer synthetic reagents as lithium aluminium hydride. The treatment of reaction mechanism from the standpoint of fundamental electronic theory has been given much greater prominence throughout the book than was the case in earlier editions. There is no doubt that in this, as in many other ways, the utility of an already much valued textbook has been considerably enhanced.

J. B. STENLAKE.

METHODEN DER ORGANISCHEN CHEMIE (Houben-Weyl). Volume II. Analytische Methoden. Fourth Edition. Edited by Eugen Müller. Pp. xxiv + 1070 (including 252 illustrations) and Index. Georg Thieme Verlag, Stuttgart, 1953. D.M. 139.00.

The second volume of the new fourth edition of Houben-Weyl is devoted entirely to the application of analytical methods in organic chemistry. An extensive introductory section deals with methods of elementary analysis, both qualitative and quantitative. As in the rest of the book, the treatment is comprehensive, giving experimental details for all the more important analytical methods. Semi-micro, micro and macro methods of analysis are described and the section concludes with a short account of ultra-micro methods. By far the greater part of the book is devoted to a first class survey of analytical methods available for estimating organic functional groups. The treatment is systematic and includes all the more important types such as carbon-carbon, hydroxyl, carbon-oxygen functions and functional groups containing nitrogen and sulphur.

The remainder of the book which constitutes Part II consists of five sections, each devoted to some specialised aspect of organic analysis. General gasometric methods of analysis are described, including both chemical and physical methods, together with a number of more specialised techniques for particular classes of gaseous product. The study of melting and freezing points, boiling points and condensation temperatures forms the subject of yet another of these specialist sections. Thermal analysis and chromatographic analysis are each accorded an individual section of the book. The treatment is both theoretical and practical. The latter section is excellent and detailed, and provides a wealth of valuable information in all branches of chromatography. The concluding section is devoted to the analytical control of solvents and the analysis of solvent mixtures. Throughout the book the bibliography is extensive, seemingly complete and up to date. There are many excellent diagrams of both conventional and novel pieces of apparatus. This new volume would be a most valuable addition to any library.

J. B. STENLAKE.

(ABSTRACTS *continued from p.* 573).

At present there appears to be no place for the thiosemicarbazones in the treatment of pulmonary tuberculosis except possibly as a last resort in patients who have failed to respond to all other antituberculosis drugs. S. L. W.

War Gases, Physiological and Biochemical Effects of. H. Collumbine. (*Brit. med. Bull*, 1954, **10**, 18.) Whether gross tissue damage (as by the vesicants) or dysfunction (as by the lethal agents) is produced, it appears that some biochemical disturbances may be the fundamental "key" action of the war gases. Thus, the visible skin damage caused by mustard gas and the nitrogen mustards is accompanied by metabolic changes in the skin, for example, inhibition of glycolysis, which has been shown to be due to the inhibition of

(ABSTRACTS *continued on p.* 576.)

LETTER TO THE EDITOR

Alkaloids of *Duboisia leichhardtii*

SIR,—I have read with interest the paper[1] by Rosenblum and Taylor. It seems very likely that their "Base B" is in fact similar to the "Base D" that I described[2]. This was isolated in 0·06 per cent. yield from a specimen of the drug containing 4·1 per cent. of total alkaloids, but differed from "Base B" in that it was optically inactive. Hence the authors' statement that I thought *d*-α-methylbutyryltropëine to be present is unfounded. I was able to prove that "Base D" consisted of tropine esters, but having less than 0·5 g. of the hydrobromide available, I did not succeed in identifying the acid produced on hydrolysis. It was evidently a mixture, and appeared to contain a valeric acid. By analogy with my earlier work on poroidine and *iso*poroidine[3] I suggested that *iso*valeric acid might be present, a suggestion that now seems to have been incorrect.

It is satisfactory that this problem now appears to have been solved, and I share the authors' interest in the isolation of a butyric ester alkaloid from a *Duboisia*, species of which have previously only yielded minor alkaloids that were esters of pentoic or pentenoic acids.

Stafford Allen & Sons Ltd., WM. MITCHELL.
London, N.1.
June 4, 1954.

REFERENCES

1. Rosenblum and Taylor, *J. Pharm. Pharmacol.*, 1954, **6**, 410.
2. Mitchell, *J. chem. Soc.*, 1944, 480.
3. Barger, Martin and Mitchell, *ibid.*, 1938, 1685.

(ABSTRACTS *continued from p.* 575.)

hexokinase. Hexokinase is an -SH enzyme and mustard gas attacks both the oxidised and the reduced forms. The mustard compounds can also produce other cellular changes. They can cause heritable mutations, can affect chromosome structure and can inhibit mitosis. The permeability of the local skin capillaries is altered within a few minutes, resulting in a loss of fluid and protein from the plasma so that local œdema occurs, the plasma volume and plasma protein content may fall and hæmoconcentration is produced. In addition serious damage is done to the hæmopoietic tissues, and these tissue changes are reflected by alterations in the cellular content of the blood. The whole metabolism of the bone marrow is depressed. Lewisite can also inhibit hexokinase, but there are differences in the gross pathology and the metabolic disturbances produced by lewisite and the mustard compounds, attributable to the presence of a tervalent arsenic atom in the lewisite molecule. Lewisite has a strong inhibitory action on the pyruvate oxidase system by combining with the SH groups in protein which are essential for the activity of this enzyme system. Dimercaprol, by forming stable ring compounds with lewisite, renders it relatively non-toxic and prevents it from inhibiting the pyruvate oxidase enzyme system. The lung irritants, such as phosgene, are, like the vesicants, able to produce profound shifts in body water merely by acting on the local exposed capillary vessels. The main toxic action of phosgene, however, is on the lung; the underlying mechanism of the effect on the lung capillaries is not known, but there is evidence that it may be enzymic in nature. The organophosphorus compounds produce their effects by inhibiting cholinesterase and so allowing acetylcholine to accumulate peripherally at cholinergic nerve-endings and possibly centrally in the brain and spinal cord, the body thus poisoning itself by its own production of acetylcholine.