ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

Ergot Alkaloids, Identification and Separation of. H. Hellberg. (*Farm. Revy*, 1951, **50**, 1733.) I, *Systematic Extraction.* The partition ratios between buffers of varying *p*H and ether or benzene have been determined for a number of ergot alkaloids, with the object of devising improved methods of separation. Ether-water partition ratios are quoted for ergocristinine, ergotaminine, ergotamine, ergometrinine, ergometrine and *d*-lysergic acid; benzene-water ratios are also given for ergocristinine, ergotaminine and ergotamine. Distinct *p*H-partition curves are obtained for the extraction of individual alkaloids by both ether and benzene. Existing official and non-official methods of assay are discussed and criticised in the light of the experimental results. The partition values so obtained give support to the method, suggested by Knudsen and Grove on the basis of a mathematical treatment, for the separation of ergotamine, and ergotaminine by systematic extraction. Losses of alkaloids, which may amount to 10 per cent. with this experimental method, are attributed to unspecified ageing phenomena in the ergotamine solution. II, *Countercurrent Distribution.* Craig's counter-current distribution technique is employed experimentally to obtain distribution curves for the partition of a number of ergot alkaloids between benzene and various phosphate buffers. The experimental curve for ergotaminine closely follows the theoretical one calculated from the known partition ratios according to the method of Craig. Agreement between experimental and theoretical curves for ergotamine is less satisfactory; this is attributed to the probability of impurity in the sample. The use of Craig diagrams in the identification and assay of ergot alkaloids is described and methods based on this technique are suggested for the estimation of physiologically active ergot alkaloids in dispensed medicines. A preliminary attempt has been made, with some success, to resolve ergotoxine into its components by application of the extended " double withdrawal " distribution technique.

J. B. S.

ANALYTICAL CHEMISTRY

Alkaloids, Colorimetric Determination of. F. J. Bandelin. (*J. Amer. pharm. Ass.*, 1950, **39**, 493.) It was found that a number of alkaloids could be precipated quantitatively from aqueous solutions with ammonium reineckate. An aqueous solution of the alkaloid containing sulphuric acid was taken, excess of ammonium reineckate solution added, and the precipitated alkaloidal reineckate was filtered off, dissolved in acetone and made up to definite volume. The acetone solution of the alkaloidal reineckate was then examined spectrophotometrically for its light absorption at 525 mμ. The pure alkaloidal salts (2 to 10 mg.) used in this investigation and found to give satisfactory results were: atropine sulphate, quinine sulphate, strychnine sulphate, emetine hydrochloride, hyoscine hydrobromide, cinchonidine sulphate, cinchonine, quinidine sulphate, sparteine sulphate, hydrastine hydrochloride, cocaine hydrochloride, and pilocarpine nitrate. The method is not applicable

to morphine, ephedrine and colchicine, which are not completely precipitated by ammonium reineckate. A method is given for the determination of alkaloids in tablets based on this assay. Various organic bases other than alkaloids gave insoluble reineckates and therefore interfered with the determinations. R. E. S.

***p*-Aminobenzoic Acid Derivatives, Separation of, by Paper Chromatography.** E. Kelemen, B. Tanos and D. Halmagyi. (*Biochem. J.*, 1950, **47**, 138.) Urine, 2·5 to 20 μl., was applied directly to the chromatogram paper without any preliminary treatment. The chromatogram was developed by the upward-running method using *n*-butanol saturated with water. Ehrlich's reagent was used as the colouring agent. Ochre-yellow spots appeared on spraying, even at room temperature. Results must be observed within about one hour, before the paper dries. *p*-Aminobenzoic acid had $\mathbf{R_F}$ value 0·68 to 0·72, *p*-aminohippuric acid 0·07 to 0·100 and *p*-aminosalicylic acid 0·26 to 0·30 and the normal variations in urine *p*H and salt concentration had little effect on these values. The method permitted the detection of as little as 1 μg. of each compound and of one of the compounds in the presence of high concentrations of the other two. Where possible the amount of substance present should not exceed 20 μg. as this causes the spots to overlap. With less than this amount the area of the spots may be used for quantitative comparisons (error ± 5 to 12 per cent.). Elution of unsprayed areas followed by photometric determination failed to give better results. Examination of samples of normal urine showed that urea gave a lemon coloured spot ($\mathbf{R_F}$ 0·25 to 0·31) which could be separated from *p*-aminosalicylic acid by using phenol or *iso*-butyl alcohol. The $\mathbf{R_F}$ values in *iso*-butyl alcohol were 0·40 to 0·45 for the acid and 0·20 to 0·25 for the urea, and in phenol 0·57 to 0·60 and 0·65 to 0·70 respectively. With plasma levels of 2 mg. of *p*-aminobenzoic acid/100 ml., resulting from oral or intravenous administration of this compound, it was not detectable in the urine, the chromatogram showing that *p*-aminohippuric acid was being excreted. Even with higher plasma levels of *p*-aminobenzoic acid, *p*-aminohippuric acid was the main excretion product.

A. D. O.

Barium, Limit Test for. K. B. Berg and F. Reimers. (*Dansk Tidsskr. Farm.*, 1950, **24**, 291.) It has previously been shown that the reproducibility of limit tests for sulphate can be considerably increased by the use of a barium chloride solution in which there has been precipitated a barely perceptible amount of barium sulphate. In the reverse case of precipitation of traces of barium by sulphate, the precipitation is much more satisfactory from the beginning, and, in the absence of salts, seeding with barium sulphate is unnecessary. The precipitation of traces of barium differs from that of traces of sulphate in that the opalescence is more reproducible, attains its maximum more quickly, and is only slightly influenced by shaking or the presence of nitrates. Change of temperature has little influence on the precipitation. The best results are obtained if the solution to be tested is poured on to the reagent, and then shaken. In the presence of salts, especially nitrates, citrates and tartrates, it is necessary to use the seeding method, as follows. To 1 drop of a barium chloride solution containing 100 μg. of barium, 1 ml. of 2N sulphuric acid is added. The mixture is shaken and allowed to stand for 1 minute. To this reagent 10 ml. of the solution to be tested is added, the mixture is shaken for 10 seconds, and the turbidity is observed after 5 minutes. Comparison liquids are either

a blank composed of the above reagent with 10 ml. of water, or a mixture of 5 ml. of the barium solution with 1 ml. of 2N sulphuric acid. G.M.

Calcium Products, Assay of, by Schwarzenbach Method. A. M. Matocks and H. R. Hernandez. *J. Amer. pharm. Ass.*, 1950, **39**, 519.) An investigation was made into the use of disodium ethylenediaminetetracetic acid in the determination of calcium in pharmaceutical products. In preliminary work the calcium salts were dissolved in water or in dilute hydrochloric acid when required, *p*H 10 buffer and 4 to 5 drops of indicator (Eriochrome Black-T) were added, and solutions were titrated with the disodium ethylenediaminetetracetic acid containing small amounts of magnesium chloride. The end-points were sharp but variable results were obtained due to a small amount of precipitate present in the solution at the end of titration. It was found that much more reliable results could be obtained if an excess of reagent were added before making the solution alkaline; a calcium complex was formed and prevented its precipitation from alkaline solution. The excess could then be titrated with a standardised solution of magnesium chloride. The method required not more than 15 minutes for 2 assays including the weighings, and a high precision was obtained, representing a considerable improvement over the official oxalate method. In some cases such as calcium hypophosphite and tribasic calcium phosphate the method was satisfactory whereas the oxalate method cannot be applied. R. E. S.

Digitalis, Chemical Assay of. B. E. Lindewald and I. Petrell. (*Farm. Notisbl.* 1950, **59**, 187.) In the method of Soos for the colorimetric assay of digitalis, the extract of the drug, purified by lead acetate, is extracted with chloroform. Actually this extraction only recovers about 80 per cent. of the glycosides, but a quantitative yield may be obtained by shaking out from alcohol (25 per cent.). The colorimetric determination is then carried out, using Kiliani's reaction. Using the modified method, the quotient indicating the relation of the biological activity of *Digitalis lanata* and *D. purpurea* to digitoxin is $3{\cdot}5 \pm 0{\cdot}4$, in place of the figure of $4{\cdot}5 \pm 0{\cdot}4$ given by Soos. G. M.

Iodine, Determination of, in Organic Compounds. K. Bucher and H. Käsermann. (*Pharm. Acta Helvet.*, 1951, **26**, 1.) The following method may be used for diiodotyrosine, thyroxine, chiniofon, iodophthalein, iodoxyl and thyroid. About 0·1 g. of substance is dissolved in 20 ml. of water, with the addition, if necessary, of a little alkali, and treated with 20 ml. of 5 per cent. solution of potassium permanganate and 10 ml. of 50 per cent. sulphuric acid. The mixture is kept in gentle ebullition for 5 minutes, cooled, and decolorised with sodium metabisulphite. Potassium permanganate solution is added drop by drop until there is a permanent yellow colour. After the addition of starch, 0·2 per cent. solution of sodium metabisulphite is added from a micro burette until the blue colour just disappears. After the addition of 15 ml. of concentrated hydrochloric acid and 5 ml. of 10 per cent. potassium cyanide solution, the mixture is titrated with 0·1N potassium iodate. It is important to filter the permanganate solution, otherwise difficultly-soluble particles may remain undissolved. In the case of chiniofon, chlorine cannot be determined in the same solution, as some is lost. The method is less suitable for thyroid on account of the large amount of material to be oxidised and the small amount of iodine present. In this case the method of the British Pharmacopœia is to be preferred. G. M.

Iron, Colorimetric Determination of, with Sodium Phenylpyruvate. R. Castagnou and G. Gaucher. (*Bull. Trav. Soc. Pharm. Bordeaux.*

1950, **88,** 104.) The colour given by ferric salts with sodium phenylpyruvate may be used for the colorimetric determination of iron, the limit of sensitivity being 2·5 mg/l. With a 1 per cent. solution of the reagent, full colour develops practically immediately for concentrations of iron above 0·05 g./l.; for lower concentrations a more dilute reagent (0·05 per cent.) should be used. After attaining its maximum the colour gradually fades. The optimum *p*H is 3·5, and the reaction is specific for iron. G. M.

Nitrates, Titrimetric Determination of. Z. G. Szabo and L. Bartha. (*Nature,* 1950, **166,** 309.) The procedure given is based on the fact that silver sulphate catalyses the reduction of nitrates to ammonia in a suitable concentration of sodium hydroxide. The reduction is effected in a boiling 3 per cent. sodium hydroxide solution containing ammoniacal silver sulphate, by the action of ferrous hydroxide precipitated from a measured sample of ferrous ammonium sulphate. When the reaction is completed, the mixture is acidified with sulphuric acid and the excess of ferrous iron is titrated with potassium permanganate. The ferrous ammonium sulphate must be employed for the reduction in large excess owing to the formation of ferrous-ferric oxide and a blank titration must also be carried out. 8 moles of $Fe(OH)_2$ are necessary for the reduction of 1 mole of nitrate. Constant errors are encountered at different nitrate concentrations and the results can be corrected. The ions Al^{3+}, Zn^{2+}, Cd^{2+}, As^{5+}, Sn^{4+}, Mo^{6+}, U^{6+}, W^{6+}, Cl^-, PO_4^{3-}, $B_4O_7^{2-}$, CH_3COO^-, ClO_4^- do not interfere with the method. The interference of the ions: V, As^{3+}, Sn^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, Br^-, ClO_3^-, CO_3^-, HCO_3^-, $S_2O_8^{2-}$ can be easily eliminated or compensated. R. E. S.

Phenolphthalein, Determination of, in Presence of Emodins. S. Ljungberg. (*Pharm. Acta Helvet.* 1950, **25,** 351.) A quantity of material (tablet powder) corresponding to 5 to 100 mg. of phenolphthalein and not more than 0·3 g. of emodin drug or extract, is shaken out with four 10 ml. quantities of acetone. The extracts are filtered and evaporated to dryness, the residue being taken up to 10 ml. of alcohol. This solution is passed through a column of 10 g. of alumina (in 10 mm. tube), and the column is washed with alcohol until the liquid running through no longer gives a red colour with alkali. The solution is made up to a definite volume, and a portion corresponding to 0·1 to 0·5 mg. of phenolphthalein is made up to 25 ml. with the addition of 2 ml. of 0·5N alcoholic potash. The extinction is then determined at 550 mμ. The figures given indicate good results in the presence of cascara, frangula, senna, podophyllin, colocynth and aloin.

G. M.

Picrolonates and Calcium, Determination of, with Cetyl Pyridinium Bromide. C. C. Washbrook. (*Analyst,* 1950, **75,** 621.) The method depends on the fact that picrolonic acid and its salts form methylene blue complexes which are soluble in organic solvents. It has been found that a mixture of nitrobenzene and trichloroethylene removes the dye complex in a single extraction. Two alternative procedures were devised; in the first the aqueous picrolonic acid solution was treated with an aqueous solution of methylene blue hydrochloride, the dyestuff complex separated by partition with the solvent and the mixture titrated with aqueous cetyl pyridinium bromide solution. When sufficient had been added, the dyestuff was liberated and transferred to the aqueous layer when the two phases were shaken together. The end-point, which is observed in the solvent phase, is indicated by the complete transfer of methylene blue to the aqueous phase. Detection of the transfer of the last traces of methylene blue may be aided by the addition

of a small quantity of an oil-soluble red dyestuff to the solvent phase. In the second procedure an aqueous solution of picrolonic acid was titrated with cetyl pyridinium bromide solution to form a complex which was then extracted with chloroform as a yellow solution, the end-point of the titration being determined in the manner used by Barr *et al.* (*J. Soc. chem. Ind.*, 1948, **67**, 45), with bromophenol blue as the indicator; the excess of cetyl pyridinium bromide forms a complex with the bromophenol blue and passes into the chloroform layer which then becomes green. The titration procedures described above were applied to the estimation of calcium with picrolonic acid, the general technique using lithium picrolonate being used, and the concentration of the picrolonate being determined by titration with cetyl pyridinium bromide; for this application the methylene blue procedure was preferred, as the end-point was more clearly indicated. The calcium solution should be treated either to eliminate or reduce the concentration of alkali metal ions before the determination is made; barium, strontium, lead, copper, thorium, iron, manganese, zinc and some organic bases formed sparingly soluble picrolonates and should be absent from the test solution. Errors involved were of the order of 3 per cent. R. E. S.

Sulphonamides, Potentiometric Titration of. J. P. LaRocca and K. L. Waters. (*J. Amer. pharm. Ass.*, 1950, **39**, 521.) A satisfactory method, utilising potentiometric titration, was adapted to the quantitative determination of the sulphonamides and was found to give excellent results in the assay of all the sulphonamides official in the U.S.P.XIII. A platinum electrode and a calomel electrode were used in connection with the potentiometers, the titrant being added in 0·1 ml. portions and the end-point determined by means of differential curves (Δ^v/Δml. against ml.); for most practical purposes the volume of titrant added at the point of maximum rise in potential was the equivalent volume, thereby eliminating the necessity of drawing the differential curves. Samples were prepared for titration according to the procedure given in the U.S.P.XIII for the various sulphonamides and the solution was then titrated to a maximum rise in potential. It was unnecessary to add ice to the solution and the titrant was added in 5-ml. quantities to within 1 ml. of the calculated equivalence point, further 0·1-ml. quantities being added until a maximum rise in potential was obtained. All samples were assayed both potentiometrically and by the official method, the sodium nitrite solution being standardised separately for each method using pure sulphonamide as reference standard, since the molarity as determined by the individual methods differed significantly. Results are given for 8 sulphonamide powders and 6 sulphonamide tablets; in general, the potentiometric method gave slightly higher and more precise results than those obtained by the U.S.P. method. R. E.S.

ORGANIC CHEMISTRY

L-Ascorbic Acid, Uniformly Labelled with ^{14}C, Synthesis of. A. A. Bothner-By, M. Gibbs and R. C. Anderson. (*Science*, 1950, **112**, 363.) A product having a specific activity of 80 μc./mg. was obtained by the following procedure, based on the synthesis of Reichstein and Grüssner. Allow bean leaves to photosynthesise in an atmosphere of $^{14}CO_2$, hydrolyse the sucrose and precipitate with ethanol. Hydrogenate the precipitate (mainly glucose) to sorbitol, in the presence of Raney nickel, oxidise to sorbose using *Acetobacter suboxydans*, centrifuge, pass through ion exchange columns, crystallise and decolorise. Dilute with carrier, acetonate in the presence of sulphuric acid, extract the diacetonesorbose with ether and oxidise with

alkaline permanganate, extracting any unchanged diacetonesorbose with ether and treating with a further quantity of the reagent. Extract the diacetone-2-ketogulonic acid with ethyl acetate at *p*H2, reflux with water and crystallise the 2-ketogulonic acid, esterify using methanol and diazomethane, crystallise from methanol-acetone, treat, under nitrogen with the theoretical quantities of sodium methoxide and of hydrogen chloride in methanol and finally purify. A further quantity of L-ascorbic acid, having a lower specific activity may be obtained by adding carrier to the oily residue from the methanol-acetone solution, crystallising and carrying out the final stages of the synthesis. G. B.

Nicotinic Acid, By-product from Manufacture of. F. K. Dittmar. (*Pharm Zentralh.*, 1951, **90**, 7.) In attempting to use nicotinic acid nitrate for the purification of nicotinic acid obtained from the oxidation of nicotine, it was found that if the crude material was heated with water for some hours a crystalline precipitate differing from nicotinic acid or its nitrate was formed. This substance was neutral in reaction, gave a reaction for the pyridine nucleus, and had m.pt., after purification, of 275°C. Apparently it is present in the original crude material. It is suggested that this substance is a very stable nicotinic anhydride. G. M.

Piperettine. F. S. Spring and James Stark. (*J. chem. Soc.*, 1950, 1177.) Piperettine was isolated in a crude state as an amorphous powder, m.pt. 100° to 112°C. from the mother liquors, after the removal of piperine, of an alcoholic extract of *Piper nigrum*. Purification was effected by chromatography on alumina and crystallisation from ethyl acetate in the form of yellow rods with a pronounced green sheen m.pt. 146°C. Piperettine, $C_{19}H_{21}O_3N$, like piperine is almost insoluble in dilute acids and alkalis, gives a blood red colour with concentrated sulphuric acid and a positive Rabat test for methylenedioxy groups. Ethanolic potassium hydroxide hydrolysis yielded piperidine and a yellow acid, piperettic acid, m.pt. 223° to 224°C., which was identified by its reactions and by synthesis at 7-(3:4-methylenedioxyphenyl) hepta-2:4:6-trienoic acid. Condensation of the acid chloride of piperettic acid with piperidine confirmed the structure of 7-(3:4-methylenedioxyphenyl) hepta-2:4:6-trienopiperidide for piperettine. J. B. S.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Pherentasin, Chemical Studies of. N. S. Olsen and H. A. Schroeder. (*J. exp. Med.*, 1950, **92**, 561.) Pherentasin is soluble in water, chloroform or ethanol in concentrations of up to 90 per cent. It can be extracted from aqueous solution by chloroform provided the aqueous solution is alkaline. It is of small molecular size, dialysable and non-protein in nature; acid solutions are stable but alkaline solutions are unstable. The activity is lost on treatment with nitrous acid and prolonged ketenisation indicating that an amino group is essential for activity. On treatment with ketene for a relatively short period, and reaction with hydroxylamine and semicarbazide, the activity is markedly decreased, suggesting the presence of an active carbonyl group. Chromatographic studies indicate that the amino group is probably primary. H. T. B.

Pherentasin, A Vasoactive Material Obtained from Blood. H. A. Schroeder and N. S. Olsen. (*J. exp. Med.*, 1950, **92**, 545.) The arterial blood of many hypertensive patients contains from 1 to 20 μg./l. of

a substance which on intravenous injection into rats induces a prolonged pressor response. It can be obtained as an extract by the following method. The blood is drawn into 3 volumes of alcohol, and more alcohol is added up to a total of 11 volumes to precipitate protein. To the clear filtrate concentrated hydrochloric acid is added and the liquid evaporated nearly to dryness in an atmosphere of nitrogen under reduced pressure, the temperature not rising above 35°C. Further purification may be effected by treatment with anionic and cationic exchange resins and by chloroform extraction. The best yield is obtained from patients with renal hypertension; smaller yields are obtained from patients with hypertension of neurogenic or endocrine origin while none of the substance appears to be present in the blood of patients with malignant hypertension and it is rarely present in the blood of normotensive patients. H. T. B.

BIOCHEMICAL ANALYSIS

Acetone in Blood and Urine, Determination of. R. Nunnikhoven and E. C. Noyons. (*Pharm. Weekbl.* 1950, **85**, 865.) The usual methods for the determination of acetone are lacking in accuracy or specificity. The authors prefer one based on that of Lester and Greenberg, as follows. 0·2 ml. of blood or urine is mixed with 1 ml. of water and 3 ml. of 5 per cent. solution of trichloracetic acid; 3 ml. of the solution is then transferred to a 25 ml. stoppered tube with 2 ml. of 0·1 per cent. solution of 2·4 dinitrophenylhydrazine in 2N hydrochloric acid, and 2 ml. of carbon tetrachloride, and shaken for 10 minutes. The aqueous layer is removed by suction, and the tetrachloride solution is washed twice with water. It is then shaken for 3 minutes with 3 ml. of 0·5 N sodium hydroxide and, after removal of the alkali, the extinction is determined at 420 mμ or 350 mμ, the latter wave-length giving the higher reading. A blank determination is carried out without the blood or urine. For concentrations of the order of 0·1 mg. per cent. the error is 5 per cent. Larger errors may be due to the following causes: acetone in the air of the laboratory or in the distilled water; leakage through the stopper of the tube; or use of too small a tube to permit of effective shaking. G. M.

Adrenaline and Noradrenaline in Blood, Fluorimetric Determination of. A. Lund. (*Acta Pharmacol. Toxicol.*, 1950, **6**, 137.) Both adrenaline and noradrenaline may be determined simultaneously in the same blood sample if minor modifications are introduced in the author's original fluorimetric method for determination of adrenaline in blood (*Acta Pharmacol. Toxicol.*, 1949, **5**, 231), where adrenaline is isolated from plasma in weakly alkaline solution followed by elution with acetic acid. Noradrenaline behaves in the same manner; at *p*H 8·5 it is adsorbed quantitatively on alumina and eluted completely with acetic acid. Noradrenaline, analagously with adrenaline, is oxidised to noradrenochrome by manganese dioxide. Noradrenochrome is converted by sodium hydroxide to noradrenolutine, which, by irradiation with ultra-violet light, gives the same yellowish fluorescence as the product from adrenaline. The difference in oxidisability between adrenaline and noradrenaline permits determination of the two substances in the same sample. Adrenaline is oxidised quantitatively to adrenochrome within the entire *p*H range of 3 to 7, whereas only about 5 per cent. of noradrenaline is oxidised to adrenochrome at *p*H 3·0, though quantitative oxidation takes place at *p*H 6·5. The acetic-acid eluate has a *p*H of about 4. By adding 0·2 N hydrochloric acid to an aliquot part of the eluate

to give a *p*H of 3·0 and shaking with manganese dioxide for about 60 seconds, complete oxidation of adrenaline to adrenochrome is obtained, but only 5 per cent. of the noradrenaline is oxidised. By adding to another aliquot of the eluate 0·8 M sodium phosphate to give a *p*H of 6·5, and shaking with manganese dioxide for 20 seconds, complete oxidation of both adrenaline and noradrenaline to adrenochrome and noradrenochrome respectively is obtained. These will both, by rearrangement with sodium hydroxide in oxygen-free solution, give a stable yellowish-green fluorescence.

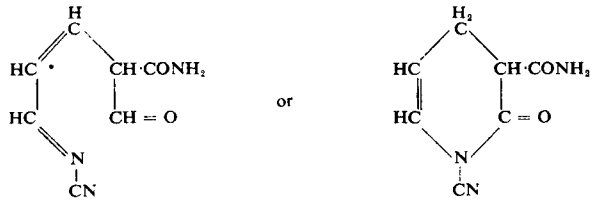
S. L. W.

Lead in Urine, Polarographic Determination of. R. W. R. Baker. (*Biochem. J.*, 1950, **46**, 606.) Two relatively rapid methods for the polarographic determination of pathologically increased lead in urine are described, together with a modification for the estimation of lower concentrations. It was found that the diffusion current of lead could be readily and accurately determined in 0·2 M dipotassium hydrogen citrate (*p*H 5·2), and that in this medium the waves were not distorted by the formation of maxima; the half-wave potential was found to be −0·49 V. The lowest concentration of lead in the polarograph cell which gave a readily measurable diffusion current was of the order of 500 μg./l, and concentration of the metal from normal urines (less than 100 μg./l.) was therefore necessary. In the first method used, rapid but rough, a precipitate of calcium phosphate was formed in the urine, separated, washed, dissolved as completely as possible in a citrate solution and the lead determined polarographically. In the second and more accurate procedure, calcium was precipitated as oxalate at *p*H 4·5, the solid was "ashed" with perchloric acid and the calcium precipitated from alkaline solution as phosphate, which dissolved completely with the lead in a citrate buffer, the second precipitation as phosphate being necessary as it was difficult to buffer the ashed perchlorate solution reproducibly and with sufficient accuracy without increasing the volume to an undesirable extent. A blank determination was important and was obtained from the difference in the apparent lead content of two volumes (25 and 5 ml.) of urine; experimental details are given. Recovery was almost quantitative over the range 100 to 1800 μg./l. In choosing the method to be adopted the more exact procedure was only necessary when the final undissolved materials in the quicker method were not small. The general method was applied to cases of lead intoxication where there was evidence that 2:3-dimercaptopropanol increased the excretion of lead in the urine. Estimates were obtained of the diffusion coefficients of the complex lead ion in citrate buffer in the presence and absence of calcium.

R. E. S.

Nicotinamide and Nicotinic acid, Colorimetric Determination of. E. S. Brusse. (*Pharm. Weekbl.*, 1950, **85**, 569.) In view of the inconsistencies in the results reported by various workers for the nicotinic acid content of blood and urine, it is evident that methods of assay previously used are not reliable. The author has therefore examined more closely the colorimetric reaction of Koenig. The action of cyanogen bromide on nicotinic acid is usually carried out at *p*H 6 to 7·5. Actually, when this reaction is performed at different *p*H values, the colour ulfimately obtained shows two maxima at *p*H 4 and 6 to 8 respectively. Action at *p*H 6 to 8 gives glutaconic aldehyde which subsequently reacts with the aromatic amine used, whereas at *p*H 4 the reaction takes a different course without loss of pyridine nitrogen. Crystalline products corresponding to the latter reaction were isolated from

both nicotinamide and nicotinic acid. They did not contain bromine, but formed hydrazines. It is probable that these compounds have the structure either



Both the compound obtained at *p*H 6 to 8 and that at *p*H 4 give coloured products with aromatic amines, though the colour intensity is greater with the latter. In alkaline solution, the action of cyanogen bromide on nicotinamide, but not on nicotinic acid, gives a fluorescent compound (Scudi reaction). As a result of these experiments the author recommends that the reaction should be carried out in an acetate buffer at *p*H 4. The best amine to use is sulphanilamide, which gives the greatest colour intensity. G. M.

Procaine in Organs, Determination of. P. Terp. (*Acta pharmacol.*, 1950, **6**, 269.) The following method for determining procaine and *p*-aminobenzoic acid in the same organic material is described. The procaine in solution is stabilised by addition of sodium fluoride 5 mg./g. of tissue and freezing to $-15°$C.; solid organs are homogenised and diluted with water Urine is diluted with water and hydrochloric acid; the dilution must be 0·2N in hydrochloric acid. 6 ml. of blood is diluted with water to 20 ml. and left for 15 minutes to hæmolyse; 2 parts of the diluted blood (or homogenate) are deproteinised by mixture with 1 part of 10 per cent. trichloracetic acid solution and filtered. The total amount of free procaine plus free *p*-aminobenzoic acid is determined by colorimetry in a sample of the filtrate or the urine dilution. The total amount (free and acylated) of procaine plus *p*-aminobenzoic acid is found by heating a sample of the filtrate for 45 minutes in a boiling water-bath after addition of 0·1 vol. of 2N hydrochloric acid, colorimetry being performed after cooling. The *p*-aminobenzoic acid concentration is determined in the filtrate after removal of procaine by extraction with chloroform-isopropanol (3 to 1) in alkaline solution. The amount of free *p*-aminobenzoic acid is determined colorimetrically and the amount of free plus acylated *p*-aminobenzoic acid is determined colorimetrically after heating in a water-bath for 45 minutes. Colorimetry is performed after diazotisation and conjugation in 0·2N acid; the disodium salt of 1-sulphomethylamino-naphthalene-8-sulphonic acid is used as a coupling agent. The absorption is read at 550 mμ in a Beckman spectrophotometer. S. L. W.

Vitamin A, Influence of Tocopherols on the U.S.P. XIV Assay. S. H. Fox and A. Mueller. (*J. Amer. pharm. Ass., Sci. Ed.*, 1950, **39**, 621.) The geometric procedure of Morton and Stubbs can be used for the correction of irrelevant absorption which is linear in the wave-band 300 to 350 mμ. This correction procedure gives low results for vitamin A in the presence of tocopherols, which exhibit non-linear absorption in this spectral region, but their absorption can be allowed for by filling the compensating cell of the spectrophotometer with the solution under examination, treated so as to destroy the vitamin A, while preserving the tocopherols. The following modification of the U.S.P. XIV method is suggested. Carry

out the saponification in the presence of 25 mg. of pyrogallol, and dissolve the unsaponifiable matter in hexane to give a solution containing 8 to 15 U.S.P. units of vitamin A/ml. Tocopherol-containing solution: place 20 ml. in a 30 to 35 ml. glass-stoppered reaction tube, add 3 ml. of 60 per cent. v/v sulphuric acid, shake vigorously for 15 sec. and centrifuge immediately. Evaporate 5 ml. to dryness under carbon dioxide, using a warm water-bath, cool and add 5 ml. of isopropanol. Vitamin A containing solution: evaporate a quantity of the hexane solution, and dissolve the residue in a corresponding volume of isopropanol. G. B.

CHEMOTHERAPY

Amidone, Synthesis of Compounds Related to. A. L. Morrison and H. Rinderknecht. (*J. chem. Soc.*, 1950, 1478). Two compounds in the amidone series, 1-methylallylamino-3:3-diphenylhexan-4-one (I,R = Me, R′ = CH_2:CH.CH_2) and the corresponding 1-diallylamino derivative (I,R = R′ = CH_2:CH.CH_2) were prepared in an attempt to reduce the depressant effect upon respiration exhibited by amidone. The following synthetic route was used:—

$$Ph_2C(CN).CH_2.CH_2Cl \xrightarrow{HNRR'} Ph_2C(CN).CH_2.CH_2.NRR' \xrightarrow{C_2H_5MgI} Ph_2C(COEt).CH_2.CH_2.NRR'$$

(I)

When tested for analgesic action (I;R = Me, R′ = CH_2:CH.CH_2) and (I;R = R′ = CH_2:CH.CH_2) had respectively one-half and one-eighth of the potency of (I; R = R′ = Me). A new synthesis of 3-dimethylamino-1:1-diphenylbutyl cyanide (amidone nitrile) is reported, but only poor yields were obtained. A. H. B.

Ketobemidone, Synthesis of. A. W. D. Avison and A. L. Morrison. (*J. chem. Soc.*, 1950, 1469.) The synthesis of 4-*m*-hydroxyphenyl-1-methyl-4-piperidyl ethyl ketone (ketobemidone) was achieved by condensing *m*-methoxybenzyl cyanide with methyldi-(2-chloroethyl)amine, in the presence of sodamide, to produce a cyanopiperidine which was converted to the ethyl ketone by the use of ethyl magnesium bromide. Demethylation of this product with hydrobromic acid yielded ketobemidone, previously reported to be about ten times as active an analgesic as pethidine. A. H. B.

Pethidine, Compounds Related to. A. L. Morrison and H. Rinderknecht. (*J. chem. Soc.*, 1950, 1467.) Various substances related to pethidine are reported upon. These included bemidone, *N*-allylnorpethidine (allyl group replacing methyl group in pethidine) thioesters and a compound with the piperidine ring of pethidine ruptured. Secondary alcohols, obtained by the reduction of ketones prepared from 4-cyano-4-phenyl-1-methylpiperidine (the precursor of pethidine) and their acetyl esters were also prepared. As in the amidone series, reduction of the ketone to a secondary alcohol reduced the analgesic activity greatly, but, unlike the amidone series, acetylation of these alcohols did not completely restore the activity. All the substances reported were less active than pethidine. A. H. B.

Tertiary Carbinols and Derivatives from Mannich Bases as Analgesics. A. L. Morrison and H. Rinderknecht. (*J. chem. Soc.*, 1950, 1510.) The possibility that such a compound as Ph_2C (O.CO.C_2H_5).$CH_2.CH_2.NRR'$, in which are combined features of both amidone and pethidine, might possess

considerable activity, was considered. Compounds of this type were prepared by the action of phenylmagnesium bromide on the Mannich base made from acetophenone and secondary amines, followed by acetylation of the tertiary alcohol. Acetyl derivatives of the carbinols prepared by the action of aryl- and alkyl-magnesium halides on Mannich bases derived from cyclohexanone and l-tetralone were also prepared. The tertiary alcohols were dehydrated by heating with 98 per cent. formic acid, and the unsaturated product hydrogenated. In an attempt to simulate the piperidine ring of morphine 6-phenyl-3-methyloctahydro-5:6-benz-1:3-oxazine and 6:6-diphenyl-3-methyltetrahydro-1:3-oxazine were synthesised. None of the compounds possessed analgesic activity greater than that of pethidine. Some, however, exhibited considerable antihistaminic and spasmolytic properties. A. H. B.

PHARMACY

DISPENSING

Morphine Solutions, Stability of. N. Thörn and A. Ägren. (*Svensk farm. Tidskr.*, 1951, **55**, 61.) Determination of the oxydimorphine content of 2-year old injection solutions of morphine showed the figure to be very low, on an average 0·03 per cent., while the content of morphine was not appreciably changed. Oxydimorphine itself does not undergo any further change on keeping, so that the figures obtained represent the full amount of the decomposition. Discoloration of the solutions does not depend on the temperature of sterilisation, but increases with increasing *p*H value. A solution in glycerin-alcohol-water shows somewhat less discoloration. The quality of the morphine used is of considerable importance with respect to the development of colour. G. M.

Suppository Bases, Pharmacological Investigation of. H. Hofmann and U. H. Hornbogen. (*Pharm. Zentralh.*, 1950, **89**, 369.) The absorption of sodium salicylate from suppositories was determined by following the concentration of salicylate in the urine. A number of synthetic bases were compared with cocoa butter. Synthetic bases which were found to be superior to cocoa butter were Lapusol (cetyl phthalate), Postonal (polymerised ethylene oxide), Suppobasin (an "oxide wax"), K-bases (synthetic paraffins). Suppositol (a hardened neutral fat) was unsatisfactory as it produced local irritation. Synthetic bases should not be considered as mere substitutes for cocoa butter and may be expected ultimately to replace the latter completely. G. M.

NOTES AND FORMULÆ

***p*-Nitrosulphathiazole.** (*New and Nonofficial Remedies, J. Amer. med. Ass.*, 1950, **143**, 1155.) *p*-Nitrosulphathiazole contains not less than 97·5 per cent. and not more than the equivalent of 102·5 per cent. of $C_9H_7O_4N_3S_2$, mol. wt. 285·29, and is a pale yellow powder; m.p. 255° to 262°C. Slightly soluble in alcohol; very slightly soluble in chloroform, ether, and water; practically insoluble in benzene; freely soluble in ammonia and sodium hydroxide solution. When 0·1 g. is dissolved in 10 ml. of acetone containing 2 ml. of 10 per cent. sodium acetate and 5 ml. of silver nitrate solution is added, a yellow flocculent precipitate is produced. On heating the powder in an ignition tube it turns brown, emitting the odour of nitrobenzene and sulphur dioxide; on further heating a sudden evolution of brown fumes, characteristic of the nitro-group, occurs. Loss on drying at 105°C. for 4

hours, not more than 1 per cent. Sulphated ash not more than 1 per cent. For the assay, 0·5 g. is warmed on a steam-bath with 30 ml. of glacial acetic acid and 5 g. of zinc granules; 15 ml. of hydrochloric acid is added 1 ml. at a time till all is dissolved. The colourless solution is cooled, diluted with an equal volume of water and filtered through cotton. The filter is rinsed with 50 ml. of water and the mixed filtrate and washings boiled for 5 minutes with 10 ml. of dilute sulphuric acid; after cooling, 5 ml. of dilute hydrochloric acid and a few crystals of potassium bromide are added and the mixture is titrated with 0·1 N sodium nitrite, using starch iodide paper as indicator. The volume required minus that used for a blank titration similarly treated gives the titration reading. Each ml. of 0·1 N sodium nitrite is equivalent to 0·02853 g. of $C_9H_7O_4N_3S_2$. Used only for rectal injections in chronic ulcerative colitis and proctitis. Gravimetric assay of a suspension is described. L. H. P.

Pyranisamine Maleate. (*New and Nonofficial Remedies, J. Amer. med. Ass.*, 1950, **143,** 1156.) Pyranisamine maleate is *N*:*N*-dimethyl-*N'*-(*p*-methoxybenzyl)-*N'*-(2-pyridyl)-ethylenediamine maleate, $C_{17}H_{23}ON_3 . C_4H_4O_4$, mol. wt. 401·45. It is a white crystalline powder with a faint odour; m.pt. 100° to 102°C. Very soluble in water and chloroform, freely soluble in alcohol, slightly soluble in ether and benzene. On adding 5 per cent. sodium hydroxide solution to an aqueous solution the oily free base is obtained. Aqueous solutions are clear and colourless and have a *p*H between 4·5 and 5·5. Loss on drying *in vacuo* over phosphorus pentoxide for 4 hours, not more than 0·5 per cent. Sulphated ash, not more than 0·1 per cent. On adding sulphuric acid an immediate red solution is obtained. On adding a saturated solution of ammonium reineckate to a solution of pyranisamine maleate, a pink precipitate is formed. A 0·002 per cent. solution shows an ultraviolet absorption maximum at 2440 Å ($E^{1\ \text{per cent.}}_{1\ \text{cm.}}$ $=420 \pm 4$) with minor peaks at about 2840 Å and 3060 Å, and minima at about 2340 Å, 2680 Å, and 2860 Å. The ratio of optical densities at 2440 Å and 3060 Å should be between 3·2 and 3·5. Methods for obtaining crystals of maleic acid (m.pt. 128° to 133°C.) and fumaric acid (sublimes at about 200°C.; m.pt. in sealed tube, above 275°C.) are described. Pyranisamine maleate is assayed spectrophotometrically. The number of mg. of $C_{17}H_{23}ON_3 . C_4H_4O_4$ per ml. of the solution is the optical density at 2440 Å divided by 42. It should contain not less than 97 per cent., nor more than the equivalent of 101 per cent. Nitrogen, by a micro-Kjeldahl method, should be not less than 10·26 per cent. and not more than 10·57 per cent. An assay for tablets is described. L. H. P.

Sulfoxone Sodium. (*New and Nonofficial Remedies, J. Amer. med. Ass.*, 1950, **143,** 1259.) Sulfoxone sodium is a mixture of disodium [sulphonylbis-(*p*-phenyleneimino-)]-dimethanesulphinate tetrahydrate ($C_{14}H_{14}O_6N_2S_3Na_2 \cdot 4H_2O$; mol. wt. 520·51) and about 10 per cent. of sodium bicarbonate or disodium phosphate. It is a pale yellow powder; odour characteristic; very soluble in alcohol. Loss on drying *in vacuo* at 60°C. for 20 hours, not more than 20 per cent. The limit for heavy metals is 20 p.p.m., and the test is described. When a 1 per cent. aqueous solution is shaken with test-solution of iodine and chloroform no colour appears in either layer on separation. Nearly white crystals of *p*-*p'*-diamino-diphenylsulphone, melting at about 175°C., are formed when a 3·3 per cent. aqueous solution of sulfoxone sodium is refluxed for 10 minutes with Fehling's solution, cooled and filtered, followed by washing of the precipitate with

water, solution of the organic matter in hot alcohol, filtration, dilution with water, removal of the alcohol and slow cooling. For the assay an accurately weighed quantity equivalent to 0·250 g. is dissolved in 500 ml. of water. To 4 ml. of this solution 1 ml. of 20 per cent. toluenesulphonic acid and 0·5 ml. of dilute hydrochloric acid are added and the mixture is warmed for 30 minutes in a boiling water-bath, cooled and diluted to 100 ml. with water. 1 ml. of the hydrolysed solution is transferred to a test-tube, while 1 ml. of a standard aqueous solution containing 5 ml. of a 0·1 per cent. w/v acetone solution of *p-p'*-diamino-diphenylsulphone (m.pt. 175° to 177°C.) in 500 ml. is placed in a second tube. To each is added 1 ml. of 10 per cent. hydrochloric acid, 5 ml. of water, and 1 ml. of a 0·1 per cent. sodium nitrite solution, and after exactly 3 minutes 0·5 ml. of a 0·5 per cent. sodium sulphamate solution, followed 2 minutes later by 5 ml. of a 0·5 per cent. solution of *N*-(1-naphthyl)-ethylenediamine dihydrochloride. The colour produced after 10 minutes at 5600 Å is determined. The percentage of anhydrous disodium [sulphonylbis-(*p*-phenyleneimino)]-dimethanesulphinate is equivalent to

$$\left(\frac{\text{Density of Standard Solution}}{0{\cdot}020\text{ mg.}} \times 100 \times 1{\cdot}806\right) \div \left(\frac{\text{Density of sample solution}}{0{\cdot}010\text{ mg.}}\right)$$

and should be not less than 77 per cent. Sulfoxone sodium is used in leprosy. L. H. P.

PHARMACOLOGY AND THERAPEUTICS

Colloidal Iron as Hæmatinic. A. J. Creskoff. (*Amer. J. med. Sci.*, 1950, **220**, 553.) A preparation of colloidal iron and a casein hydrolysate obtained by papain digestion, issued under the name ferrocol, is a potent and well tolerated hæmatinic. It contains 20 per cent. of iron and is administered in the form of tablets or capsules, the total daily dose being 1·2 g., equivalent to 240 mg. of iron. For maintenance, dosage may be reduced. 25 patients with chronic hypochromic microcytic anæmia were treated with the drug. The average initial blood hæmoglobin content was 65 per cent. and over a period of 9 weeks the average gain in hæmoglobin was 16 per cent. There were no signs of intolerance. In a second group consisting of 23 patients, mainly women attending an antenatal clinic, all of whom had shown intolerance to ferrous gluconate or sulphate, treatment produced no signs of intolerance whatever. H. T. B.

Liquorice Extract, Deoxycortone-like Action of. J. A. Molhuysen, J. Gerbrandy, L. A. De Vries, J. C. De Jong, J. B. Lenstra, K. P. Turner and J. G. G. Borst. (*Lancet*, 1950, **259**, 381.) Previous observations that gastric ulcer patients treated empirically with a paste consisting of powdered liquorice extract and water developed œdema, headache and shortness of breath were confirmed by clinical experiments. Even when no clinical œdema developed, the use of the drug resulted in retention of water, sodium and chloride; hæmoglobin and total serum protein decreased; venous pressure, blood pressure and pulse pressure rose considerably, and the output of potassium was much increased. The harmful effect, especially in the elderly, of potassium loss on the myocardium, overburdened by the increased venous pressure and the rise in blood pressure, explains the occurrence of cardiac asthma in subjects using liquorice in sweets or drugs. The effect of a liquorice extract by mouth is, in almost all respects, similar to that of injections of large doses of deoxycortone,

but it lasts longer. A patient with Addison's disease, however, not responding to ACTH, did not respond positively to treatment with liquorice extract, and a patient with rheumatoid arthritis responding favourably to ACTH showed little or no improvement after the use of liquorice extract. S. L. W.

Morphine Derivatives, Addiction to. H. F. Fraser and H. Isbell. (*J. Pharmacol.* 1950, **100,** 128.) Morphinan, 6-methyldihydromorphine and dihydrocodeinone were all found to induce a morphine-like euphoria when given in sufficient dosage to former morphine addicts, and must all be regarded as possessing addiction liability. Dihydrocodeinone was found very effective in relieving signs of abstinence from morphine, and 6-methyldihydromorphine, though relatively ineffective in abolishing the objective signs of abstinence, when given in high doses relieved the subjective complaints associated with morphine withdrawal. Evidence of partial tolerance to the sedative effects was observed during chronic administration of all three drugs and definite abstinence syndromes were observed following withdrawal. The signs of abstinence were most severe after withdrawal of morphinan, less severe after dihydrocodeinone, and mild after 6-methyldihydromorphine. The addiction liability of morphinan is approximately equal to that of morphine. S. L. W.

Phenacetylcarbamide in Convulsive Disorders of Children. H. M. Keith (*Proc. Mayo Clin.,* 1950, **25,** 594.) This is a preliminary report on the treatment of 35 children with phenurone (a proprietary brand of phenacetylcarbamide) for periods varying from 3 to 20 months. A considerable number of the children had gross neurologic or psychiatric defects and many were mentally retarded. All had been treated with other drugs, but were still having difficulty. Of the 35 patients observed for 3 months or more, 8 are considered well and have not had any known attacks, 15 have improved, and 12 have not benefited. The drug is employed in a dosage of 1·5 to 5 g. daily. Side reactions were relatively few; 4 patients had morbilliform rash and one patient became jaundiced, but a generalised carcinomatosis may have been partly responsible for this. These observations confirm the reports of other workers that the drug is a useful anti-epileptic. S. L. W.

Phenylacetylurea in Convulsive Disorders. S. C. Little and R. R. McBryde. (*Amer. J. med. Sci.,* 1950, **219,** 494.) The effect of the administration of phenylacetylurea (phenurone) was studied in thirty-two patients subject to recurrent convulsive disorders. The maximum dose was 6 g. daily, the average being 2·08 g. daily for periods ranging from 2 weeks to 10 months. Other anti-convulsant drugs were not discontinued during the investigation. Patients were closely observed for toxic symptoms, complete blood counts and urine analyses being performed regularly. Maximal improvement occurred within the first 2 months of administration, and in comparison with the best prior treatment, the reduction in frequency of seizures was grand mal 54 per cent., petit mal 33 per cent., and psychomotor disorders 66 per cent. Phenylacetylurea appeared to be responsible for most of the improvement in psychomotor seizures, but improvement in grand mal attacks could be attributed to other treatment. The maximum improvement was obtained during the first 2 months. In 5 cases the drug was discontinued after from 2 weeks to 8 months because of the development of toxic symptoms which affected chiefly the central nervous system or gastrointestinal tract. H. T. B.

Quinidine Lactate, Intravenous Injection of. A. H. Clagett. (*J. Amer. med. Sci.*, 1950, **220**, 381.) A study was made of the intravenous administration of quinidine lactate in 13 patients, those selected being cases, often with paroxysmal ventricular tachycardia, in whom oral dosage had been ineffective or whose condition was too serious to allow time for trial of the drug by mouth. Other cases were those in whom surgery of the chest or heart necessitating cardiac manipulation was to be performed. These patients were given oral quinidine pre-operatively and, if tolerated, quinidine lactate was added to the intravenous fluids during operation. Dosage varied from 0·4 g. to 3·25 g. The smallest dose given to a case of paroxysmal ventricular tachycardia to be followed by a return to regular sinus rhythm was 0·8 g. A solution of 0·65 g. of quinidine lactate in 10 ml. of water was added to 50 ml. of a 5 per cent. solution of glucose, and the mixture allowed to enter a vein at a rate not exceeding 2 ml. per minute. The patient was kept under constant observation and administration discontinued immediately upon re-establishment of regular rhythm, or on the appearance of any toxic reaction. In this series the only toxic manifestation was nausea and vomiting which occurred in 3 patients. Quinidine lactate is considered to be an effective and relatively safe drug for intravenous administration and to be life-saving in cases where prompt action is required or oral administration is contra-indicated. H. T. B.

Streptomycin-Bacitracin-Polymyxin Combination, Polymyxin B, and Streptomycin with Glucuronolactone, Effect of on the Intestinal Flora of Man. H. Welch, W. A. Randall and C. W. Price. (*J. Amer. pharm. Ass.*, 1950, **39**, 486.) The effects of polymyxin 100 mg. (in tablets, once daily), a mixture of streptomycin 100 mg. and glucuronolactone 400 mg. (in tablets, 5 tablets 4 times daily), and a mixture of streptomycin 250 mg., bacitracin 5,000 mg., polymyxin 20 mg. (in tablets, one tablet 4 times daily) on the intestinal flora of man were studied. The administration of streptomycin-bacitracin-polymyxin resulted in the virtual elimination of coliform bacteria from the fæces for as long as the drug was given, while the same was substantially true for streptomycin-glucuronolactone, although disappearance of the coliform bacteria for not quite so rapid. The administration of polymyxin alone markedly reduced the coliform count but did not, in any case studied, cause complete elimination of this group of organisms. The fæcal streptococci were greatly reduced by streptomycin-bacitracin-polymyxin, by streptomycin-glucouronolactone, and to a lesser extent by polymyxin B. Results indicated that with any preparation containing streptomycin the development of coliform bacteria resistant to the drug occurred. The streptomycin-bacitracin-polymyxin combination proved quite effective in the treatment of colitis and chronic diarrhœa, four cases of the former and twelve cases of the latter being treated with excellent results. R. E. S.

Thiouracil and Propylthiouracil, Prolonged Treatment with. S. U. Greenberg and M. Bruger. (*Amer. J. med. Sci.*, 1950, **220**, 373.) A report is given of a study of the long term use of thiourea derivatives in the treatment of thyrotoxicosis. Observations on 70 cases of toxic diffuse goitre over the past 5 years show that in order to be adequate a course of treatment must be of at least a year's duration. The usual initial dose of thiouracil was 600 mg. daily, reduced to 300 mg. daily when the basal metabolic rate was reduced to normal range, and then further reduced until the minimum maintenance dose was obtained—usually 100 mg. daily. Later, propyl-thiouracil was substituted and has since been used exclusively. For this

substance the initial dose was 300 mg. daily, later reduced to between 50 and 100 mg. In 30 of the 39 cases who were adequately treated and followed up, treatment for approximately a year produced remissions of 6 months or longer after discontinuance of the drug and 25 of these cases showed remissions for longer than a year. Nine had relapses within a year. The observations suggest that, provided treatment is adequate, recurrence after remission for 6 months is unusual and the probability of recurrence after remission for a year is remote. A higher proportion of relapses occurred in males than in females. Propylthiouracil may be used effectively for periods longer than a year in patients who refuse surgery or for whom it is inadvisable, or who have serious complications. In none of the patients with thyrotoxic exophthalmos did the condition progress during treatment, and in 50 per cent. of the cases the proptosis receded partially or completely. In 13 of 27 cases administration of the drug was accompanied by a decrease in the size of the thyroid gland; in 2 cases it enlarged during treatment, while in the remainder it was unchanged. In 9 patients the toxic symptoms were severe enough to necessitate withdrawal of the drug. With thiouracil, withdrawal was necessary in 7 out of 37 patients; with propylthiouracil the proportion was 2 out of 46. One developed granulocytopenia while on thiouracil; the condition cleared up when the drug was withdrawn but promptly recurred on resuming treatment with propylthiouracil. Seven patients on propylthiouracil and 19 on thiouracil developed granulocytopenia. They were treated with pyridoxine hydrochloride, usually 60 mg. daily in three or four divided doses, increased to 150 mg. if no appreciable response occurred after a week and up to 225 mg. in one case. This treatment produced a distinct granulocyte response. H. T. B.

Vitamin B_{12} Orally for Pernicious Anæmia. L. M. Meyer, A. Sawitsky, B. S. Cohen, M. Krim and R. Fadem. (*Amer. J. med. Sci.*, 1950, **220**, 604.) The results obtained on giving vitamin B_{12} orally to 7 patients with pernicious anæmia in relapse show that there is no clear-cut universal oral dose which is adequate in the treatment of this disease. Evidence accrued that the deficiency of the intrinsic factor was not always complete and that the absorption and utilisation of the vitamin varied in individual cases. In 3 cases good clinical responses followed oral doses of from 75 μg. to 300 μg. per day but the reticulocyte response was absent or submaximal. In 1 case reticulocytosis was satisfactory on 100 μg., but the erythrocytes did not rise above 3·65 million even when the dose was raised to 200 μg. although a completely satisfactory response was obtained on 20 μg. parenterally. One patient alone showed signs of neurological involvement before treatment and his peripheral neuritis cleared up during therapy although the blood picture did not become normal. 2 of the 7 patients did not respond to oral therapy but reacted well to parenteral treatment. H. T. B.