ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ANALYTICAL

Aneurine, Microbiological Assay of. J. R. Villanueva. (*Nature, Lond.*, 1955, **176**, 465.) Aneurine, biotin, riboflavine, pyridoxine, nicotinic acid, inositol and pantothenic acid (this latter in the form of its calcium salt) were tested as growth-promoting factors for *Tuberculina persicina*. The vitamins were added aseptically to a synthetic basal medium containing potassium phosphate, magnesium sulphate, potassium nitrate, dextrose and agar, the final pH being adjusted to 5·2. After incubation for 20 days at 20° C., the plates to which aneurine had been added showed good growth of the fungus colony and displayed a pigmentation of the medium; those lacking this factor remained colourless. Further experiments, devised to ascertain the optimum levels of aneurine concentration for pigment production, were made with liquid cultures which were incubated for thirty days, at the end of which time striking differences in the colour of the liquids were observed. Measured spectrophotometrically, these differences were related to the amount of aneurine present in the original culture medium. Negligible pigment formation occurred in the liquids of the control flasks, or in those in which the aneurine concentration was lower than 5×10^{-3} μg./1. Above 5×10^{2} μg./1. of aneurine there was a marked decrease in pigment formation. Further experiments are being made with *T. persicina*.

R. E. S.

Barbiturates, Interference to the Ultra-violet Spectrophotometry of. A. S. Curry. (*Nature, Lond.*, 1955, **176**, 877.) The presence of a phenolic substance, isolated in four cases along with barbiturates during the pathological examination of four livers from various cases of sudden death, is reported. The substance exhibits ultra-violet absorption characteristics in both 0·5N ammonia and in acid solution, which are very similar to those of barbiturates. Interference by this substance in the spectrophotometric estimation of barbiturates isolated from such material is therefore possible, the quantity of the substance present being such as to suggest barbiturate concentrations of 1 to 4 mg./100 ml. The interfering substance is readily separated from barbiturates by chromatography on paper using *n*-butanol/5N ammonia (R_F 0·95). The spots fluoresce in ultra-violet light, give no reaction with the mercuric sulphate/diphenylcarbazone reagent for barbiturates, but give a blue colour with ferric chloride/ferricyanide. Another compound having similar ultra-violet absorption characteristics has also been isolated during the course of examination of the contents of a stomach. The liver of the same person yielded a similar substance in the alkali-soluble and ether-soluble fraction.

J. B. S.

Corticotrophin, Chromatographic Studies on. H. B. F. Dixon and M. P. Stack-Dunne. (*Biochem. J.*, 1955, **61**, 483.) Corticotrophin concentrates have been chromatographed in sodium phosphate buffers (pH 6·7) on ion exchange resins. The resin used was of the weak carboxylic acid type specially prepared by grinding and elutriation and of such particle size as to give a flow rate of 5 ml./sq. cm./hour under gravity when packed in a column 30 to 40 cm.

high. The active components have been resolved into a number of fractions, of which the main one has been designated corticotrophin A_1. This is probably identical with the β-corticotrophin of Bell. The chromatographic results suggest that this fraction is essentially homogeneous. The resolved component fractions were separated from salts by adsorption at pH 3 on a carboxylic acid resin or by extraction of the material into phenol. The other components, corticotrophins A_2 and A_3 moved more rapidly than A_1 on the resin columns. A_2 is formed from A_1 by alkaline treatment, which is thought to cause some loss of amide ammonia. The formation of A_3 and the fact that A_2, unlike A_1, shows two spots on paper ionophoresis suggests that other changes are involved, such as the unmasking of acid groups or the masking of amino groups by acyl migration. J. B. S.

Galenical Preparations, Chromatographic Examination of. P. Lundgren. (*Svensk farm Tidskr.*, 1955, **16**, 389.) A method which has been applied to the assay of a number of galenical preparations is based on distribution chromatography on silica with an aqueous phase of suitable pH. Examples are given of the application of the method to the extraction of nitroglycerin, bromural, phenacetin, etc., from tablets, of alkaloids from their salts and to the analysis of a number of tablets containing alkaloids with synthetic chemicals. The method, as applied to a tablet containing barbitone, phenacetin and papaverine hydrochloride, is as follows: 1½ tablets are rubbed down with 2 ml. of 2M hydrochloric acid and then mixed with silica (Hyflo Super Cel) to form an almost dry powder which is then packed into a chromatograph column (column 1). Another column (column 2) is prepared from 2 g. of silica and 1 ml. of 5M sodium hydroxide suspended in ether. Column 1 is washed through with 150 ml. of ether at 1 to 2 ml. per minute, which is allowed to drip on to column 2 which itself is dripping at the same rate. Removal of the solvent from the eluate gives the phenacetin. To column 2 is added a solution of 0·5 ml. of acetic acid in 10 ml. of ether and, when this has been taken up by the column, 50 ml. of ether is added. The eluate is evaporated to dryness and the residue is disolved in 20 ml. of sodium carbonate solution (10 per cent.) washed twice with two 10 ml. portions of sodium carbonate solution, and filtered. The filtrate is titrated with 0·1N silver nitrate solution to a permanent turbidity. A blank test is carried out with 40 ml. of the sodium carbonate solution. One ml. of the silver nitrate corresponds to 0·01842 g. of barbitone. Column 1 is eluted with 50 ml. of chloroform and the eluate is evaporated to dryness. The residue is dissolved in 25 ml. of 2M hydrochloric acid and made up to 250 ml. The papaverine is then determined by the spectrophotometer at 309 mμ, using 0·2N hydrochloric acid as blank. The value for E (1 per cent. 1 cm.) for papaverine hydrochloride is 219·7. G. M.

Lignocaine, Titrimetric Assay with Reinecke's Salt. J. M. Hanquin and C. Lapiere. (*J. pharm. Belg.*, 1955, **10**, 246.) Lignocaine and other local anæsthetics may be assayed by precipitation from an acid solution with a standard solution of ammonium reineckate. The precipitate is removed by filtration and the excess of reagent in an aliquot quantity of the filtrate is determined by hydrolysing in alkaline solution, and titrating with silver nitrate in the presence of nitric acid. If the substance under examination is in the form of its hydrochloride, allowance must be made for the quantity of chloride ion which reacts with the silver nitrate. This method is applicable to lignocaine, procaine and tutocaine, using samples of about 20 mg. An alternative method in which the precipitated reineckate is washed, dissolved in acetone and titrated with silver

nitrate after hydrolysis with alkali is satisfactory for lignocaine, but losses occur in washing the precipitates obtained from procaine and tutocaine. The method has not proved to be successful with other local anæsthetic agents. G. B.

Morphine, Determination of, by Exchange Resins. E. Brochmann-Hanssen. (*Medd. Norsk farm. Selsk.*, 1955, **17**, 76.) The apparatus used consists of a stoppered extraction tube which has a stop-cock below and is kept warm by means of heating tape. A plug of glass wool is placed in the bottom. For the assay of opium, 0·1 g. of the drug is mixed in the tube with 1 g. of Dowex 50-X_2 (H^+) and 25 ml. of hot water. The mixture is shaken mechanically for 15 minutes, being kept at 70° to 80° C. The liquid is drained off and the tube washed with water and placed on top of a column containing Dowex 1-X_1, previously washed with 50 ml. of 4 N ammonia in methanol (70 per cent. by volume). The alkaloids are eluted from the extraction tube with 50 ml. of methanolic ammonia onto the column which is washed with methanol and then with water to remove the ammonia. The amphoteric alkaloids are finally removed from the column by 0·1 hydrochloric acid, collecting the eluate in a 50-ml. volumetric flask. The morphine is determined by the method of Pride and Stern (*J. Pharm. Pharmacol.*, 1954, **6**, 390) using iodic acid and nickel chloride. In a modification the final assay is done by spectrophotometry, with an allowance for the slight yellow colour of the solution. The results obtained are about 25 per cent. higher than those by the lime method of the United States Pharmacopeia XIV (which does not use a correction factor).

G. M.

Organic Phosphate Insecticides, Paper Chromatography of. J. W. Cook. (*J. Assoc. off. agric. Chem. Wash.*, 1955, **38**, 826.) An investigation of the conversion of organic phosphates to *in vitro* cholinesterase inhibitors by *N*-bromosuccinimide and ultra-violet light has been made. Chromatograms were produced by depositing at the origin point, from anhydrous ether solution, either 2 or 20 mg. of the organic phosphate on strips of paper followed by spraying with a 4 per cent. solution of mineral oil in anhydrous ether. After chromatography with water as the mobile phase, they were dried at room temperature and sprayed with a fresh solution of *N*-bromosuccinimide in methyl chloroform. Other strips were spotted with the organic phosphate but were sprayed with *N*-bromosuccinimide at the origin before being treated with oil and chromatographed. Further strips were spotted by the same procedure as before but the papers were exposed to a strong ultra-violet light for 45 minutes before they were treated with oil and chromatographed. All strips were tested for *in vitro* cholinesterase inhibitors as described previously (*J. Assoc. off. agric. Chem. Wash.*, 1955, **38**, 150). In general, it was found that systox, parathion, diazinon, sulphatepp, TEPP and triethylphosphate were converted to more potent cholinesterase inhibitors by treatment with *N*-bromosuccinimide and ultra-violet light; the resulting compounds were more soluble in water than in oil.

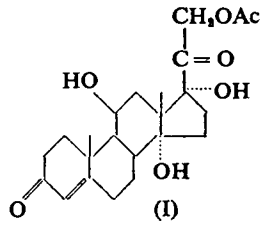
R. E. S.

***Rhamus frangula*, Determination of Anthranols in.** H. Mühlemann. (*Pharm. Acta Helvet.*, 1955, **30**, 350.) Absorption curves of chrysazin-9-anthranol triacetate, 10-glucosylchrysazin-9-anthranol hepta-acetate and emodin-9-anthranol tetra-acetate all show the same form with three peaks, of which the central one is the higher. In the case of the first two compounds, the difference between this maximum and the minimum of the curves was found to run parallel with the molecular weights, and it is reasonable to assume that the same

relation holds for emodin-9-anthranol tetra-acetate and reduced glucofrangulin acetate. On this basis the difference between E (1 per cent. 1 cm.) maximum (395 mμ) and minimum (320 mμ) for the latter compound was calculated as 65·7. This method was used for observing the concentration of frangula extracts in the course of attempts at purification. Actually it was found necessary to take the minimal extinction between 320 and 350 mμ rather than a definite wavelength. By using this method a fraction was finally obtained which should represent 100 per cent. of the glucofrangulinanthranol acetate. This compound could not be obtained in a crystalline form, but the figures obtained by elementary analysis and for acetyl content agreed with the theoretical values. It gave a value for E (max.–min.) of 64, which agreed well with that previously calculated. In these glucosides, an increase in the hydroxyl groups causes a displacement of the maximum towards longer wavelengths, while the entry of sugar into the molecule flattens the maximum. G. M.

ORGANIC CHEMISTRY

Corticoids, Biologically Active, A New Class of. E. J. Agnello, B. L. Bloom and G. D. Laubach. (*J. Amer. chem. Soc.*, 1955, **77**, 4684.) A new class of corticosteroids which display varying degrees of glucocorticoid activity are reported. The compounds are derivatives of hydrocortisone and cortisone functionally substituted in ring D. The introduction of the various nuclear substituents was readily effected by chemical transformations of a dihydroxylated product obtained from the microbiological oxygenation of 11-desoxy-17α-hydroxycorticosterone. The dihydroxylated product was shown to be I; it is more active than hydrocortisone acetate in the thymus involution assay and has been found to be an active anti-inflammatory agent in rheumatoid arthritis. A. H. B.



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BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Diethyltin Dichloride and Triethyltin Sulphate, Biochemistry of. W. N. Aldridge and J. E. Cremer. (*Biochem. J.*, 1955, **61**, 406.) It has been shown that diethyltin dichloride and triethyltin sulphate influence the biochemical mechanisms of rat-brain brei and rat-liver mitochondria in different ways. The response of diethyltin dichloride is similar to that of phenlyarsenious acid, but the biochemical symptoms of triethyltin sulphate and diphenylchloroarsine are not identical. Evidence is given that diethyltin dichloride inhibits α-keto acid oxides with citrate as substrate, as does phenylarsenious acid. There is also some evidence that diethyltin dichloride has some other actions at the concentrations which inhibit α-oxoglutaric oxidase. Unlike diphenylchloroarsine, triethyltin sulphate possesses little or no affinity for sulphydryl groups, but with rat-brain brei or rat-liver mitochondria it causes a consistent lowering of α-keto acid levels. The various steps of the respiratory chain are unaffected by approximately 100 times the concentration effective against oxidation. Triethyltin sulphate is a highly specific inhibitor of phosphorylation processes associated with oxidation. The hypothesis that the triethyltin ion replaces an essential ion in the phosphorylation mechanism is considered, and rejected. It appears to interfere with oxidation as a consequence of its inhibition

of phosphorylation. There is some evidence that the inhibition of phosphorylation is responsible for the generalised muscular weakness, which is a clinical symptom of poisoning by triethyltin sulphate. J. B. S.

BIOCHEMICAL ANALYSIS

Esterified Fatty Acids, Assay of, and its Application to Blood Serum. M. Jarrier and J. Polonovski (*Bull. Soc. Chim. biol., Paris*, 1955, **37**, 495.) The method depends on the conversion of the esters into alcohols and hydroxamic acids according to the equation: $RCOOR' + NH_2OH = R'OH + RCONHOH$. The hydroxamic acids yield a purple-red ferric complex while free fatty acids do not react. The method is especially useful for the determination of small quantities of esters (of the order of 1 mg.) mixed with free fatty acids. Quantities of ethereal solution representing 1 to 6μ equiv. of ester are placed in tubes and the contents dried *in vacuo*. The residue is dissolved in 0·3 ml. of 2·5 per cent. ethanolic hydroxylamine hydrochloride solution and 0·3 ml. of 2·5 per cent. ethanolic sodium hydroxide solution is added. After 1 hour, 10 ml. of ferric perchlorate solution is added and the tubes are kept at 25° C. for 20 minutes, after which the extinction is measured at 250 mμ. The quantity of ester is determined by means of a reference curve prepared by plotting extinctions obtained in a similar experiment with a pure sample of ester, for example ethyl palmitate. For the determination of fatty acid esters in blood serum, a sample of about 0·25 ml. of serum or 2 mg. of lipids is required, a preliminary treatment being necessary, either precipitation with a 3:1 mixture of ether and ethanol or extraction with methylal/methanol mixture. G. B.

Fibrin, Determination of, in Plasma. K. Christensen (*Scand. J. clin. Lab. Invest.*, 1955, **7**, 246.) A new and accurate method is described for the estimation of fibrin in plasma, based on the digestion of fibrin by trypsin. Blood is withdrawn into a 2 ml. citrated centrifuge tube, centrifuged and 0·5 ml. of plasma transferred to a siliconed test tube. The plasma is recalcified by addition of 0·5 ml. 1/40M calcium chloride. The mixture is stirred with a roughened 5 mm. glass rod and the rod is left in the tube for 30 minutes. Serum is squeezed from the clot attached to the rod and it is washed by immersion in physiological saline. The rod is transferred to a 5 ml. graduated test tube containing 1 ml. of a 0·1N ammonium chloride-ammonia buffer of pH 9. To this is added 0·125 ml. of a solution containing 50 mg. of trypsin in 20 ml. of 0·0025N hydrochloric acid. After incubation for 1 hour at room temperature, when the clot is digested, the rod is removed, rinsed with buffer and the volume made up to 5 ml. The extinction of the solution at 280 mμ is measured, buffer containing the same amount of trypsin being used as a blank. The result is obtained from a standard calibration curve. G. F. S.

Mercury in Biological Materials, Determination of. D. Polley and V. L. Miller. (*Analyt. Chem.*, 1955, **27**, 1162.) A sample of biological material or soil was prepared by digestion in concentrated sulphuric acid with dropwise additions of 50 per cent. hydrogen peroxide. The analysis of the solution for mercury was based on the addition of an excess of an alcoholic solution of a diorganic mercurial which reacted with a weakly acid solution of mercury to form two molecules of the corresponding organic mercury compound; the resulting organic mercurial was determined by the colour formed from reaction with dithizone. Four dimercurials di-*p*-tolylmercury, diphenylmercury, dinitrophenyl-mercury, and bis-*m*-($\alpha\alpha\alpha$-trifluorotolyl) mercury, were found to react quantitatively but required different reaction conditions; the ditolyl compound

was chosen as it was more stable towards acid and had the most favourable solubility ratio. The spectrophotometric curve for the resulting dithizonate had a minimum at 480 mμ. Fuming sulphuric acid was tried in place of the concentrated acid in the digestions but it offered no advantages and caused more violent digestions. Much of the success of the digestion was believed to be due to a gentle oxidation, avoiding a sudden vigorous reaction when mercury was lost. In the absence of chloride there was an increasing loss of mercury due to adsorption on glass with increasing acidity, reaching 18 per cent. at 1·8N; there was no adsorption of mercury in 24 hours from a solution 0·3N in chloride. 1 mg. of iron, cobalt, nickel, zinc, cadmium, lead, iron, copper, manganese, or bismuth did not interfere, but silver required an additional extraction of the chloroform phase. Using a spectrophotometer amounts down to 0·5 μg. could be determined; the precision of the procedure as applied to mercury (0 to 100 μg.) in soil samples was 5 per cent. R. E. S.

Mercury in Urine, Determination of. A. C. Rolfe, F. R. Russell and N. T. Wilkinson. (*Analyst*, 1955, **80**, 523.) A trial of published methods gave low recoveries of mercury when it was added to fresh urine as mercuric sulphate; if the urine was allowed to stand after the addition of the mercuric sulphate the results obtained by each method were even lower. In the method developed, 50 ml. urine was oxidised by heating with nitric acid and potassium permanganate in a 350 ml. glass pressure bottle; excess permanganate was removed with ammoniacal hydroxylamine solution. An aliquot of this solution containing up to 100 μg. of mercury was extracted with dithizone in toluene followed by re-extraction into 5N hydrochloric acid. Ammoniacal hydroxylamine was then added with a further dithizone extraction, excess being removed with sodium hydroxide. After dilution with toluene the extinction of the solution was measured with a Spekker photoelectric absorptiometer, using Calorex H 503 heat filters and Ilford No. 602 blue filters in conjunction with a tungsten-filament lamp. Toluene was used in the comparison cell and it was necessary for a blank determination to be carried out on all reagents used. The amount of mercury was obtained from calibration curves prepared using known amounts of standard mercuric sulphate solution. The method could be used in the presence of copper. Mercury was determined over a range of 0 to 100 μg. with an accuracy of ± 1 μg. below 50 μg. and ± 3 μg. for amounts between 50 and 100 μg. R. E. S.

CHEMOTHERAPY

Bis-*iso*quinolinium and Bis-quinolinium Salts, Antifungal Activities of. H. O. J. Collier, M. D. Potter and E. P. Taylor. (*Brit. J. Pharmacol.*, 1955, **10**, 343.) The antifungal activities of polymethylene bis-quinolinium and bis-*iso*-quinolinium salts with 10 to 20 methylene groups were determined against a human strain of *Trichophyton mentagrophytes*. In both series activity increased with chain length up to the tetradecamethylene member; activity showed a marked drop with the eicosane member. The tetradecamethylene and hexadecamethylene members of both series inhibited growth in Sabourand's broth of 11 strains of 6 species of pathogenic fungi, at concentrations between 0·3 and 10 μg./ml. Human serum and hair slightly decreased the antifungal power of the tetra- and hexa-decamethylene bis-*iso*quinolinium salts; bovine bile markedly antagonised the action of the hexadecamethylene member. Spores of *T. mentagrophytes* in saline suspension were still viable in the presence of hexamethylene bis-(*iso*quinolinium methosulphate) after 24 hours at 20° C. However, incubation of the spores in Sabourand's broth containing 1·25 μg./ml. of the compound, caused 100 per cent. mortality after 7 days at 27° C. G. P.

PHARMACY

NOTES AND FORMULÆ

Enteric Coated Tablets, Disintegration of, in Simulated Digestive Juices. R. Crisafio, J. Taylor and L. G. Chatten. (*Drug Standards*, 1955, **23**, 1.) Disintegration tests were carried out with an apparatus similar to that described in the U.S.P. XIV, modified to provide a regulated rubbing action on each tablet, and using a larger disintegration chamber. Commercial enteric-coated tablets were tested using simulated gastric juice prepared according to the formula of Toplis (pH 1·6) and the one proposed for the U.S.P. XV (pH 1·2). Of 64 products examined, 31 failed to resist the action of the gastric media for a period of 1 hour under the conditions of the test. Tablets which did not disintegrate in the acid media were tested in simulated intestinal juice, Toplis (pH 8·0) and U.S.P. XV (pH 7·5) and the disintegration times recorded. No significant difference was found to exist between the results with the two gastric media, but significant differences were observed between the alkaline media. With some products the two alkaline media gave similar results, whereas others showed considerable differences, possibly as a result of the difference in pH between the media. The application of this method of testing is discussed in the light of previous investigations and of the relationship between *in vitro* and *in vivo* tests. G. B.

Enteric Coated Tablets, The Disintegration of. N. E. Brindamour and H. G. DeKay. (*Drug Standards*, 1955, **23**, 10.) Tablets coated with cellulose acetate hydrogen phthalate, which had been shown to be 93 per cent. efficient when tested radiographically, were compared with commercial enteric-coated tablets, using a series of artificial gastric and intestinal juices and rat gastric juice, *in vitro*. The apparatus described in the U.S.P. XIV was used, tablets being weighed before the test, and after periods of 1, 2 and 3 hours in the gastric juices. Only unbroken tablets were used in estimating the loss in weight due to the corrosive action of the gastric juices. Disintegration times were measured in the alkaline juices, using the same apparatus. The tablets were also tested in the rat stomach and intestine, *in vivo*. As a result of these experiments, the authors recommend the following solutions for testing the tablets: gastric solution, sodium chloride 2 g., pepsin 3·2 g., hydrochloric acid 2·5 ml., water to 1000 ml.; intestinal solution, pancreatin 10 g., calcium chloride 10 per cent. solution 10 ml., 0·2M dipotassium phosphate 250 ml., 0·2M sodium hydroxide 118 ml., ox bile extract 4 g., water to 1000 ml. G. B.

Neomycin, Release of, from Selected Ointment Bases. W. T. Hill, Jr., J. F. Bester and O. H. Miller. (*Drug Standards*, 1955, **23**, 80). Steel cylinders filled with ointments containing neomycin in various bases were placed on agar plates seeded with a standardised suspension of the spores of *Bacillus subtilis*, and incubated. The degree to which neomycin was released from the bases was assessed from measurements of the zones of inhibition produced. Neomycin was most readily released by washable emulsion bases such as hydrophilic ointment U.S.P., carbowax bases and jelly bases such as those containing methylcellulose and carboxymethylcellulose, and from a base containing Spans 40 and 45. Oily and absorption bases released neomycin to a lesser extent. Bentonite base was not suitable since the antibiotic, being cationic, becomes firmly bound to the bentonite. Neomycin cracks emulsions formed with sodium lauryl sulphate and precipitates certain gums from jelly bases. The ointments were re-examined after 30 and 60 days' storage at room temperature

and a slight decrease in potency was observed in aqueous ointments over 60 days. It is recommended that these ointments should be freshly prepared and the packages dated. G. B.

Polyvinylpyrrolidone as an Adjunct to Antibacterials. H. Sheinaus and G. J. Sperandio. (*Drug Standards*, 1955, **23**, 96.) Solutions of many antibacterial agents were tested by the cylinder-plate method against *Micrococcus pyogenes* var. *aureus*. Tests were repeated with the addition of varying amounts of polyvinylpyrrolidone, which had previously been shown to have a negligible antibacterial action. The zones of inhibition remained unchanged for most of the preparations tested, including antibiotics, mercury compounds, quaternary ammonium compounds and dyes. Polyvinylpyrrolidone decreased the effect of chloroxylenol, zinc sulphate and iodine, while in the presence of polyvinylpyrrolidone the effect of sodium hypochlorite was substantially increased. In the case of hexachlorophene, an optimum concentration was observed, beyond which the antibacterial effect decreased. The sodium hypochlorite/polyvinylpyrrolidone mixtures were assayed for available chlorine, and an inverse relationship was found to exist between size of zone of inhibition and volume of titration solution required. It is suggested that either sodium hypochlorite combines with polyvinylpyrrolidone, or iodine which is released in the assay process (U.S.N.F.IX) may be held as a complex with it. G. B.

Quaternary Ammonium Salts, The Relationship of Charge Density, Antibacterial Activity and Micelle Formation of. J. A. Cella, L. A. Harriman, D. N. Eggenberger and H. J. Harwood. (*J. Amer. chem. Soc.*, 1955, **77**, 4264.) A series of four phenyl-containing quaternary ammonium salts $[R(CH_3)_2C_{12}H_{25}N]Cl$ was compared with the series of *cyclo*hexyl analogues. In both series the cyclic structure is separated from the nitrogen atom by from 0 to 3 methylene groups. The antibacterial results do not substantiate an earlier hypothesis that the antibacterial activity of quaternary ammonium salts is influenced by the charge density on the nitrogen atom. In the series studied, an inverse relationship between antibacterial activity and critical micelle concentration was shown. It is suggested that simple steric effects are a major factor in determining the tendency towards micelle formation and the biological activity of cationic surface active agents. These phenomena may be a function of the ability of the molecules to undergo close packing which in turn influences the size of the micelle or the extent of interaction with the bacterial surface. A. H. B.

Tablet Lubricants, Water-soluble. M. Smilek, F. P. Cosgrove and E. P. Guth. (*Drug Standards*, 1955, **23**, 87.) Tablets of sodium bicarbonate, ascorbic acid, calcium lactate and nicotinic acid were prepared from granules lubricated with polyoxyethylene monostearates (Myrj 51 and 53) and polyoxyethylene lauryl alcohol (Bryj 35). The lubricating agents were dissolved in acetone and added to the granules which were dried in air. Lubricating properties were assessed by measuring the force required to eject a tablet from a hand machine, and by determining the minimum quantity of lubricant necessary to prevent granules sticking to the punches of a rotary machine. All polyoxyethylene compounds tested had about the same efficiency as lubricants, approximately one third that of magnesium stearate. The tablets disintegrated rather more rapidly than those made with magnesium stearate. They did not swell, but gradually dissolved, leaving thin wafer-like films which finally also dissolved. It is suggested that these substances would be useful as lubricants for the preparation of lozenges and buccal tablets. G. B.

PHARMACOLOGY AND THERAPEUTICS

Alphaprodine Hydrochloride and Levallorphan Tartrate; Effects on Respiration. M. Swerdlow, F. F. Foldes and E. S. Siker. (*Amer. J. med. Sci.*, 1955, **230**, 237.) Alphaprodine hydrochloride (1 : 3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride) is a short-acting analgesic which can be used with advantage to supplement nitrous oxide-oxygen thiopentone sodium anæsthesia. Levallorphan tartrate ((−)-3-hydroxy-*N*-allylmorphinan tartrate) is a narcotic antagonist. A study of the effect of these two drugs on respiration was carried out on 210 conscious patients who underwent surgery under low spinal or epidural anæsthesia. The changes of respiratory rates were measured in 120 patients, in three groups of 40, breathing room air, who were given 1 mg./kg. of alphaprodine. The drug was given to one group before, to the second together with, and to the third after levallorphan tartrate in doses of either 0·01 or 0·02 mg./kg. It was shown that alphaprodine caused a marked depression of the respiratory rate; that levallorphan tartrate given after, together with or before, corrected or prevented this fall to a large degree; that there was no marked difference between the two dose levels of levallorphan; and that there were no significant effects on pulse rate or blood pressure. In the second part of the study kymographic tracings were made of the respiration of 90 patients, in three groups of 30, breathing oxygen in a closed circuit. One mg./kg. of alphaprodine was given to all patients, and levallorphan was given to the first group before, to the second together with, and to the third after the analgesic in doses of 0·01, 0·02 and 0·04 mg./kg. It was shown that alphaprodine affected alveolar ventilation rate, minute volume, and respiratory rate to a greater extent than depth of respiration. Levallorphan given after, together with or before alphaprodine corrected or prevented the respiratory depression, but was more effective in counteracting the decrease in depth of depression than the rate. The best effects were obtained with a dose of 0·04 mg./kg. of levallorphan. Good results were also obtained, especially with the higher dosage of levallorphan, against the alphaprodine-induced decrease of tidal volume, depression of minute volume and depression of alveolar ventilation. The authors conclude that levallorphan tartrate offers considerable protection against the respiratory depression induced by alphaprodine hydrochloride. S. L. W.

Bradykinin and Substance P, Comparative Study. B. Pernow and M. Rocha e Silva. (*Acta physiol. scand.*, 1955, **34**, 59.) Both these substances are known to be polypeptides having a slow contracting effect upon several smooth muscle structures but causing a fall in blood pressure. Such effects are not influenced by atropine, antihistamines or ganglion-blocking drugs. Both substances are rapidly destroyed by chymotrypsin. However, bradykinin is less strongly adsorbed on aluminium oxide than substance P. Bradykinin has a higher R_F value than substance P, using butanol/acetic acid/water solvent. Furthermore, these two substances give separate peaks of activity when subjected to paper electrophoresis. On pharmacological test preparations, the effect of bradykinin on smooth muscle structures is slower than that of substance P. The hen cæcum is very sensitive to substance P but rather insensitive to bradykinin. The depressor action of substance P is more pronounced than that of bradykinin. M. M.

Chlorpromazine, Reversibility of Induced Psychosis with. B. E. Schwarz, R. G. Bickford and H. P. Rome. (*Proc. Mayo Clin.*, 1955, **30**, 407.) Psychic disturbances induced by 50 μg. of lysergic acid diethylamide (LSD-25) or by

400 mg. of mescaline, given orally to normal human subjects, had similar symptomatic patterns. The most striking effects common to both drugs were affective reactions, such as mania, anxiety, uncontrollable laughing and crying, withdrawal and suspicion. Visual hallucinations, synæsthesia and disturbances in the body image were particularly prominent. Thought disturbances consisted of loosening of association, blocking, increased communicability and loquaciousness. Catatonia was present to some degree in most subjects. In addition, mescaline frequently, and LSD-25 occasionally, caused nausea, vomiting, mydriasis and blood pressure variations. Chlorpromazine (25 mg. intramuscularly) administered at the height of the psychosis (two hours after LSD-25 administration or three hours after mescaline) returned mental conditions to normal. EEG changes induced by the hallucinogenic drugs also reverted to normal patterns, in most cases, after chlorpromazine. The implication of neurohumoural agents in the actions of these drugs is discussed. G. P.

2:4-Dichloro-6-phenylphenoxyethyl Diethylamide, a Potentiating Agent, Inhibition of Drug Metabolic Pathways by. J. R. Fouts and B. B. Brodie, (*J. Pharmacol.*, 1955, **115**, 68,) Blockade of drug metabolism has been described for diphenylpropylacetic acid and its β-diethylaminoethyl ester (SKF-525-A). Similar activity has now been demonstrated for 2:4-dichloro-6-phenylphenoxyethyl diethylamine HBr (Lilly 18947). This compound prolonged duration of sleep induced in mice by hexobarbitone, by inhibiting the metabolism of the barbiturate. *In vitro*, the enzyme systems present in the supernatant fractions of centrifuged liver homogenates which effected the oxidation of the side-chain of hexobarbitone, dealkylation of aminopyrine, deamination of amphetamine, ether cleavage in codeine, hydroxylation of acetanilide and conjugation of morphine were inactivated by the potentiating agent. The inhibitory activity of Lilly 18947 for most of these reactions was comparable with that of SKF-525-A (on the codeine ether-cleavage and hydroxylation of acetanilide, however, Lilly 18947 was considerably the more potent) and it is likely that the two substances have similar modes of action. Preliminary evidence suggests that Marsilid, (1-*iso*propyl-2-*iso*nicotinyl hydrazide), also acts on the same metabolic pathways. G. P.

Diethylaminoethoxyethylphenyl-1-*cyclo*pentane Carboxylate, Antitussive Activity of. S. Levis, S. Preat and F. Moyersoons. (*Arch. int. Pharmacodyn.*, 1955, **103**, 200.) This compound, one of a series of phenyl*cyclo*alkanecarboxylic acids studied for antitussive activity, is more active than codeine phosphate and has a low toxicity. Antitussive activity was determined in anæsthetised cats in which the superior laryngeal nerve was stimulated from a constant current square wave stimulator. Spasms of coughing were recorded from a thread attached to the skin of the abdomen. The percentage of inhibition and duration were determined for each compound. This compound has only a weak vasodepressor action and no effect on respiration. The compound also has antispasmodic, local anæsthetic and weak mydriatic actions. G. F. S.

Glycyrrhetinic Acid, Effects of, on Salt and Water Metabolism. E. E. Galal. (*Brit. J. Pharmacol.*, 1955, **10**, 305.) DOCA-like activity on sodium and potassium metabolism in man has been reported for liquorice extracts and glycyrrhetinic acid. Beneficial effects were also obtained with these drugs in patients with Addison's disease. In this study, however, they had no effect on sodium or potassium balance in adrenalectomised rats. Even with prolonged treatment with glycyrrhetinic acid there was no significant improvement in the

level of serum electrolytes, body weight or survival time. The acid had an anti-diuretic action in normal water-loaded rats, conscious or anæsthetised, and on a conscious dog. This action was still present in neurohypophysectomised rats. Increased tubular reabsorption was suggested as the mode of action where the acid was given parenterally; delay in water absorption from the alimentary tract was sufficient to account for the water-retaining effect of the drug when given orally. It was concluded that the actions of the drug are different from those of DOCA. G. P.

5-Hydroxytryptamine in Mental Diseases and its Antagonism to Lysergic Acid Derivatives. A. Cerletti and E. Rothlin. (*Nature, Lond.*, 1955, **176**, 785.) 2-Brom-(+)-lysergic acid diethylamide (BOL-148), like lysergic acid diethylamide (LSD-25), antagonised peripheral actions of 5-hydroxytryptamine (5-HT). The antagonism of 5-HT on the isolated uterus and kidney of the rat, and on the blood pressure and bronchi in cats, by BOL-148 was equal to or slightly greater than that of LSD-25. The potentiation of barbiturates by 5-HT was also antagonised to the same degree by both agents. Specificity for the antagonism was high. There was no anti-adrenaline, antihistamine or anti-acetylcholine activity with the doses used. However, BOL-148 had none of the central excitatory actions of LSD-25; on the contrary it induced sedation in normal and waltzing mice. Also, LSD-25 in small doses caused bradycardia and a fall in blood pressure in cats, whereas doses up to 1 mg./kg. of BOL-148 were inactive in this respect. In man BOL-148 had none of the hallucinogenic actions shown by LSD-25; the only effects experienced were sedation fatigue and sometimes nausea. It was concluded that the pharmacological antagonism of 5-hydroxytryptamine by LSD-25 can no longer be held to explain the hallucinogenic activity of LSD-25 on the brain. G. P.

Iron-Dextran Intramuscular Hæmatinic, Pharmacology of. L. E. Martin, C. M. Bates, C. R. Beresford, J. D. Donaldson, F. F. McDonald, D. Dunlop, P. Sheard, E. London and G. D. Twigg. (*Brit. J. Pharmacol.*, 1955, **10**, 375.) Iron combined with low-molecular-weight dextran (iron-dextran or "Imferon") was compared with saccharated iron oxide for hæmatinic activity and general toxicity. Uptake of iron-dextran from the blood by the cells of the reticulo-endothelial system was slower, and *in vitro* anticoagulant activity less, with iron-dextran than with saccharated iron oxide. The urinary and fæcal iron excretion was of the same order for the two agents. Acute toxicity in mice of iron-dextran was about one-third of that of saccharated iron oxide. Heavy iron precipitation and hæmorrhage in the lungs of rabbits was observed after doses of saccharated iron oxide equivalent to 150 mg. Fe/kg. Iron-dextran at a dose-equivalent of 500 mg. Fe/kg. caused only slight deposition and no hæmorrhage. Domestic piglets, which suffer from a naturally-occurring hypochromic anæmia during the first weeks of neonatal life were given intramuscularly a dose of iron-dextran corresponding to 26 mg. Fe/kg. During the first 14 days after injection they utilised 93 per cent. of the dose of iron administered. G. P.

6-Mercaptopurine in Acute Leukæmia. F. G. J. Hayhoe. (*Lancet*, 1955, **269**, 903.) This report is based on a study of 15 adults with acute leukæmia treated with 6-mercaptopurine during the last two years. Four of the cases were lymphoblastic, 6 myeloblastic, and 5 monocytic. The 6-mercaptopurine was given usually in a single daily oral dose at an initial rate of 2·5 mg./kg. Most patients therefore received 120 to 200 mg. daily during the early stages of treatment. Dosage was maintained at this level until suppression of leukæmic

proliferation became manifest by a fall in the peripheral leucocyte-count and by a reduction in the proportion of primitive cells in the blood and bone-marrow or, in unresponsive patients, until an adequate therapeutic trial had been continued for 3 weeks. When evidence of response was obtained intermittent therapy or maintained treatment at a lower dosage was administered until definite leucopenia was produced. When a complete remission was obtained by this means the drug was discontinued and not resumed until relapse threatened. Where remission was only partial frequent intermittent courses of treatment were given in an attempt to prevent recrudescence. Seven of the patients experienced remission, which was partial in 5 and complete in 2. The complete remissions occurred in patients with myeloblastic and lymphoblastic leukæmia and lasted respectively 3 months and more than 8 months. The partial remissions were obtained on 1 patient with myeloblastic, 1 with lymphoblastic and 3 with monoblastic leukæmia. Gastro-intestinal toxic effects were not observed in most of the patients, but in 2 cases anorexia, nausea and vomiting were unpleasantly severe. The author concludes that 6-mercaptopurine is at present probably the agent of choice in myeloblastic and monoblastic leukæmia of adults. S. L. W.

Nitrogen Mustard and Tretamine (Triethylene Melamine), Hæmopoietic Depression from. R. G. Mrazek and T. J. Wachowski. (*J. Amer. med. Ass.*, 1955, **159**, 160.) Nitrogen mustard and tretamine have been proved to be effective drugs in the treatment of the malignant lymphomas but they may cause severe and uncontrollable depression of the hæmopoietic system. In the present study 100 patients with malignant lymphoma were treated with either one or other of the drugs, a total of 189 courses being given. Hæmopoietic depression occurred in 54 of the 100 patients; 8 had alarming bone marrow depressions and 5 of these died. The incidence of complications did not appear to be related to the specific disease process. Previous treatment with irradiation or chemicals was the factor most directly related to the occurrence of peripheral blood depression. A second factor of importance was the general condition of the patient; the bone marrows of those patients who were debilitated or had widespread disease were affected most by the medication. The patients with early disease tolerated initial courses of either drug without appreciable drops in blood cell count. It is imperative that the hæmatological status of all patients be known before treatment is instituted and that frequent checks be made as treatment progresses. Hæmopoietic depression may be observed 10 to 51 days after the beginning of treatment and careful observation should continue for at least this period. Once a serious leucopenia or thrombocytopenia has occurred the only effective treatment is repeated transfusion. Eighty-one per cent. of the patients in this series improved under treatment, but residual malignant lymphoma was present in all the patients who came to autopsy. S. L. W.

Noradrenaline and Adrenaline Content of Cat Organs, Effect of Amine Oxidase Inhibitors on. U. S. von Euler and S. Hellner-Björkman. (*Acta physiol. scand.*, 1955, **33**, Suppl. 118, 21.) A study is made of the effect of various amine oxidase inhibitors (propamidine, methylamphetamine, choline-*p*-tolyl-ether, ephedrine and cocaine) on the adrenaline and noradrenaline content of the cat heart, spleen and liver. In no instance were highly significant changes observed, though increased noradrenaline figures in the heart were observed after propamidine in several cases. Increased adrenergic nerve activity caused by carotid occlusion, carotid sinus denervation or electrical stimulation of the splenic nerves had no consistent effect on the catechol amine content of the organs in the presence of amine oxidase inhibitors. M. M.

Noradrenaline and Adrenaline, Urinary Excretion during Recumbency and Standing. U. S. von Euler, R. Luft and T. Sundin. (*Acta physiol. scand.*, 1955, **34**, 169.) The free catechol amines in the urine of 15 healthy adults were assayed, subsequent to extraction, on the blood pressure of the cat and the hen rectal cæcum. It was found that when the person was placed on a tilting table at an angle of 75 degrees for 3 or 4 hours, there was a considerably increased urinary output of noradrenaline in comparison with the corresponding excretion in the recumbent position. This increased production of noradrenaline is interpreted as the result of reflex activation of the vasomotor system induced by the orthostatic fall of the systolic blood pressure. The excretion of adrenaline in urine during the tilting test showed a slight to moderate increase, probably depending on various stress factors during standing. M. M.

Noradrenaline in the Treatment of Severe Shock. I. E. W. Gilmour. (*Brit. med. J.*, 1955, **2**, 1248.) (−)-Noradrenaline bitartrate was used in the treatment of 4 cases of shock caused respectively by hæmorrhage and post-operative collapse (two cases), post-anæsthetic inhalation of gastric contents combined with anoxia, and toxæmia. One of the hæmorrhage cases died from pulmonary embolism but in the other three cases almost immediate improvement in the blood pressure followed its administration. The noradrenaline was given by intravenous drip in the form of 4 ml. of Levophed in 1000 ml. of glucose-saline, the rate of administration varying from 18 to 80 drops per minute but in one case where 80 drops per minute was insufficient the concentration was doubled. The blood pressure must be taken every minute initially until it is stabilised, the rate of drip being varied accordingly. It is suggested that noradrenaline should only be used in severe shock when other "orthodox" methods have failed. H. T. B.

Pennyroyal Poisoning. W. B. Vallance. (*Lancet*, 1955, **269**, 850.) This is a report of a fatal case of poisoning after the use of pennyroyal as an abortifacient. The drug was taken by a healthy married woman aged 24, in the third month of pregnancy, and produced abortion, vaginal bleeding, hæmolytic anæmia, and acute tubular necrosis of the kidney, with death from uræmia on the 14th day. Before admission to hospital, and subsequent to the abortion which was followed by heavy bleeding, she developed a widespread rash and pyrexia; she also complained of nausea, vomiting, abdominal pain, and diarrhœa. It was not possible to ascertain how much pennyroyal was taken, but in any case the effect of the drug on any particular person is unpredictable. One teaspoonful of the oil has been known to produce convulsions, and there is a case on record where a patient recovered from coma following ingestion of 15 ml. of essence of pennyroyal. S. L. W.

***Rauwolfia serpentina* Benth., Anti-acetylcholine and Antihistamine Actions of the Total Alkaloids.** M. L. Chatterjee and H. F. Hausler. (*Nature, Lond.*, 1955, **176**, 701. Experiments were carried out on isolated strips of guinea-pig ileum in Dale's bath, containing oxygenated Ringer-Locke's solution at 35° C., and the modifications caused by varying concentrations (10^{-6} to 10^{-4} g./ml.) of extracts of *Rauwolfia serpentina* (total alkaloids extracted in 2 per cent. hydrochloric acid) on the action of acetylcholine (10^{-8} g./ml.) or of histamine (10^{-8} to 10^{-7} g./ml.) were studied. A concentration of the extract of 5×10^{-5} g./ml. and stronger, completely annulled the effect of 10^{-8} g./ml. of acetylcholine. Extracts of rauwolfia in concentrations of 5×10^{-5} g./ml. and stronger, applied 30 to 50 sec. before the addition of histamine, inhibited the action of 10^{-8} or 5×10^{-8} g./ml. of the latter. A stage of slight potentiation of the action of

(ABSTRACTS *continued on p.* 224).

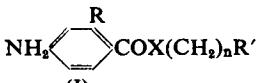
sentences such as this are common. "The therapeutic comparison between the disease behaviour in the control and the trial group is necessarily restricted to that of one or the other nosographic criterion which has been chosen for observation by the investigator because he considered it representative of the disease." The author is also inconsistent in his use of abbreviations (e.g., the tangent of an angle is referred to as tg. on p. 169 and tang on p. 355, and it is difficult to see why the orthodox symbol tan is avoided) and not always accurate in his references (e.g., to Burns, for Burn, on p. 255 and p. 349). The non-mathematical should be warned that in spite of the clinical approach, they will not be spared much algebra and an occasional and perhaps unnecessary flavour of trigonometry. MILES WEATHERALL.

(ABSTRACTS *continued from p.* 219).

both acetylcholine and histamine was noted in a few cases during the phase of recovery of the action of acetylcholine and histamine on repeated changing of the bath fluid after an earlier observation of the action in the presence of rauwolfia extract. A. H. B.

Riboflavine Excretion Technique, Reliability in Determining Availability of Coated Tablets. D. G. Chapman and J. A. Campbell. (*Canad. J. Biochem. Physiol.*, 1955, **33**, 753.) Determination of the urinary excretion of riboflavine in human volunteers is a valid and reliable procedure for determining the physiological availability of coated tablets. Eight volunteers receiving a normal diet were given 1, 3 and 5 mg. amounts of riboflavine. Excretion was the same whether these amounts were given as single or divided doses. With doses of 1, 3, 5, 7·5 and 10 mg. there was a linear relationship between the excretion and the dose, but the response line did not pass through the origin. In calculating the availability of riboflavine from a tablet, a curve for each subject should be referred to and there is a suggestion of a slope difference between subjects. G. F. S.

Thiocaine and Related Compounds, Alkoxy Analogues of, Corneal Anaesthetic Activity and Toxicity. F. P. Luduena and J. O. Hoppe. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 393.) Procaine and a series of its derivatives of the general formula (I) below were tested for anæsthetic activity on the rabbit cornea. The concentration required to produce anæsthesia lasting for 5 minutes was calculated and compared with the concentration of cocaine required to produce the same effect. The LD50 of each substance was determined in mice and compared with that of cocaine. Replacement of the oxygen atom (X) in procaine by S resulted in a sixfold increase in activity and toxicity. In the sulphur analogue (thiocaine), introduction of a 2-propoxy group at R produced a 130-fold increase in activity with a 13-fold increase in toxicity. In this series (where X = S) activity increased with the length of the 2-alkoxy side chain, the 2-hexyloxy derivative being particularly active. Toxicity increased with the length of side-chain, but to a lesser extent. In the procaine series (X = 0), activity and toxicity also increased with the length of the 2-alkoxy group. A moderate increase in activity was obtained by substituting a methylpiperidyl group for the diethylamino group in the thiocaine series. The ratio of activity to toxicity (taking cocaine as 1) varied from 0·16 for thiocaine to 8·3 for its 2-hexyloxy derivative. All the compounds except procaine, thiocaine and 2-ethoxyprocaine were more active than cocaine, and all the 2-alkoxy derivatives of thiocaine were more active than cinchocaine. G. B.



(I)

X=O or S