ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

Canescine, Isolation and Structure of. M. W. Klohs, F. Keller, R. E. Williams and G. W. Kusserow. (*J. Amer. chem. Soc.*, 1955, 77, 4084.) Canescine ($C_{32}H_{38}O_8N_2$), a new alkaloid, was isolated from the crude reserpine fraction obtained from the roots of *Rauwolfia canescens* by the application of chromatography using acid washed alumina as the adsorbent. On rapid crystallisation from methanol it was obtained as fine needles whereas slow crystallisation yielded prisms, both forms melting at 232–234° C., $[\alpha]_D^{24}$ $-138 \pm 2°$ (*c* 1·0 in chloroform). Ultra-violet data is recorded. On basic hydrolysis with dilute methanolic sodium hydroxide, canescine yielded canescic acid and one molecule of 3 : 4 : 5-trimethoxybenzoic acid. Selenium dehydrogenation of methyl canescate yielded yobyrine. A tentative structural formula for canescine is proposed. The new alkaloid has the same order of sedative activity as reserpine and hypotensive activity comparable to reserpine and rescinnamine.

A. H. B.

***Datura innoxa*, New Alkaloid From.** E. Steinegger and F. Gessler. (*Pharm. Acta Helvet.*, 1955, **30**, 279.) Paper chromatography of the alkaloids from the root of *Datura innoxa* Miller indicated the presence of an alkaloid with an R_F of 0·9. This was obtained only from plants in the later stages of development. The base had m.pt. of 44° to 46° C., and the picrate 77° to 78° C.

G. M.

Recanescine, a New Sedative Principle of *Rauwolfia canescens* Linn. N. Neuss, H. E. Boaz and J. W. Forbes. (*J. Amer. chem. Soc.*, 1955, 77, 4087.) Recanescine ($C_{32}H_{38}O_8N_2$) was isolated by chromatography of the mother liquor from crystallisation of reserpine on acid-washed alumina using benzene as eluent. Hydrolysis of the alkaloid yielded 3 : 4 : 5-trimethoxybenzoic acid and methyl recanescate, characterised as a tosyl ester. Reductive cleavage of recanescine gave recanescic alcohol and 3 : 4 : 5-trimethoxybenzyl alcohol. Infra-red and ultra-violet data are given; from this and other evidence the structure of recanescine as 11-desmethoxyreserpine is suggested. Recanescine has the same pharmacological properties as reserpine in monkeys and rabbits (sedation, myosis and ptosis) and anæsthetised cats and dogs (blood pressure lowering, apparent enhancement of the pressure response to adrenaline and inhibition of blood pressure response to bilateral carotic occlusion).

A. H.B.

ANALYTICAL

Aneurine and Riboflavine, Estimation of. K. V. Giri and S. Balakrishnan. (*Analyt. Chem.*, 1955, **27**, 1178.) Circular paper chromatography is used for the separation and estimation of aneurine and riboflavine in multivitamin preparations. Solutions containing the vitamins were spotted on the circumference of a 2·2-cm. circle at the centre of an 18-cm. Whatman No. 1 paper. While still damp, the paper was exposed for about 20 minutes to the vapours of cyanogen

bromide and ammonia contained in two petri dishes; when dry it was removed, and a cylindrical paper wick was placed at its centre. It was then developed using 1-butanol-acetic-acid-water until the solvent boundary had run almost to the edges of the circle, when the chromatogram was removed, air-dried, and observed under ultra-violet light. The fluorescent bands of thiochrome and riboflavine, which showed distinctly on the chromatogram, were cut and eluted with 6 ml. of water and shaken in extraction cylinders. The fluorescence of the solutions was measured in a Klett fluorimeter against water blanks using the necessary filters for aneurine and riboflavine. Standard curves for amounts of vitamins ranging from 0·56 to 2·24 μg. were linear and replicate determinations gave a reproducibility of about 10 per cent. The thiochrome band was stable on the paper but the riboflavine began to deteriorate after 14 days. Good recoveries were obtained in the analysis of multivitamin preparations. R. E. S.

Atropa Alkaloids, Colorimetric Determination of. F. M. Freeman. (*Analyst*, 1955, **80**, 520.) An experimental study has been made of the Vitali Morin colour reaction between acetone and aromatic nitro-compounds in the presence of sodium hydroxide. With acetone or pyridine as the solvent, and ethanolic potassium hydroxide as the base, the colour stability was poor, being critically dependent on the water content of the reaction mixture. Sodium methoxide in benzene-methanol was found to be superior to ethanolic potassium hydroxide but the most promising results were obtained by the use of tetraethylammonium hydroxide with dimethylformamide as the solvent. In the final procedure 0·05 to 0·15 mg. of the alkaloid was nitrated with 0·2 to 0·3 ml. of fuming nitric acid and, after evaporation, 0·3 ml. of 25 per cent. aqueous tetraethylammonium hydroxide and dimethylformamide were added. After setting aside for 5 minutes the extinction at 540 mμ was measured. Graphs of colour stability and times are given for two hyoscyamine solutions; reaction mixtures containing up to 10 per cent. of water showed little change in the rate of fading compared with mixtures containing below 0·1 per cent. The reaction was also applied successfully to the determination of phenylacetic acid, benzylpenicillin and dibenzylethylenediamine penicillin. R. E. S.

Copper in Plant Materials, Determination of. S. Andrus. (*Analyst*, 1955, **80**, 514.) A method is described for the rapid absorptiometric determination of copper in plant materials. Organic matter is destroyed by digestion for 30 minutes with sulphuric, nitric and perchloric acids until colourless followed by heating to fuming with hydrogen peroxide (100 volume). The copper, after dilution of the acid solution, is extracted with a solution of zinc dibenzyldithiocarbamate in carbon tetrachloride, and the extinction measured at a wavelength of 440 mμ against a blank determination; the amount of copper present is obtained from a standard curve prepared using a solution of copper sulphate. The method was free from interference by other metals commonly present in plants and amounts of copper varying from 10 to 40 μg. were satisfactorily recovered in the presence of 1000 μg. quantities of iron, cobalt, manganese and molybdenum. A study of the digestion procedure showed that there was no loss of copper and in experiments in which 5·0 p.p.m. copper were added, amounts varying from 4·9 to 5·3 were recovered. R. E. S.

Hydrocortisone, Determination of. C. R. Szalkowski, M. G. O'Brien and W. J. Mader. (*Analyt. Chem.*, 1955, **27**, 944.) A method is given which is based on the yellow colour produced by hydrocortisone in a mixture of sulphuric and glacial acetic acids; the colour, with a maximum absorption at 470 mμ can,

be used for the identification and colorimetric determination of hydrocortisone when mixed with cortisone, and in preparations. The colour produced by hydrocortisone in sulphuric acid showed a maximum at 390 mμ and a broad band between 445 and 475 mμ; the addition of glacial acetic acid produced a lower 390 mμ maximum with a peak at 470 mμ. All absorptions were measured after 1 hour. The test distinguished between hydrocortisone and cortisone since with cortisone the absorption at 470 mμ was negligible. The absorption values for 30 additional steroids in sulphuric acid and in sulphuric/acetic acids are recorded. Hydrocortisone, corticosterone, 21-hydroxypregnanetrione-3:11:20-œstradiol, œstrone, and stilbœstrol produce a fluorescent yellow colour with the mixed acid reagent suggesting that the fluorescence reaction can be used for identification purposes. A procedure for the determination of hydrocortisone in ointments is given; for an ointment made to contain 10 mg. of hydrocortisone per g. the standard deviation for 12 assays was 0·2 mg. per g. with an average of 10·2 mg. per g. R. E. S.

Opium Alkaloids, Paper Chromatography of. J. Reichelt. (*Pharmazie*, 1955, **10**, 234.) The method employed has been described previously by the author (*Pharmazie*, 1954, **11**, 968). The paper is impregnated with a mixture of formamide and ethanol (1 + 1), and the reproducibility of the results depends on the ratio of these compounds, the maintenance of a uniform process of impregnation, the temperature during the development and the degree of saturation of the chamber by the solvent vapour. Solvents used for development are benzene-chloroform (2 + 3 parts by volume) and benzene. Illustrations are given of the separation, with the former mixture, of mixtures of thebaine, heroin and papaverine, of morphine, codeine, ethylmorphine and dihydroxycodeinone, and of ethylmorphine and codeine in a ratio of 1:30. With benzene, a separation of codeine, dionine, dicodide and eucodal may be attained. Dragendorff's reagent is used for making the spots visible. Separation of dicodide and eucodal is not very good, since the spots are too close together. The method is not suitable for the identification of morphine, dilaudid and cotarnine, which remain at the starting point. It may be employed for the identification of alkaloids in pharmaceutical preparations (tablets, etc.), after a preliminary extraction of the alkaloids. G. M.

Surface-Active Agents Containing Polyoxyethylene or Polyoxypropylene Group, Detection of. M. J. Rosen. (*Analyt. Chem.*, 1955, **27**, 787.) It was found that all types of compounds containing the polyoxyethylene group could be detected by pyrolysis in 85 per cent. phosphoric acid, the volatile products being led into an aqueous solution of sodium nitroprusside containing a water-soluble secondary amine, such as diethanolamine; under these conditions the polyoxyethylene group decomposes to yield acetaldehyde which produces a blue colour with the sodium nitroprusside and the secondary amine. The test could also be used to detect the polyoxypropylene group; here the polyoxypropylene group decomposes under the conditions of the test to yield propionaldehyde (which can be isolated as the 2:4-dinitrophenylhydrazone from the water-soluble fraction of the pyrolysis products) and its polymers, which produce orange colours with sodium nitroprusside and diethanolamine. Positive results were obtained in the presence of the ester, alkylaryl, sulphide, sulphonate, sulphate, amino, amido, and phosphate groups. Glycerides interfered under the conditions of the test, decomposing to acrolein, which also gives a blue colour with sodium, nitroprusside and diethanolamine. Colours are described for a large number of surface active agents. R. E. S.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Cholinesterase Standards. J. H. Fleisher, S. Spear and E. J. Pope. (*Analyt. Chem.*, 1955, **27**, 1080.) The preparation of cholinesterase standards, which are stable for as long as 6 months, is described. A 1 per cent. solution of the enzyme is made in a stabilising medium containing potassium chloride, bovine hæmoglobin, bovine albumin, and phosphate buffer adjusted to pH 7·4; this is spotted on to filter paper discs which are cut out and dried. Four methods are given for the determination of the enzyme using the discs. In the colorimetric method each disc is eluted in potassium chloride solution, aliquots of eluate being incubated with acetylcholine-phosphate solution for 10 minutes at 25° C., and the residual acetylcholine being determined colorimetrically by the Hestrin (*J. biol. Chem.*, 1949, **180**, 249), procedure. For the electrometric method each disc is eluted in buffer solution and at known intervals, acetylcholine is added and the initial pH is taken followed by incubation at 25° C., and reading of the pH value after exactly 60 minutes. In the titrimetric method discs are eluted with potassium chloride-gelatin solution at pH 7·4, acetylcholine is added followed by small volumes of standard sodium hydroxide to maintain the pH at 7·4, the volumes of sodium hydroxide and the time added being recorded. In the manometric method, a disc prepared with the 0·2 per cent. enzyme is cut into several thin ribbons which are placed in the main section of a Warburg vessel and covered with 2 ml. of 0·025M bicarbonate buffer, pH 7·4, containing 0·03M magnesium chloride. The side arms receive 0·2 ml. of 0·11M acetylcholine. The vessels are attached to their manometers, which are then transferred to the water bath at 25° C. and gassed with 5 per cent. carbon dioxide-95 per cent. nitrogen for 15 minutes while shaking. The remainder of the procedure is carried out in the usual manner. The carbon dioxide output in microlitres was plotted against time, and found to be linear throughout the 60-minutes interval studied. The cholinesterase activity found by these four procedures varied by 2 to 3 per cent. and the discs were considered to be satisfactory and reproducible standards. R. E. S.

Noradrenaline and Adrenaline, Free and Conjugated, in Urine, Diurnal Variations in. U. S. von Euler, S. Hellner-Björkman and I. Orwén. (*Acta physiol. scand.*, 1955, **33**, Suppl. 118, 10.) Determining the 24 hour urinary excretion of noradrenaline and adrenaline in healthy adults, a mean value of 27 μg. for noradrenaline and 4·3 μg. for adrenaline was found. The output of both amines was considerably reduced during the night. The total catechol amines (i.e. free and conjugated) showed approximately the same distribution as the free amines but were about twice the amount. There was no difference between the sexes. M. M.

BIOCHEMICAL ANALYSIS

Adrenaline and Noradrenaline, Fluorimetric Micromethod for Differential Estimation of. U. S. von Euler and I. Floding. (*Acta physiol. scand.*, 1955, **33**, Suppl. 118, 45.) Previous fluorimetric methods for the estimation of adrenaline and noradrenaline are insufficiently specific for these two amines when biological material is tested. Modifying Ehrlén's method, a differential oxidation of adrenaline and noradrenaline with potassium ferricyanide at pH 3·5 and

6·0 is achieved. By addition of zinc sulphate complete oxidation of adrenaline is achieved in a few minutes at pH 3·5 while only some 2–4 per cent. of the noradrenaline is oxidized in the same time. Fading of the fluorescence in alkali is prevented with ascorbic acid. M. M.

Bromide in Body Fluids, Determination of. G. Hunter. (*Biochem. J.*, 1955, **60**, 261.) A micromethod for the estimation of bromide in presence of chloride and in the absence of organic matter is based on the quantitative conversion of bromide into bromate by hypochlorite; bromine is then liberated under suitable conditions followed by quantitative conversion to tetrabromorosaniline which is measured spectrophotometrically. The organic matter in 1 ml. blood was destroyed with a negligible carbon residue by ignition at 600° C. for 30 min.; under these conditions loss of bromide by volatilisation varied between 2 and 5 per cent. Amounts of bromine as low as 1 μg. can be determined with a standard deviation of less than 5 per cent. and an extreme range of variation of less than 10 per cent. of the mean. Values found for the distribution of bromide in a blood were: whole blood 1·26 mg. per 100 ml., corpuscles 0·98 mg. per 100 ml., plasma 1·43 mg. per 100 ml. R. E. S.

Œstriol, Œstrone and Œstradiol in Urine, Determination of. J. B. Brown. (*Biochem. J.*, 1955, **60**, 185.) A new chemical method is described for the separate estimation of œstriol, œstrone and œstradiol-17β in the urine of men and non-pregnant women. The method is based on that of Clayton (1949, Thesis, University of Edinburgh) and involves acid hydrolysis, ether extraction, a new phase-change purification procedure for the phenolic fraction depending on methylation of the phenol group, separation of the œstrogen methyl ethers by chromatography on alumina columns, colorimetric measurement using an improved Kober colour method, and spectrophotometric correction for interfering chromogenic material. Experimental studies are given for the hydrolysis of conjugated œstrogens, the ether extraction, the separation process, the methylation, the chromatography, and the colour development and estimation, together with details of the final method. Recovery experiments, in which known amounts of œstriol, œstrone and œstradiol-17β were added to portions of acid-hydrolysed 24 hr. male urines, yielded results between 80 and 90 per cent. even at levels corresponding to 4 μg. per day. Typical figures are shown for female and male urine and the specificity, accuracy, and sensitivity of the method are discussed. R. E. S.

Serum and other Proteins, Chromatography of. H. G. Boman. (*Nature, Lond.*, 1955, **175**, 898.) A system is described for the anion exchange chromatography of a number of differing proteins. "Dowex 2" resin, 200–400 mesh, in the chloride form was used and results are given for the chromatography of serum from a patient with prostatic cancer. The amount applied was 0·5 ml. of serum dialysed against 0·02 M tris (hydroxymethyl) aminomethane buffer at pH 7·2. Elution was carried out with 0·02 M buffer and then with stepwise increases to molarities of 0·1, 0·2, 0·4 and 1·0 of buffer, keeping the pH constant at 7·2; the protein in each fraction was followed by measurement of the extinction at 280 mμ. The different fractions from the experiment were tested also for acid phosphatase; most of the phosphatase activity (82 per cent. of the activity applied) was found in the third zone (0·2 M). The second protein fraction (eluted with 0·1 M buffer) consisted of almost pure albumin while the fourth was a well-defined γ-globulin fraction; the third fraction was probably α_1- and α_2-globulin. A commercial sample of human serum albumin was studied on a

similar column the main peak containing 52 per cent. of the amount applied was not eluted until the buffer concentration is increased to 0·4 M. Using the same chromatographic technique it was possible to purify a vegetable acid phosphatase from a crude extract. R. E. S.

CHEMOTHERAPY

Diaminodiphenoxyalkanes, Symmetrical, Schistosomicidal Activity of. C. G. Raison and O. D. Standen. (*Brit. J. Pharmacol.*, 1955, **10**, 191.) The schistosomicidal activity of a series of *pp'*-diaminodiphenoxyalkanes was assessed by oral administration to mice, guinea-pigs and rabbits infected with *S. mansoni* and *S. japonicum*. High activity was found in some 300 members of the series. The primary amines and mono-methylamines showed a peak of activity at an alkane chain length of 7 to 8. The dimethylamines were unique in showing an alternation of activity with changes in alkane chain length *n*, odd-numbered members being more active than even-numbered adjacent members; peak activity again occurred with $n = 7$. All the remaining mono- and di- alkylamines (C_2 to C_5) showed peaks at $n = 4$ and $n = 7$ to 8 and in general showed decreasing activity with increase in size of the alkyl groups on the nitrogens. The most active of the diaminodiphenoxyalkanes were several times more active than lucanthone or tartar emetic against *S. mansoni* or *S. japonicum* infections in mice. Altering the position of the amino groups from the *para* position or quaternisation of the nitrogens gave compounds with no schistosomicidal activity. G. P.

PHARMACY

NOTES AND FORMULÆ

Chlorophyll, Bacteriostatic Action of. R. Ammon and L. Wolff. (*Arzneimitt.-Forsch.*, 1955, **6**, 312.) Preliminary trials with 5 samples of chlorophyll showed that only two of these had any appreciable bacteriostatic action. These two were both water soluble preparations without added copper, one being a sodium chlorophyllin and the other a sodium magnesium chlorophyllin. Positive results were obtained with gram-positive bacteria, of which 10 different organisms were used in the tests. The concentration required was high, e.g., against *Staphylococcus London* Oxford, the chlorophyll was 833,000 times weaker than penicillin, 10,000 times weaker than streptomycin, and 333,000 times weaker than chloramphenicol. The action is bacteriostatic only and not bactericidal. G. M.

Essential Oils, Stabilisation with Antoxidants. L. E. Fryklöf. (*Farm. Revy*, 1955, **54**, 341.) The effect of the addition of antoxidants to turpentine oil has been reported previously (*Farm. Revy*, 1954, **53**, 367). These experiments have now been extended to other essential oils. In all, about 40 samples of oils of anise, bergamot, lemon, fennel, lavender, peppermint and rosemary were tested. The results showed that, under normal storage conditions, the induction period can be considerably prolonged by the addition of 0·01 per cent. of nordihydroguaieretic acid, butoxyanisole, or propyl gallate. It is however essential that the stabiliser should be added before the oil has undergone an appreciable amount of deterioration, i.e. during the manufacture. Traces of iron present in the oil may give rise to a yellow or red colouration, and the efficiency is reduced. The addition of 0·05 per cent. of citric acid or of ethylenediaminetetra-acetic acid increases the effect of the antoxidant when trace metals

are present. Storage at a low temperature (not exceeding 5° C.) is also desirable. Ethanol is ineffective in preventing oxidation, and its effect appears to depend on the preferential oxidation of the ethanol to acetaldehyde, the smell of which can be detected in oils which have been so treated. G. M.

Pyrogens in Injection Solutions. J. Kessler. (*Pharm. Acta Helvet.*, 1955, **30**, 211.) The experiments of the author relate to isotonic solutions of glucose, sodium chloride, etc., which were exposed to the air for a considerable period before the bacterial count was determined and the solution was sterilised. In testing, it is essential that the temperature and reactions of the animals should be observed for several days before injection of the solution. Some animals showed a temperature rise as great as 1° C. after a non-pyrogenic injection; and with infected, and sterilised, solutions, no correlation could be observed between degree of infection and pyrogenic reaction. Solutions which had a count of 500,000 bacteria per cent. before sterilisation sometimes gave a negative pyrogen result. On the other hand, injections which produced a considerable temperature rise in healthy guinea-pigs failed to show any unfavourable result when administered to patients. G. M.

PHARMACOGNOSY

Ergot, Determination of Alkaloids in Individual Sclerotia of. M. Hecht and W. Rumpel. (*Sci. Pharm.*, 1955, **23**, 73.) A single sclerotia is powdered with the aid of a coarse steel file, and 30 to 200 mg. of the powder is treated in a centrifuge tube with 10 ml. of ether and 1 drop of ammonia (10 per cent.) for each 25 mg. of powder. After shaking for 2 hours, and settling, 2 ml. of the solution is pipetted into another centrifuge tube and evaporated at a low temperature under vacuum. The residue is taken up in 1·0 ml. of a 4 per cent. solution of tartaric acid in 50 per cent. methanol, treated with 1 ml. of 10 per cent. zinc acetate solution, and warmed to about 35° C. After the resulting precipitate has settled, 1 ml. of the solution is treated with 2 ml. of reagent (0·2 g. of *p*-dimethylaminobenzaldehyde in a cooled mixture of 35 ml. of water and 65 ml. of concentrated sulphuric acid with 0·03 ml. of ferric chloride solution). After 20 minutes the blue colour is determined photometrically to give the total alkaloids. Another portion of 7 ml. of the ether extract is evaporated almost to dryness, then taken up with 2 ml. of 2 per cent. ammonium sulphate solution, and the remainder of the ether is removed. The solution is shaken out with 2 ml. of benzene, centrifuged, and the benzene is removed. This is repeated three times with 1 ml. of benzene each time. Turbid solutions are treated if necessary with 1 ml. of light petroleum. The water-soluble alkaloids are then determined as before, by treating 1 ml. of the aqueous solution with 2 ml. of the reagent. The results obtained show considerable variations in the alkaloid content of different sclerotia from the same strain of ergot. They are summarised in the table below. The alkaloidal contents are given as mg. per cent., calculated as ergotamine base (for total alkaloids) or ergometrine base (for water-soluble alkaloids).

Type of ergot	Total alkaloids			Water soluble alkaloids		
	Maximum	Minimum	Mean	Maximum	Minimum	Mean
Ergotoxine strain (I) ..	1200	258	811	123	25	63·5
Ergotoxine strain (II) ..	1190	202	933	103	25	60
Ergotamine strain (I)	560	360	500	31	17	21
Ergotamine strain (II) ..	465	340	398	17	10	14
Mixed alkaloid strain ..	810	405	586	77	13	30

G. M.

PHARMACOLOGY AND THERAPEUTICS

Adrenaline, Modification by Drugs of the Response of the Rat's Uterus to. M. Holzbauer and M. Vogt. (*Brit. J. Pharmacol.*, 1955, **10**, 186.) Twenty-seven drugs, among them the better-known adrenergic blocking agents, were tested for modification of the inhibition by adrenaline of the carbachol contractions of the non-pregnant rat's uterus. The halo-alkylamines, notably dibenzyline, sensitised the uterus to adrenaline and isoprenaline and have proved useful in biological assays of these compounds. Lysergic acid diethylamide and dihydro-ergotamine antagonized the inhibitory action of adrenaline. The effects of isoprenaline were less affected than those of adrenaline, so that this property could be made use of in distinguishing adrenaline from isoprenaline. β-Tetrahydronaphthylamine and 5-benzyloxygramine increased and Medmain slightly decreased the sensitivity to adrenaline. 5-Benzyloxygramine was the only substance encountered which sensitised more consistently to adrenaline than to isoprenaline. Veratramine in low concentrations increased the sensitivity of some uteri to adrenaline, but the action was evanescent and disappeared spontaneously or with higher concentrations of veratramine. The anti-amine-oxidases, ephedrine and iproniazid had no effect on the inhibitory action of adrenaline. G. P.

Adrenaline Stabilisation in the Adrenal Gland, a Possible Mechanism of. D. G. Humm, M. Roeder, M. Landew and E. E. Clark. (*Brit. J. Pharmacol.*, 1955, **10**, 163.) The oxidation of dihydroxyphenylalanine (DOPA) and adrenaline, estimated manometrically, was decreased on incubation with extracts of adrenal medulla homogenates. Boiling of the extract before incubation destroyed its antioxidant activity; addition of 10^{-3}M copper, cobalt or manganese to the extract also resulted in a loss of activity. Dialysis of the extract increased activity. Neither sulphydryl compounds nor ascorbic acid were responsible for the antioxidant effect and evidence pointed to a protein being involved. It was suggested that this protein, by forming a complex with adrenaline in the gland, prevents its oxidation under physiological conditions. G. P.

Antihistamine Drugs, Bronchoconstrictor and Bronchodilator Actions of. D. F. Hawkins. (*Brit. J. Pharmacol.*, 1955, **10**, 230.) Twelve well-known antihistamine drugs were found to have bronchoconstrictor action within the range of concentrations 10^{-6} to 10^{-4}, when tested on the isolated guinea-pig tracheal chain. In spinal cats and anæsthetised dogs intravenous doses within the range 1 mg. to 10 mg./kg. had similar effects. There was no correlation between antihistamine and bronchoconstrictor activities of the drugs tested. In concentrations higher than 10^{-4} the antihistamines caused relaxation of the guinea-pig tracheal chains. Mepyramine, promethazine and antazoline had similar constrictor and dilator effects on isolated human bronchial chains. The bronchoconstrictor action of mepyramine 10^{-5} on guinea-pig tracheal chains was not antagonised by atropine 10^{-5}; atropine 10^{-4} had itself a constrictor action. These direct actions of the antihistamines were suggested as being "histamine-like" and may be due, at least in part, to histamine-releasing properties of the drugs; they may be a factor limiting the therapeutic activity of the antihistamines in asthma. G. P.

Chlorpromazine, Complications of Therapy. J. Lomas, R. H. Boardman and M. Markowe. (*Lancet*, 1955, **268**, 1144.) This report is based on observation of 800 mental hospital patients treated with chlorpromazine between November, 1953, and the end of 1954. Though all types of mental cases were treated the great majority were acute or chronic psychoses. The

dosage varied considerably, but the most common procedure was to start with 150 mg. daily and to increase rapidly to 300 mg. daily; a few patients received up to 800 mg. daily. The duration of treatment varied from a few weeks to several months. The majority of patients received the chlorpromazine by mouth and were ambulant from the start. Most patients were receiving barbiturate sedation. The total number of toxic reactions recorded in the 800 patients was 59 (7·4 per cent.). Of the side-effects hypotension is the only one requiring special precautions and then only in the aged and those with cardiac dysfunction. Toxic manifestations included jaundice, blood dyscrasias, skin reactions and œdema, pyrexia, and epilpetic fits. Of these, jaundice and blood dyscrasias may prove fatal and are regarded as absolute contraindications to continuing treatment with chlorpromazine; previous liver dysfunction should also be regarded as a contraindication. Whereas the dosage at the time of the toxic reaction, the total dosage, and the method of administration, appeared of no significance, the duration of treatment before the reaction was much more constant. The greatest incidence of pyrexia was at the beginning of the second week, and both jaundice and skin reactions came on about 2 weeks later. Only in the case of epileptic fits was this time relationship not observed. Toxic reactions, except for epileptic fits, were very rare after the end of the 5th week. It is suggested that the toxic effects are due to sensitisation, and some support is lent to this suggestion by the development of eosinophilia in a few cases. The fact that the epileptic fits had no relationship either to dosage or duration of treatment suggests that chlorpromazine has epileptogenic properties which may lead to manifest fits in susceptible people. S. L. W.

Cyanacetic Acid Hydrazide, Antituberculous Activity of. M. Barnett, S. R. M. Bushby, R. Goulding, R. Knox and J. M. Robson. (*Brit. med. J.*, 1955, **2**, 647.) Cyanacetic acid hydrazide has been found to be as toxic as isoniazid and to have only one-fiftieth of the antituberculous activity of isoniazid *in vitro*. The LD 50 dose in mice was 230 mg. per kg. intravenously compared with 170 mg. per kg. for isoniazid. Strains of *Mycobacterium tuberculosis* resistant to isoniazid were generally resistant to cyanacetic acid hydrazide, but two isoniazid resistant strains were found which were sensitive to cyanacetic acid hydrazide. The lower antituberculous activity of cyanacetic acid hydrazide was confirmed *in vivo* in mice, where 2·0 mg. of isoniazid, given twice daily subcutaneously, gave complete protection; while doses of cyanacetic acid hydrazide ten times as great gave incomplete protection. By the intracorneal test in mice 0·3 mg. of cyanacetic acid hydrazide daily had no suppressive effect, and combined with 4 mg. per day of streptomycin the effect was only the same as streptomycin alone. The results suggest that isoniazid and cyanacetic acid hydrazide act in the same way. It is suggested that cyanacetic acid should not be used alone clinically and it is unlikely that there will be many instances where cyanacetic acid hydrazide will be more effective than isoniazid. G. F. S.

Dinitro-o-cresol, Potentiation of Barbiturate Anæsthesia by. E. F. Edson and F. M. Carey. (*Brit. med. J.*, 1955, **2**, 104.) A series of experiments using rats showed that, in the presence of sufficiently high dosages of dinitro-*o*-cresol to cause characteristic DNC-poisoning, 5 out of 6 barbiturates tested were significantly potentiated in rapidity of onset, depth, and duration of narcotic effects. The action of the two thiobarbiturates tested—thiopentone and thialbarbitone—was potentiated to such an extent that normally non-fatal anæsthetising doses led to almost immediate cyanosis and death. Of the four oxygen barbiturates examined, pentobarbitone, amylobarbitone, and phenobarbitone, were markedly potentiated by DNC but hexobarbitone did not

appear to be significantly influenced. The results obtained suggest that barbiturate potentiation is only likely to occur with DNC dosages high enough to cause characteristic signs of poisoning and profound disturbance of cellular oxidation-phosphorylation processes. Low dosages, causing no obvious DNC-poisoning, did not appear to increase barbiturate narcosis. The authors strongly recommend that barbiturate drugs, especially thiobarbiturates, should not be used for the induction of surgical anæsthesia in a person suffering from DNC-poisoning and that barbiturate sedation in such cases should be carried out with comparatively small doses. S. L. W.

Histamine Liberation in the Rat and Mouse. J. F. Riley and G. B. West. (*Arch. int. Pharmacodyn.*, 1955, **102**, 304.) The chronic administration of the histamine liberator, compound 48/80, to rats and mice resulted in a loss of tissue histamine and of mast cells in the ears and subcutaneous connective tissue. The drug was injected intraperitoneally once or twice daily, in doses increasing to 1 mg. daily for rats and 300 μg. daily for mice, for up to 31 days. With the first injection the rats showed visible skin œdema, shock, erythema followed by cyanosis of the ears, itching and some prostration. Under the same conditions mice showed weakness, erythema and cyanosis, but few signs of severe itching or œdema. With both species the maximum tolerated dose was used, but histamine and mast cell depletion was only moderate in mice, whereas in rats depletion was almost complete. It was concluded that histamine release plays only a small part in the action of compound 48/80 in mice. G. P.

6-Mercaptopurine in the Treatment of Leukæmia and Allied Disorders. J. R. Fountain. (*Brit. med. J.*, 1955, **1**, 1119.) This is a study of a small unselected series of patients suffering from leukæmia or allied disorders treated with a purine antagonist 6-mercaptopurine (Purinethol), an analogue of adenine and hypoxanthine. None of the patients received other forms of chemotherapy previous to, or as a supplement to, treatment with 6-mercaptopurine. The initial dose of the drug was 2·5 mg./kg. by mouth daily. The same dosage scheme was used both for patients with acute or with chronic leukæmia and in all instances the daily amount was divided into doses of 25 or 50 mg. A delay of 7 to 28 days was usual before the drug took effect. Of 13 patients with acute leukæmia 7 responded to treatment; 5 developed a complete clinical and hæmatological remission lasting from 7 weeks to 7 months, 2 showed temporary and partial improvement, and 6 failed to respond to treatment, 4 dying within the first week. Of 7 patients with chronic myeloid leukæmia a varying response was observed in 6, the other patient dying within a week of starting treatment. Subjective improvement—increase in well-being, activity, appetite and weight—was observed in 4 cases, and objective improvement—diminution in size of spleen, lymph nodes, etc.—was observed in 5 cases. The leucocyte count fell in all 6 cases. Two patients with chronic lymphatic leukæmia showed no clinical or hæmatological improvement after 1 month's treatment, and 2 patients with multiple myeloma and one with erythroderma also failed to benefit. An important feature of the drug is its low toxicity. Apart from depressing bone-marrow function no definite toxic side-effects were observed. Hæmorrhage, a possible complication, did not occur. No evidence was seen of megaloblastic erythropoiesis. The results show that 6-mercaptopurine may produce temporary remissions in some cases of acute leukæmia and modify the course of chronic myeloid leukæmia but continuous therapy seems essential if the beneficial effects are to be maintained. Although the remissions are only temporary, with the knowledge that aminopterin, amethopterin, ACTH and cortisone, and

6-mercaptopurine may all produce clinical and hæmatological remissions in acute leukæmia, symptomatic relief may be obtained by sequential use of these drugs. S. L. W.

Oxamycin, Clinical Observations on. H. J. Robinson, C. Morgan, D. W. Richard, B. M. Frost and E. Alpert. (*Antibiotic Med.*, 1955, **1**, 351.) Oxamycin is a broad-spectrum antibiotic produced by a strain of *Streptomyces garyphalus* (a comparison of oxamycin and cycloserine indicates that these products are identical). Oxamycin is a zwitter-ionic, crystalline material, somewhat unstable in acidic and neutral solutions but highly stable to prolonged treatment with base. It is active *in vitro* and *in vivo* against gram-positive and gram-negative bacteria and is efficacious against rickettsial infections and certain protozoa. It also inhibits some strains of *Mycobacterium tuberculosis* in concentrations of 5 to 10 μg./ml. but in experimental tuberculosis in mice only slight activity could be demonstrated; an *in vivo* potentiating effect of combinations of oxamycin and dihydrostreptomycin has been reported. A total of 47 patients were concerned in this study: 25 with various non-infectious diseases (in most cases cardiovascular disease) were employed for tolerance studies; the remaining 22 patients had various bacterial infections of which pneumococcal lobar pneumonia was the most common. In the first group doses of 0·2 g. twice daily were well tolerated, but when doses of 1·6 to 2·4 g. daily were given in divided doses every 6 hours toxic symptoms occurred in 11 out of 13 patients. The toxicity appeared to be confined to the central nervous system. Lethargy and somnolence were the most frequent side-effects, but other reactions included vertigo, opthalmoplegia, blurred vision and disorientation. All the effects were transient and disappeared within 1 or 2 days of withdrawing the drug. Four patients tolerated the 2·4 g./day dose level without showing toxic signs and one of them received 39·8 g. over a 25-day period. Of the 22 patients with bacterial infections 19 tolerated a daily dose of 0·8 g. of oxamycin; 3 patients became lethargic after 4 to 5 days of treatment; 2 of these subsequently became disoriented and one (with impaired renal function) developed convulsive seizures. Of the 17 cases of pneumonia oxamycin produced a good therapeutic effect in 3 cases, a moderate improvement in 6 cases, and no response in 8 cases. All of the latter cases responded dramatically to penicillin; there was some suggestion that penicillin may act synergistically with oxamycin. S. L. W.

Phenytoin Sodium, Megaloblastic Anæmia due to. G. M. S. Ryan and J. W. B. Forshaw. (*Brit. med. J.*, 1955, **2**, 242.) Three cases of megaloblastic anæmia, which were probably induced by phenytoin sodium, are described. The patients had been taking 200 or 300 mg. of phenytoin sodium, daily, in conjunction with phenobarbitone, over periods of several years. This condition is rare, and no further cases were discovered from a survey of 102 epileptic patients on phenytoin sodium therapy. The anæmia is corrected by folic acid therapy; the response to vitamin B_{12} is variable. In view of the rarity of the condition and the excellent response to treatment the use of this drug is not contraindicated, but it is probably wiser to change to another anticonvulsant drug in those patients who develop a megaloblastic anæmia. S. L. W.

Piperoxan in the Treatment of Adrenaline Overdosage. B. J. Freedman. (*Lancet*, 1955, **269**, 575.) The author reviews 11 fatal and 3 non-fatal published cases of overdosage of adrenaline and concludes that the minimum lethal subcutaneous dose for an adult is about 4 mg. and the maximum tolerated dose 7 to 8 mg. A description is given of a case in which an asthmatic was given intramuscularly 5 ml. instead of 5 minims of a 1 : 1000 solution of 80 per cent.

adrenaline and 20 per cent. noradrenaline with recovery following the intravenous injection of 10 mg. of piperoxan (2-(1-piperidylmethyl)-1 : 4-benzodioxane hydrochloride). Piperoxan is one of a number of dioxanes which are adrenergic blocking agents but it has the advantage of exerting no sympatholytic action unless given in amounts equal to 40 to 80 times the effective adrenolytic dose. In phæochromocytoma intravenous doses of 0·25 mg./kg., injected during 2 minutes, cause a fall of blood-pressure which is fully developed at the completion of the injection and may remain so for a few minutes. The blood-pressure gradually rises to its original level in 15 to 25 minutes. Side effects, such as tachycardia, headache and flushing, may occasionally occur. In accidental overdosage of adrenaline, an adult weighing 10 stones should be given intravenously without delay 15 mg. of piperoxan or 30 mg. if the dose of adrenaline was 20 mg. of more. H. T. B.

Polymyxin B and E, Release of Histamine by. S. R. M. Bushby and A. F. Green. (*Brit. J. Pharmacol.*, 1955, **10**, 215.) Polymyxins B and E injected subcutaneously in rats were about as active as compound 48/80 in releasing skin histamine remote from the site of injection, and causing degranulation of the mast cells of the mesentery. In guinea-pigs the responses to intradermal polymyxin B or E (measured by leakage of dye from the capillaries) were slightly less than with 48/80. In dogs and cats, however, the histamine liberating activity of the two antibiotics was not great, a small rise in blood histamine occurring in dogs associated with vasodepressor and bronchoconstrictor effects. The tachyphylaxis observed with repeated doses of the polymyxins was also associated with decreased histamine liberation. The doses used in the experiments approximated to lethal doses (5 to 10 mg./kg.) and toxic effects observed were severe vascular engorgement, particularly of the liver and a resulting fall in blood pressure and respiratory depression. These observations may be related to the observation that antihistamines abolish some of the side effects of polymyxin in man. G. P.

Pyrexin, Relation to some Bacterial Pyrogens. V. Menkin. (*J. Lab. clin. Med.*, 1955, **46**, 423.) The paper reports the results of an extensive investigation of the relation between bacterial pyrogens and pyrexin, the heat-stable, crystalline, pyrogenic factor isolated from the euglobulin fraction of acid inflammatory exudates. It has been suggested that its presence in exudates explains the primary mechanism of fever with acute inflammation, but as rabbits acquired a tolerance to repeated doses of 0·25 mg. of pyrexin the suggestion has been questioned. Since the pyrexin concentration in exudates varies from 1·2 to at least 9·8 mg./ml., this development of tolerance was reinvestigated using higher doses, 2 series of rabbits being given daily injection for 10 days of 0·5 ml. of saline containing 4 to 15 mg. of pyrexin. No evidence of any acquired tolerance was found either in the temperature elicited or in the duration of fever. Studies were next undertaken to determine the effect on the pyrogenic activity of the serum, of the intravenous injection into rabbits of various doses of two different bacterial pyrogens. The pyrogenic activity of the serum was found to be localised primarily in the euglobulin fraction but it was not established whether the euglobulin fraction had been converted to a pyrogenic factor or whether a pyrogen-euglobulin complex had been formed. Incubation of blood serum and a bacterial pyrogen *in vitro* resulted in equal distribution of pyrogenic properties in the euglobulin and the alpha- and beta-globulin fractions. In contrast to the bacterial pyrogens, pyrexin, when

(ABSTRACTS—*continued on page* 69)

The importance of biological assays is again emphasised by the inclusion of sections dealing with assays of antibiotics, serological and bacteriological products, hormones and Dextran Sulphate. The test for retardation of insulin effect for Injection of Protamine Zinc Insulin has been amended to allow guinea-pigs as well as rabbits to be used as experimental animals. The fact that it is usual to take the blood sample from the heart rather than from the ear vein in the case of guinea-pigs (Stewart and Smart, *J. Pharm. Pharmacol.*, 1953, **5**, 939) appears to have been overlooked, and it is not made sufficiently clear that the guinea-pig may also be used for the testing of I.Z.S. preparations. The test for pyrogens has been rewritten and now takes the form of a sequential sampling technique designed to use a minimum number of rabbits.

The publication of this Addendum will reassure any who may have feared that the B.P. is not keeping abreast of the most recent advances in medicine and pharmacy. The work has been well produced and proof reading has been well done the reviewer noticing no typographical errors.

The Addendum becomes official from March 1, 1956.

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injected intravenously into rabbits in doses of 1·4 to 9·9 mg., did not induce pyrogenic activity in the serum. The pyrogenic euglobin of rabbit serum, produced by the intravenous injection of bacterial pyrogens, when injected intravenously into a second rabbit, also failed to induce pyrogenic activity in the recipient rabbit's serum. When injected into dogs, the pyrogenic euglobulin of rabbit serum produced a rise in temperature, and also an initial leucocytosis and a subsequent leucopænia, and the same effects were produced by the alpha-globulin from the rabbit serum. The results suggest that pyrexin from inflammatory exudates and pyrogenic euglobulin formed in the circulatory blood by interaction of bacterial pyrogens are essentially similar in nature. H. T. B.

Pyrogens in the Production of Fever. E. Atkins and W. B. Wood. (*J. exp. Med.*, 1955, **101**, 519.) The rate of clearance of intravenously injected typhoid vaccine was studied in unsensitized, sensitized and pyrogen-tolerant rabbits by means of a passive transfer technique. The blood of unsensitized rabbits which had not previously been exposed to bacterial pyrogen remained pyrogenic for normal recipients throughout a period of 2 hours following the injection. In contrast, rabbits sensitized by having received either one or two injections of the vaccine at least 3 weeks prior to the experiment cleared their blood of the test vaccine within 30 minutes despite the fact that they exhibited the same febrile response as unsensitized rabbits. After 1 hour, however, a transferable pyrogenic substance was again demonstrable in the sera of this group. It is thought that this newly appearing substance may be of endogenous origin and may be the factor which directly affects the thermoregulatory centres of the brain. Rabbits made tolerant by repeated daily injections of vaccine have a characteristically depressed febrile response. Not only were the blood streams of such animals cleared of the injected vaccine within less than 5 minutes but samples of their sera obtained 1 and 2 hours after the injection also failed to contain demonstrable quantities of the secondary pyrogen observed in sensitized animals. The latter observation is in keeping with the suggestion that the secondary pyrogen may play a critical role in the production of fever. S. L. W.

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BOOK REVIEW

INTRODUCTION TO CHEMICAL PHARMACOLOGY, by R. B. Barlow. Pp. xiv + 343 including Index and 53 diagrams. Methuen & Co. Ltd., London, 1955. 35s.

The author states that the book is an outcome of the course in chemical pharmacology for students in chemistry commenced at the Department of Pharmacology at Oxford in 1945. Consequently the presentation of the material is such that students who have received little training in biological subjects are supplied with sufficient biological background to make the book intelligible. In the reviewer's opinion the author has succeeded in writing a stimulating and informative book which in certain sections exceeds the scope which the word "introduction" implies.

The book commences with a very short review of the theories of drug action. The next sections are arranged under the headings: (1) Drugs which produce general central nervous depression (such as general anæsthetics, hypnotics); (2) drugs which depress certain centres of the central nervous system (analgesics, anticonvulsants, etc.); (3) drugs which stimulate the central nervous system; (4) drugs which act on peripheral nerve endings of synapses (local anæsthetics, acetylcholine-like compounds, mydriatics, spasmolytics, ganglionic-blocking agents, neuromuscular blocking agents, anticholinesterases, adrenaline and related compounds); (5) drugs which act on tissues and organs (histamine and antihistamine drugs, drugs which act on heart muscle, etc.). In an appendix a brief account of the anatomy, physiology and biochemistry of the human body is given for the benefit of those readers who lack the necessary biological background.

The discussion of the drugs acting in a particular manner includes a brief description of the methods of testing, a detailed treatment of the type of compounds and a discussion of the attempts to correlate structure with activity.

A plentiful supply of structural formulæ and the use of tables greatly facilitates the reading of the text. It is unfortunate that a number of mistakes occur in these formulæ, e.g. p. 89 α-eucaine and β-eucaine, p. 75 camphor, p. 88 cocaine (incorrect stereochemically). Furthermore the piperidine ring of tropine (and related compounds) and ecgonine (and related structures) has been shown in the boat form in all cases, whereas there is much evidence available to show that it exists in the chair form. However, these are only minor blemishes in a well illustrated text.

This book will prove to be of great value to students reading for the B.Pharm. degree and it can also be highly recommended to all those who seek to get a background to the structure and action of many of the newer type drugs. The research student embarking upon the preparation of potential pharmacologically-active compounds will also derive much benefit from this introduction to the subject.

A. H. BECKETT.

(ABSTRACTS—*continued from page* 69)

Reserpine, Serotonin and Lysergic Acid Diethylamide, Interaction of in Brain. P. A. Shore, S. L. Silver and B. B. Brodie. (*Science*, 1955, **122**, 284.) Experiments in mice show that reserpine potentiates the hypnotic effects of hexobarbitone and ethanol, and lysergic acid diethylamide antagonises the potentiation. Lysergic acid diethylamide alone did not affect the hypnotic action of hexobarbitone or ethanol. The results suggest that some of the actions

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carry out further work on the assay of artemisia. We thank you for allowing us to publish this note.

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October 13, 1955.

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of reserpine may be mediated through the release of serotonin in the body. Experiments in dogs, which show a high increase in the excretion of 5-hydroxyindoleacetic acid, a major metabolite of serotonin, support this hypothesis.

G. F. S.

Silicone Aerosols, Control of Pulmonary Œdema. M. Nickerson and C. F. Curry. (*J. Pharmacol.*, 1955, **114**, 138.) Experimental pulmonary œdema, induced in rabbits by intravenous injection of adrenaline and in rats by inhalation of chlorine, was effectively controlled by the anti-foaming action of inhaled aerosols of dimethylpolysiloxane emulsions. In preliminary *in vitro* experiments with a 10 per cent. serum solution the most effective and easily handled silicone emulsion was XEC 151, (30,000 cs. dimethylpolysiloxane with 5 per cent. SiO_2), foaming being prevented where the silicone concentration was as low as 6×10^{-9}. A 10 per cent. aqueous emulsion of XEC 151 gave complete protection in rabbits against intravenous doses of adrenaline of 1 mg./kg. or less and 60 per cent. protection against 2 mg./kg. Emulsion XEF 215 (500 cs. dimethylpolysiloxane) was almost as effective as XEC 151. Death from chlorine-induced pulmonary œdema in rats was also prevented by these aerosols, but the range of exposure within which protection was obtained was much narrower than with adrenaline. It was suggested that the limits of dosage of adrenaline or chlorine against which the aerosols can protect are determined by toxic actions other than the production of pulmonary œdema. Inhalation of the aerosols did not alter oxygen transfer in the lungs of dogs and daily administration for up to 38 days did not produce inflammatory or granulomatous changes in the lungs of rats. Other workers have reported the low toxicity of these aerosols after both acute and chronic administration by various routes.

G. P.

Steroid Anæsthetic Agent. G. D. Laubach, S. Y. P'an and H. W. Rudel. (*Science*, 1955, **122**, 78.) The anæsthetic activity of a number of water-soluble steroids was compared with thiopentone sodium. The most promising of the series was hydroxydione (21-hydroxypregnane-3: 20-dione sodium succinate), which in mice and rats had intravenous anæsthetic potency equal to that of thiopentone sodium, but a much higher therapeutic index. In cats, dogs and monkeys the therapeutic index of the steroid was again high, but anæsthetic potency was only one-fourth of that of the thiobarbiturate. Respiratory depression during hydroxydione anæsthesia was relatively low and recovery rapid, uncomplicated and with minimum post-anæsthetic depression. Even with large doses of the steroid little or no endocrine activity was observed. G. P.