ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

***Delphinium Barbeyi* H, Alkaloids of.** W. B. Cook and O. A. Beath. (*J. Amer. chem. Soc.*, 1952, **74**, 1411.) This species of larkspur was found to contain a mixture of crystalline alkaloids (approximately 0·15 per cent. of the plant on a dry weight basis) plus smaller amounts of amorphous bases. By means of fractional crystallisation and chromatography, two crystalline alkaloids, lycoctonine and anthranoyllycoctonine comprising approximately 62 per cent. and 38 per cent. respectively of the crystalline bases were obtained. New empirical formulæ ($C_{24}H_{41}O_7N$, H_2O for lycoctonine and $C_{31}H_{46}O_8N_2$, $\frac{1}{2}H_2O$ for anthranoyllycoctonine) were assigned on the basis of elementary analysis of the bases and their salts and peripheral group studies. 9 derivatives of each of these alkaloids were prepared and their physical constants determined. The X-ray diffraction patterns and ultra-violet absorption spectra of lycoctonine, anthranoyllycoctonine and ajacine were determined. A. H. B.

ANALYTICAL

Acetic Acid, Titration of Bases in. P. Ekeblad. (*Svensk. farm. Tidskr.*, 1952, **57**, 201.) Approximately 0·1M solutions of bases in acetic acid containing not more than 0·15 per cent. of water are titrated with 0·1N perchloric acid in acetic acid. The perchloric acid solution is made anhydrous by the addition of acetic anhydride, but should contain a small amount of water, not more than 0·05 per cent., when tested by the Karl Fischer method, as this ensures absence of acetic anhydride. The solution is standardised against potassium acid phthalate. A suitable reagent for back titration is 0·1N triethylamine in acetic acid, standardised against the perchloric acid solution. Titration curves for sodium acetate, potassium acetate, nikethamide, phenazone, sulphanilamide and caffeine, determined with a glass electrode, are given. Blue BZL is a suitable indicator for nikethamide and stronger bases, while for phenazone and *iso*-propylphenazone, neutral red or Nile blue sulphate may be used. A mixture of Nile blue sulphate, 2 parts and Blue BZL, 1 part is recommended for sulphanilamide titrations. A table of colour changes of the indicators is given, but the colour change intervals in acetic acid are greatly affected by changes in the ionic strength of the solution. Results of sodium nitrite and perchloric acid titrations of sulphanilamide are compared. G. B.

***p*-Aminosalicylic Acid, *m*-Aminophenol Content of.** W. Seaman, J. T. Woods, W. B. Prescott and W. H. McComas, Jr. (*J. Amer. pharm. Ass., Sci. Ed.*, 1952, **41**, 207.) A colorimetric method has been reported for determining *m*-aminophenol in *p*-aminosalicylic acid and its sodium salt; the method involves the diazotisation of the sample with a subsequent hydrolysis of the diazo-compound to 2:4-dihydroxybenzoic acid, which couples with the unhydrolysed diazotised *m*-aminophenol to form a colour. The intensity of the colour was measured spectrophotometrically at 440 mμ and could be used to calculate the *m*-aminophenol content of the sample from its light absorption. Details of the method are given, together with conditions which gave satisfactory results at concentrations of *m*-aminophenol in *p*-aminosalicylic acid of

less than 1 per cent. The *m*-aminophenol content of 30 samples of medicinal grade *p*-aminosalicylic acid from various commercial sources were found by the proposed method to range from 0·01 per cent. to 0·20 per cent.; 16 samples of medicinal grade sodium *p*-aminosalicylate contained up to 0·11 per cent. of *m*-aminophenol. R. E. S.

Barbiturates and Sulpha Drugs Determination of, in Non-aqueous Solution. V. Vespe and J. S Fritz. (*J. Amer. pharm. Ass., Sci. Ed.*, 1952, **41**, 197.) Barbiturates and sulpha drugs in various pharmaceutical preparations were determined by acidimetric titration in non-aqueous solution. The sample was dissolved in dimethylformamide and titrated with 0·1N sodium methoxide, using thymol blue as indicator; the end-point was marked by a sudden change from yellow to blue. Twelve barbiturates and a number of pharmaceutical preparations of phenobarbitone were assayed satisfactorily by this procedure; powdered tablet samples could be dissolved in dimethylformamide and titrated directly. Tablets containing sulpha drugs can be titrated directly in dimethylformamide solution with sodium methoxide- Most common tablet excipients did not interfere. R. E. S.

Benzoic Acid in Foods, Detection of. E. Rathenasinkam. (*Analyst*, 1952, **77**, 101.) A modification of Mohler's test is given. The ammonium salt of the isolated benzoic acid is first prepared by a modification of Leather's procedure (*Analyst*, 1931, **56**, 299), an ethereal solution being exposed to an atmosphere of ammonia. About 1 mg. of the acid or the sodium or ammonium salt is then nitrated by heating with 150 mg. of potassium nitrate and 15 drops of sulphuric acid, sp.gr. 1·84, in a bath of boiling water for 20 minutes; after dilution to about 30 ml. and extraction with 30 ml. of ether, the ether layer is washed with two 10-ml. quantities of water and the ether removed by evaporation. The residue is dissolved in 2 ml. of a mixture of 2 volumes of acetone and 1 volume of absolute ethanol, and 1 to 2 drops of a 10 per cent. aqueous solution of sodium hydroxide are added; after gentle mixing a purple colour develops, changing slowly to violet. *p*-Hydroxybenzoic acid gives no colour in the test; *p*-chlorobenzoic acid, a reddish colour developing slowly; salicylic acid, no colour; cinnamic acid, a dirty violet changing to brown; phenylacetic acid, a green; saccharin, no colour. To detect cinnamic acid in the presence of benzoic acid 0·5 ml. of nitric acid sp.gr. 1·42 is used for the nitration; after heating for 20 minutes, the contents of the test tube are evaporated to dryness, the residue dissolved in 2 ml. of a mixture of acetone and ethanol, and 1 or 2 drops of sodium hydroxide solution are added. Under these conditions cinnamic acid gives a positive reaction (dirty violet colour changing to brown), no colour being obtained with benzoic acid. R. E. S.

Chlorinated *o*-Cresols, Determination of, with Gibbs's Reagent. K. Gardner. (*Analyst*, 1952, **77**, 160.) A method is described for the determination of chlorinated *o*-cresols after reaction with Gibbs's reagent(2:6-dibromoquinone-4-chloroimide). 10 ml. of buffer solution (containing boric acid, potassium chloride and sodium hydroxide) and 4 ml. of Gibbs's reagent were added to a solution containing the appropriate cresol in 200 ml. of water, the solution was mixed (*p*H 9·40) and allowed to stand in the dark for 16 hours, the colour, after filtration with 50 ml. of *n*-butanol and filtration into a 1-cm. or 4-cm. glass cell, being measured photometrically. Experiments were made with equimolar solutions (25×10^{-8} to 400×100^{-8}M) of phenol, *o*-cresol, 4-chloro-*o*-cresol, 4:6-dichloro-*o*-cresol and 6-chloro-*o*-cresol; it was found that

6-chloro-*o*-cresol and *o*-cresol had a greater speed of reaction than the other chlorinated cresols, which reacted at speeds greater than that of phenol itself. Calibration graphs obtained with Ilford No. 607 and No. 608 filters and a tungsten filament lamp were linear over the range 0 to 300 $\times$ 10^{-8}M, with the exception of the graph for phenol. *o*-Chloro-substitution could be detected in *o*-cresols, if phenol itself were absent, by taking two readings with different filters, since the halogen in the *ortho*-position displaced the absorption band towards the red end of the spectrum. R. E. S.

Cortisone and Related Ketol Steroids, Colorimetric Determination of. W. J. Mader and R. R. Buck. (*Anal. Chem.*, 1952, **24**, 666.) The determination depends on the fact that alcoholic solutions of steroids which contain the primary α-ketol group reduce tetrazolium salts in the presence of tetramethyl ammonium hydroxide, forming coloured solutions. 2:3:5-Triphenyl tetrazolium chloride and 3:3-dianisole-bis-4:4′-(3:5-diphenyl) tetrazolium chloride produce colours which obey the Lambert-Beer Law over a suitable concentration range; the molecular absorption of the diformazan from cortisone acetate and dianisole bisdiphenyl-tetrazolium chloride is twice that of the formazan of cortisone acetate and 2:3:5-triphenyltetrazolium chloride. Of the 17 steroids and related compounds studied, 5 contained the α-ketol group and developed colour with both dianisole bisdiphenyltetrazolium chloride and 2:3:5-triphenyltetrazolium chloride; no colour was produced with Δ^5-3-hydroxypregnene-20-one, Δ^4pregnene-17:20:21-triol-3-one, Δ^4-androstene-3:11:17-trione, Δ^4-androstene-3:17-dione, œstradiol, œstrone, progesterone, methyltestosterone, testosterone propionate, ethinyl testosterone, cholic acid, and desoxycholic acid. In the assay of an ointment containing 25 mg./g. of cortisone the standard deviation for 8 assays was 0·3 mg. per g. with an average of 25·3 mg. per g.; the standard deviation for cortisone acetate tablets was 0·3 mg. for 10 determinations with an average of 27·5 mg. per tablet. R. E. S.

Water Content of Medicinal Chemicals and Drugs, Karl Fischer Method for. E. Brochmann-Hanssen and P. Pong. (*J. Amer. pharm. Ass., Sci. Ed.*, 1952, **41**, 177.) The Karl Fischer reagent was used to determine the water content of various medicinal chemicals, powdered extracts, and ointments. A modified reagent containing ethylene glycol monomethylether was found to be more stable than one made with methanol. Details are given for procedures using a visual end-point and also for a direct electrometric titration with a "dead-stop" end-point. The direct method was not satisfactory for powdered extracts because they were not completely soluble, and the water was extracted very slowly; good results were, however, obtained by back titration. Results are quoted for the moisture content of numerous medicinal chemicals, of powdered extracts and ointments. The results obtained by the Karl Fischer method in general agreed very closely with those obtained by the official drying methods. In a few cases oven drying gave low values; titration of the oven-dried compounds accounted for this difference. R. E. S.

Metaldehyde, Identification by Kofler's Micro Method. K. Teuchner. (*Acta pharmacol. Toxicol.*, 1952, **8**, 79.) The substance under investigation is sublimed at a temperature of 130° to 140° C. on to a cover-glass which is then pressed on to a slide carrying a few particles of β-naphthol, or pyrogallol. The slide is placed on the heating apparatus of the microscope and when the eutectic point is reached, small drops of liquid are observed where the two substances meet. The temperatures at which this occurs are 128° C. for mixtures of

metaldehyde and pyrogallol and 115° C. for mixtures of metaldehyde and β-naphthol. If phenacetin is substituted for β-naphthol or pyrogallol, the m.pt. of the phenacetin is not lowered. G. R. K.

Nitrogen, Determination of. P. McCutchan and W. F. Roth (*Anal. Chem.*, 1952, **24**, 369.) A simple modification of the Kjeldahl procedure using thiosalicylic acid as the reducing agent permits the rapid determination of nitrogen in compounds such as nitrobenzene and nitromethane. It appears to be suitable for the determination of nitrogen in nitro-type compounds and in all basic and neutral forms of nitrogen compounds found in petroleum or shale oil fractions. Approximately 1 g. of thiosalicylic acid is placed in a Kjeldahl flask, 20 ml. of concentrated sulphuric acid is added followed by the requisite amount of sample which is washed down the neck of the flask with an additional 20-ml. quantity of sulphuric acid. The mixture is heated until boiling and spattering occurs (274° to 288° C.); it is then cooled to room temperature, 20 g. of potassium sulphate and 1·3 g. of clean metallic mercury are added and the determination is completed as in the regular Kjeldahl procedure with a digestion temperature of approximately 365° C. Satisfactory results were obtained in comparison with those obtained by the regular Kjeldahl and the A.O.A.C. methods. R. E. S.

Phenylmercuric Nitrate, Polarographic Characteristics of. W. L, Wuggatzer and J M. Cross. (*J. Amer. pharm. Ass., Sci. Ed.*, 1952, **41**, 80.) Solutions of phenylmercuric nitrate were mixed with buffer solution and examined polarographically after the addition of gelatin to suppress maxima, and removal of oxygen by passing nitrogen through the solution. Phenylmercuric nitrate was reduced in two steps between 0·0 and − 1·53 volts measured against a saturated calomel electrode at 24° C. In acid solutions the first wave started at zero applied potential, but above *p*H 6·7, both waves were measured and found to be of equal height. Half-wave potentials of both waves became more positive with increase in hydrogen ion concentration, and both were affected by the presence of potassium nitrate or potassium chloride as supporting electrolyte. In experiments at *p*H 9·2, the diffusion current was proportional to the concentration of phenylmercuric nitrate, and quantitative measurements were made. G. B.

Proflavine Hemisulphate, Colorimetric Estimation of. W. H. C. Shaw and G. Wilkinson. (*Analyst*, 1952, **72**, 127.) A method is described for the colorimetric estimation of proflavine hemisulphate by conversion to the quinone-imine form of 2-aminoacridyl diazonium chloride. A solution of proflavine was treated with a limited excess of nitrous acid, under controlled conditions of *p*H and temperature, and the excess of nitrous acid subsequently removed by sulphamic acid; coupling in acid solution with *N*-(1-naphthyl)-ethylenediamine dihydrochloride then gave a stable purple colour. Details are given of the effect of *p*H, temperature, of light and of concentration on the quinone-imine formation. The intensity of the colour produced by proflavine hemisulphate is greater than the original quinone-imine colour, thus increasing sensitivity. The method gave a rectilinear relation of optical densities and concentrations for quantities of proflavine hemisulphate up to 300 μg. and could be applied without modification to euflavine and acriflavine in similar amounts. The procedure was inapplicable to 5-aminoacridine but could be applied directly to the B.P.C. 1949 preparations, eye-drops, pessary, solution and solution

tablets. Difficulties were sometimes experienced in complete recovery of proflavine in the presence of fatty matter, and extraction with an immiscible solvent was sometimes necessary; ethylene dichloride was preferable to other organic solvents, losses of proflavine being reduced to a minimum by maintaining the aqueous phase at an acidity of about 0·1 N with hydrochloric acid. Results of recovery experiments are given on proflavine pessaries and on proflavine cream; the mean error (approximately − 3 per cent.) was small and the method is regarded as sufficiently accurate for routine estimations.

R. E. S.

Salts, Titration of, in Non-aqueous Solvents. J. S. Fritz. (*Anal. Chem.*, 1952, **24**, 306.) The determination of certain salts by titration as acids in non-aqueous solvents is outlined. The sample to be titrated is weighed accurately, neutralised solvent is added and the solution is titrated with 0·1N sodium methoxide to the clear blue colour of thymol blue; carbon dioxide must be excluded during the titration. The sodium methoxide is standardised against benzoic acid and the solution must be re-checked frequently. Mineral acid salts of ammonia and aliphatic amines, as well as aromatic amines, give sharp end-points; guanidine hydrochloride behaved as an acid, but the end point was poor; trimethylphenylammonium iodide was however not acidic to azo violet. Aqueous solutions could be titrated if diluted 15 times with ethylenediamine provided precipitation did not occur. Ethylenediamine and dimethylformamide were the most satisfactory solvents; in the latter solvent aromatic and higher aliphatic amine salts of organic and inorganic monobasic acids were soluble; many ammonium and lower aliphatic amine salts of monobasic acids are also soluble. Ammonium nitrate, ammonium bromide, and ammonium thiocyanate were soluble, but ammonium chloride, ammonium acetate and butylamine hydrochloride were insoluble. Salts of polybasic acids were generally insoluble. Thymol blue was found to be the most satisfactory indicator. The method as described was accurate to within $\pm$ 0·3 per cent., although by using larger samples and a more careful analytical technique, a better precision and accuracy could be obtained. R. E. S.

"Sulpha" Drugs and Sulphonamides, Titration of in Non-aqueous Solvents. J. S. Fritz and R. T. Keen. (*Anal. Chem.*, 1952, **24**, 308.) The SO_2NH-group found in "sulpha" drugs and other sulphonamides of primary amines is feebly acidic and sulpha drugs dissolved in basic organic solvents show acidic properties sufficient to permit direct titration with a strong base. The method is applicable to the determination of sulphaphthalidine, sulphasuxidine, and other sulphonamides which cannot be assayed by the diazo method. In the process given a sample of suitable size is dissolved in dimethylformamide or butylamine; a solution of thymol blue in methanol is added as indicator, the beaker is covered with cardboard provided with a small hole for the burette tip, and the titration with magnetic stirring is carried out to the first appearance of a clear blue colour. The solvents employed must be neutralised with sodium methoxide shortly before use. The sodium methoxide is standardised against benzoic acid using dimethylformamide as solvent and thymol blue as indicator; the titration of benzoic acid in butylamine gave erratic results due to gel formation. Results are given for the titration of numerous sulphonamides of primary amines; by observing the sharpness of the end-points in the two solvents an indication of the basic strength of the parent amine can be obtained. R.E.S.

Testosterone and Derivatives, Determination of. E. Diding. (*Svensk farm, Tidskr.*, 1952, **56**, 3.) Testosterone, methyltestosterone and testosterone propionate may be determined photometrically by dissolving about 0·5 mg. of the material in 2·0 ml of ethanol (95 per cent.) and adding 10 ml. of a 0·25 per cent. solution of 2:4-dinitro-phenylhydrazine in 2N of hydrochloric acid. After standing for 6 hours, the precipitate is collected in a sintered filter, washed with hydrochloric acid, then with water, and dried. The residue is then dissolved in chloroform to 100 ml., and the extinction is determined at 390 mμ. For oily solutions of testerone propionate, a quantity of the solution, containing about 3 mg., is shaken with 15 ml. of heptane and 10 ml. of ethanol (90 per cent.). The ethanolic layer is shaken with two further quantities, each of 15 ml., of *n* heptane, and a further 3 quantities, each of 10 ml., of ethanol are used to follow up the extraction. The last two quantities of heptane are washed with another 10 ml. of ethanol, and the final quantity again with a further 10 ml. The mixed ethanolic solutions are made up to volume and an aliquot is evaporated to dryness before continuing the determination as described above. G. M.

Tetracaine (Amethocaine) and Phenylephrine Hydrochloride, Spectrophotometric Determination of. R. I. Ellin and A. A. Kondritzer. (*J. Amer. pharm. Ass., Sci. Ed.*, 1952, **41**, 71.) Amethocaine solutions may be assayed by determining the optical density at 310 mμ. Phenylephrine has a negligible absorption at this wave-length. The solution in 0·1N hydrochloric acid is extracted twice with wet benzene to remove any of the decomposition product, *p*-butylaminobenzoic acid, which would interfere in the assay. The aqueous solution is neutralised with 0·01N sodium hydroxide, the optical density determined at 310 mμ and the result calculated from the absorption data for amethocaine hydrochloride solutions. The following method, based on the formation of a red colour by diazotisation is recommended for phenylephrine. Dilute a sample containing 0·5 mg. to 10 ml., and filter if necessary. To 1 ml. add 3 ml. of a 15 per cent. solution of mercuric sulphate in 5N sulphuric acid, heat on a boiling water bath for 10 minutes, cool, add 3 ml. of 0·1N sodium nitrite solution dilute to 10 ml., determine the optical density at 495 mμ, and calculate the result by reference to a calibration graph. G. B.

Tropa Alkaloids, Assay of. A. Berggron and M. Nordberg. (*Farm. Revy*, 1952, **51**, 177.) The method given is based on the hydrolysis of the alkaloids with alkali and subsequent acidification, the tropic acid formed being measured from its ultra-violet spectrum. It is assumed that any substance present other than tropic acid will have linear absorption; determination of the absorption at three wavelengths will then give data from which the tropic acid content can be calculated. The alkaloid is dissolved in sodium hydroxide and the solution is heated on a water bath for 15 minutes. After acidifying with hydrochloric acid and making up to the required volume with water the extinction is measured at 254·0, 257·5 and 261·5 mμ. The percentage of alkaloid is then calculated from the equation $X = \frac{(7{\cdot}5\,E_2 - 4\,E_3 - 3{\cdot}5\,E_1)\ \text{equiv. w.}}{427{\cdot}1}$ mg alkaloid/ml. where X is the concentration, E_1, E_2 and E_3 are the measured extinctions at 261·5, 257·5 and 254·0 mμ respectively. Results are given in which the proposed method is compared with classical methods; agreement is satisfactory. R. E. S.

Water, Hardness of, by the Versenate Method. J. E. Houlihan. (*Analyst*, 1952, **77**, 158.) The method introduced by Schwarzenbach and his co-workers

and modified by Betz and Noll (*J. Amer. Wat. Wks. Ass.*, 1950, **42**, 49), in which the calcium and magnesium ions are titrated directly with a solution of an ethylenediamine tetra-acetate salt to produce un-ionised complexes in the presence of Eriochrome black T, was used for the determination of total hardness over a range of widely differing samples; tables of results are given. The Schwarzenbach method gave results a little higher than the mixed-alkali method although considering the very different techniques employed and the large number of steps required for the second method the figures were in very good agreement; the solution strengths used were such that 1 drop of titrating solution for the Schwarzenbach method on a 25 ml. sample represented 2 p.p.m. of $CaCO_3$, whereas 1 drop for the mixed alkali method on a 200 ml. sample represented 5 p.p.m. of $CaCO_3$. R. E. S.

GUMS AND RESINS

Myrrh, Some Observations on the Constitution of. L. Hough, J. K. N. Jones and W. H. Wadman. (*J. chem. Soc.*, 1952, 796.) Extraction of myrrh with 90 per cent. aqueous ethanol removed most of the resin and left a crude polysaccharide (*ca* 40 per cent. yield), which was further purified by precipitation with acidified ethanol. This product had an equivalent weight of 547, contained 6·1 per cent. of methoxyl, gave positive tests for amino-acids, and from the nitrogen content was estimated to contain approximately 18 per cent. of protein. After its hydrolysis with acid, at least 15 amino-acids were detected on the paper chromatogram. By means of precipitation with copper sulphate, oxidation studies, and the application of ion-exchange resins and paper chromatography, it was shown that the crude acidic polysaccharide isolated from myrrh contained approximately 64 per cent. of carbohydrate containing the following monosaccharides in approximately the proportions indicated: D-galactose (4 parts), L-arabinose (1 part), and 4-methyl D-glucuronic acid (3 parts). A. H. B.

ORGANIC CHEMISTRY

Acetone, Dryness and Density of. P. Thirion and E. C. Craven. (*J. app. Chem.*, 1952, **2**, 210.) A review is given of the various figures in the literature for the density and water content of acetone samples. It is confirmed that, in a relative way, density is a good guide to water content but there remains some doubt concerning the density of dry acetone; a figure ($d_4^{20°\,C.}$, 0·7899) has been found, 0·0005 lower than was previously accepted, but still 0·0005 higher than those given recently by American workers. For the determination of water the acetyl chloride-pyridine method was used and this is recommended as a primary standard for this analysis; the Karl Fischer method was not regarded as trustworthy. It is suggested that the lower values reported by American workers may be due to the presence of *iso*propyl ether from the *iso*propanol source; a satisfactory cloud point method for the determination of *iso*propyl ether in acetone is given, using the cloud temperature of acetone (10 ml.) mixed with 25 ml. of aqueous sodium chloride solution (250 g./l.).
R. E. S.

4-Amino-6-hydroxy-*iso*phthalic acid. A. B. H. Funcke, C. van der Stelt, A. M. Simonis and W. T. Nauta. (*Pharm. Weekbl.*, 1952, **87**, 65.) In the manufacture of *p*-aminosalicylic acid by the carboxylation of *m*-aminophenol, a by-product is 4-amino-6-hydroxy-*iso*phthalic acid, which may be separated from the *p*-aminosalicylic acid by its relative insolubility in dilute nitric acid. This new acid is a stronger acid and weaker base than *p*-aminosalicylic acid. On

heating it decomposes at about 200 to 237° C. The absorption spectrum shows maxima at 238, 260 (inflexion point), 282·5 and 317 mμ. Since this acid may be present in commercial *p*-aminosalicylic acid, its pharmacological properties are of importance. The toxicity appears to be similar to that of *p*-aminosalicylic acid, and it has a small, but appreciable, tuberculostatic action. G. M.

Chloramphenicol, Analogues of. J. N. Ashley and M. Davies. (*J. chem. Soc.*, 1952, 63.) Simple analogues of chloramphenicol, in which the phenyl group was replaced by an alkyl group or by a reduced ring were prepared by standard methods. The products, namely 2-dichloroacetamido–propane-1:3-diol, -2-hydroxymethylbutanol, -2-phenylpropane-1:3-diol, -2-*p*-nitrophenylpropane-1:3-diol, -4-methylpentane-1:3-diol, -3-*cyclo*hexylpropane-1:3-diol, and -3-*cyclo*hexylpropan-1-ol had no significant bactericidal or virucidal activity. A. H. B.

Hecogenin, Source of. P. C. Spensley. (*Chem. Ind.*, 1952, 426.) An improved method is given for the isolation of hecogenin from the sisal plant. The juice of the leaves is acidified to give a 1·5N solution which is heated to near the boiling point for 3 to 4 hours; activated charcoal is then incorporated and after an hour or more is collected and washed with water. The charcoal is dried and Soxhlet-extracted with ether or carbon tetrachloride, crude sapogenin being obtained by evaporation of the solvent followed by purification; normal specimens of this sapogenin fraction can be made to yield at least 60 per cent. of hecogenin and details of methods by which the pure steroid may be obtained are being published. Sisal juice ferments rapidly when freshly collected and gradually deposits a thick greenish-yellow sediment leaving a pale yellow, almost clear, layer at the top; examination of the upper and lower layers shows that the sapogenin is concentrated in the lower layer and is present only in small amounts in the upper layer. Allowing this fermentation and discarding the upper layer affords an improved process for the extraction of the sapogenin; as a further improvement the sediment can be collected from the fermentated juice by centrifugation. By this process a greenish yellow sludge is obtained representing about 3 to 10 per cent. of the bulk of the juice from which it originated. If this sludge is dried, a brittle solid, representing about 0·5 to 2 per cent. of the original juice is obtained which yields 4 to 12 per cent. of crude sapogenin. On a large scale the dried centrifuged sludge could be produced at the sisal estates. R. E. S.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Vitamin A, Synthesis from *cyclo*Hexanone. J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker. (*J. chem. Soc.*, 1952, 1094.) 8:9-Dehydrovitamin A was prepared by two routes from 2-ethynyl-1:3:3-trimethyl*cyclo*hex-1-ene, obtained by methylation of *cyclo*hexanone and then treatment with sodium acetylide in liquid ammonia and dehydration of the resultant acetylenic alcohol. Vitamin A was obtained from 1-ethynyl-2:2:6-trimethyl*cyclo*hexanol by condensation with 6-methylocta-3:5:7-trien-2-one to give a C_{20} glycol, rearrangement, selective semi-reduction of the triple bond, and then dehydration. An alternative route *via* a C_{18} acetylenic glycol obtained by the condensation of 2:2:6-trimethyl-*cyclo*hexanone with a C_9 acetylenic alcohol, or by the condensation of 1-ethynyl-2:2:6-trimethyl*cyclo*hexanol with crotonylideneacetone, followed by rearrangement, is also described. A. H. B.

BIOCHEMICAL ANALYSIS

Aliphatic Amines, Paper Chromatography of. R. Schwyzer. (*Acta chem. Scand.*, 1952, **6**, 219.) A paper chromatographic method has been developed for the detection, separation, and identification of as little as 1 μg. of aliphatic amines in biological materials. The ascending chromatogram method was used, placing strips or cylinders of paper in small receptacles and running the chromatogram for 1 hour with Munktell paper (solvent ascends 13 to 14 cm.) or 3 hours with Whatman paper, thus minimising the losses of amines due to volatilisation; *n*-butanol saturated with 25 per cent. acetic acid was used as solvent and the amine spots were made visible by spraying with a suitable indicator solution (bromophenol blue). Blue spots appeared immediately on a yellow background, varying in the intensity of colour according to the quantity of amine present; basic amino-acids gave similar spots. Results are given and R_F values are quoted for methylamine, dimethylamine, trimethylamine, ethylamine, *n*-propylamine, *iso*-propylamine, benzylamine, phenylethylamine, cadaverine and piperidine as hydrochlorides, and arginine as free base. A combination of the method with microdiffusion techniques offers a possibility of separating amine mixtures and preparing derivatives of the components.

R. E. S.

Dinitro-*ortho*-cresol in Blood, Estimation of. D. G. Harvey. (*Lancet*, 1952, **262**, 796). Routine blood estimation is the method of choice for assessing the risk of poisoning in persons using this substance. A method is described for collecting 0·1 to 0·2 g. of blood for analysis. With simple and readily available equipment 5 to 20 μg./g. of blood can be estimated with reasonable accuracy by a modification of Parker's method (*Analyst*, 1949, **74**, 646). The estimation in urine is not a reliable guide to the blood level. S. L. W.

Lactic Acid in Urine, Microdetermination of. M. U. Tsao, M. L. Baumann and S. Wark. (*Anal. Chem.*, 1952, **24**, 722.) The method described is based on the oxidation of the lactic acid to acetaldehyde followed by the estimation of the aldehyde produced from the colour reaction with *p*-hydroxydiphenyl on sulphuric acid. An apparatus is described in detail which achieves in one step the oxidation of lactic acid with ceric sulphate and the rapid transfer of the acetaldehyde thus obtained into sulphuric acid; the colour is developed in the same tube. The effects of variations in ceric sulphate concentration, in the water content of the sulphuric acid and in the diffusion time were studied. A standard deviation of 5·5 per cent. for a single determination was found in a series of recovery experiments. A study of interfering substances showed that carbohydrates and the products of glycolysis caused the most serious interference; methods for the removal of the interfering substances are discussed.

R. E. S.

Phenols and Surface-active Agents, Fungicidal and Fungistatic Evaluation of. G. C. Walker, C. L. Porter and H. G. De Kay. (*J. Amer. pharm. Ass., Sci. Ed.* 1952, **41**, 77.) Fungistatic tests were made on 0·1 per cent. solutions of a variety of derivatives of phenol, in ethanol (95 per cent.), using the agar cup-plate method with *Trichophyton mentagrophytes* as test organism. Halogen substitution in phenol and its derivatives increased the fungistatic power, chlorine being more effective than bromine or iodine. Increased activity was also obtained by substitution of a benzyl, *cyclo*hexyl or phenyl group, but the introduction of carboxyl, methyl or hydroxyl groups had little effect. Of 20 surface-active agents tested by the same method, laurylpyridinium chloride was

the most effective fungistatic. Using *Trichophyton mentagrophytes* in a mycelial disk technique, some of the substituted phenol derivatives were fungicidal in 1 minute at concentrations of 1·0 and 0·5 per cent. Only 2:4:5-trichlorophenol and 2:3:4:6-tetrachlorophenol were effective at 0·3 per cent. Of the surface-active agents, only laurylpyridinium chloride was fungicidal in a concentration of 1 per cent. G. B.

Procaine Benzyl Penicillin, Assay of. K. R. Gottlieb. *Dansk Tidsskr. Farm.*, 1952, **26**, 1.) About 0·1 g. of the compound, dissolved in 15 ml. of ethanol, is chromatographed on 10 g. of alumina, using in all 25 ml. of ethanol for the elution. After changing the receiver, the column is then eluted with a mixture of 45 ml. of O.1N sodium acetate solution and 5 ml. of 0·1N acetic acid. This latter solution is made up to 100 ml., and the benzylpenicillin in it is determined spectrophotometrically by measuring $E_{2570} - (1/3\ E_{2800} + 1/30\ E_{3200}$.) The ethanol eluate is diluted with an equal volume of boiled water and titrated with 0·1N hydrochloric acid using bromophenol blue as indicator. A similar blank test is done by eluting another alumina column with 40 ml. of ethanol, which is used for the blank titration, followed by an elution with the buffer solution which is then used for a blank in determining the extinction. The procaine content is calculated from the titration, 1 ml. of 0·01N hydrochloric acid being equivalent to 0·02363 g. of procaine base. The method is applicable only to pure procaine benzylpenicillin. G. M.

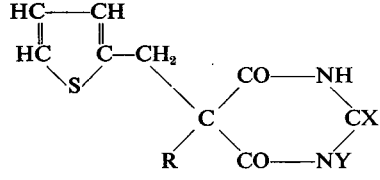
Tyrothricin, Assay of. A. K. Miller, C. Matt and J. L. Ciminera. (*J. Amer. pharm. Ass., Sci. Ed.*, 1952, **41**, 23.) The tube dilution method of the U.S.P. in which the biological activity of tyrothricin against a hæmolytic streptococcus is compared with that of a standard preparation may be modified to use a young seed culture which, together with the standard dilutions of tyrothricin in propylene glycol-ethanol mixture, may be prepared in bulk and can be stored for up to 2 weeks. An 18-hour broth culture of the test organism is prepared and 0·1 ml. is used to inoculate 5 ml. of medium in a colorimeter tube. The turbidity is determined at intervals during incubation of the tube at 37° C., until the growth curve indicates that the culture is definitely in the logarithmic phase of growth. 4 ml. of this culture is mixed with 100 ml. of medium at 37° C. and growth is checked during incubation by observing a 5-ml. sample in a colorimeter tube. At the beginning of the logarithmic phase incubation is stopped and the inoculum is stored at 5° C. For the test, 80 ml. of medium, 20 ml. of bovine serum albumen and 2 ml. of inoculum are mixed at refrigerator temperature and 5-ml. quantities are placed in tubes, to which tyrothricin solutions are added in amounts equivalent to 2·6, 4, 6 and 9 mμg. of standard tyrothricin and about 5 mμg. of the tyrothricin under test. The tubes are incubated at 37° C. until growth is sufficient, as determined by turbidity measurement in check tubes. Generally 5 to 5½ hours' incubation is required and the determination can be completed during a day's work. The standard curve is prepared from which the potency of the sample is read. The method of calculation of 95 per cent. confidence limits is given. G. B.

CHEMOTHERAPY

2-Alkoxy Analogues of Procaine and Amethocaine, Local Anæsthetic, Toxic and Irritant Effects of. F. P. Luduena and J. O. Hoppe. (*J. Pharmacol.*, 1952, **104**, 40.) Local anæsthetic activity was assessed by sciatic nerve block in guinea-pigs (duration of motor paralysis) and by the rabbit cornea method.

Intradermal irritation was determined by a modification of the trypan blue test in the clipped abdominal skin of the rabbit, and acute toxicity was measured in mice, by intravenous injection. Results are tabulated for a number of derivatives of procaine (β-diethylaminoethyl 4-aminobenzoate) amethocaine (β-dimethylaminoethyl 4-butylaminobenzoate) and closely related compounds. Local anæsthetic activity was greatest in the piperidylpropyl esters, less for the corresponding diethylaminoethyl and diethylaminopropyl series and least in the dimethylaminoethyl compounds, and the local anæsthetic activity and toxicity increased with the length of the 2-alkoxy group. These compounds had little irritant effect on the tissues, but 2-propoxy and 2-butoxy substitution of piperidylpropyl 4-butylaminobenzoate greatly increased the local irritant effect. Some of the compounds, for example, diethylaminoethyl 2-propoxy- and 2-butoxy-4-aminobenzoate had greater anæsthetic action and were less irritating than amethocaine. G. B.

Barbituric Acid Derivatives as Narcotics and Anæsthetics. H. Morren, G. Dony and S. Levis. (*J. Pharm., Belg.*, 1952, **7**, 65.) A number of 2-thienyl-barbiturates of the general formula given below, were examined.



(X = O or S, Y = H or CH_3 and R = various alkyl or alkylheterocyclic residues, *cyclo*hexyl or *cyclo*hexenyl). The compounds were prepared by (*a*) reaction of sodium diethylmalonate with an organic halide, treatment with 2-thienyl chloride and sodium, and ring closure with urea, thiourea or *N*-methyl thiourea, (*b*) as for (*a*) but interchanging the first two steps or (*c*) preparing 5-(2-thienyl) barbituric acid and allowing the sodium derivative to react with the organic halide. For the derivative R = *cyclo*hexenyl, *cyclo*hexanone was used instead of an organic halide. When tested in mice by intravenous injection, observing the effective dose, time of induction and duration of sleep and nervous symptoms, the following 3 compounds appeared most suitable as anæsthetics:— (1) R = 1-methylbutyl, X = O, Y = H, (2) R = *n*-hexyl, X = O, Y = H and (3) R = 1-methylheptyl, X = O, Y = H. These compounds were tested as anæsthetics in rabbits and dogs, the effect on arterial pressure and respiration being observed in the latter animal. Compound (2) caused some agitation in all three species, but the other two compounds are to be tested clinically. G. B.

Barbituric Acid Derivatives, Synthesis and Pharmacological Properties of. M. Ruhnek and F. Sandberg. (*Svensk farm. Tidskr.*, 1952, **56**, 70, 95, 120.) The following new amphoteric barbituric acid derivatives were synthesised:— (1) 1-(β-diethylaminoethyl)-5:5-diallyl-, (2) 1-(β-dibenzylaminoethyl)-5:5-diallyl-, (3) 1-(*N*-ethyl-*N*-α-naphthylmethylaminoethyl)-5:5-diallyl-, (4) 1-(β-diethylaminoethyl)-5-*cyclo*hexenyl-5-ethyl-, (5) 1-(β-diethylaminoethyl)-5-allyl-5-phenyl-barbituric acid. Basic derivatives prepared were (6) 1-methyl-3-(β-diethylaminoethyl)-5:5-diallyl-, and (7) 1-benzyl-3-(β-diethylaminoethyl)-5:5-diallyl-barbituric acid. An account of the method of preparation, the physical constants, and the potentiometric titration curves is given, and the detailed examination of the pharmacological action of these compounds is

recorded. None of the compounds had any hypnotic or adrenolytic action. All compounds produced a fall in the blood pressure which was unaffected by atropine, antergan or vagotomy. Compounds (1), (4) and (5) differed from the other derivatives in that they produced an autonomic ganglion block and a parasympathetic neuro-effector block. The basic barbituric acid (7) exhibited a pronounced analgesic and antipyretic action, in addition to a sedative effect. In toxic doses it produced bronchoconstriction, presumably by direct action on the muscles. A. H. B.

PHARMACY

DISPENSING

Chloramphenicol, Stability of Aqueous Solutions of. C. Trolle-Lassen. (*Arch. Pharm. Chem.*, 1951, **58**, 780.) The method used for the assay of chloramphenicol was a modification of that used in the United States Pharmacopœia. Buffered solutions (0·1 per cent.) were prepared and heated for 15 minutes at 100° C., 60 minutes at 100° C. or 20 minutes at 120° C. respectively. Stability was satisfactory at a *p*H range between 2 and 7. Much decomposition occurs outside this range, although the absorption spectrum shows little change. In basic solutions decomposition is accompanied by a drop in *p*H value, owing to hydrolysis and formation of dichloracetic acid. G. M.

NOTES AND FORMULÆ

Mercumatilin Sodium (Cumertilin Sodium). (*New and Nonofficial Remedies; J. Amer. med. Ass.*, 1952, **148**, 1124.) Mercumatilin sodium is a mixture in equimolecular proportions of theophylline and sodium mercumallylate (sodium 8 - (2′ - methoxy - 3′ - hydroxymercuripropyl)coumarin - 3 - carboxylate, $C_{14}H_{13}HgNaO_6,C_7H_8O_2N_4,H_2O$. It is not isolated from solution, which may contain a slight excess of theophylline. The mercumallylic acid used in the preparation of mercumatilin sodium responds to the following tests and standards. It is a white, odourless, bitter powder, m.pt. about 190° C. with decomposition, soluble in sodium hydroxide test solution (1 in 4·2), slightly soluble in water, ethanol, chloroform and acetic acid, and almost insoluble in ether. When refluxed with aqueous formic acid for 15 minutes, and filtered, the filtrate yields crystals of cumallylic acid (8-allylcoumarincarboxylic acid), which after washing with water and drying at 105° C. for 2 hours melt at 147° C. to 150° C. A solution in 0·1N sodium hydroxide yields no immediate precipitate or colour with sodium sulphide (absence of mercuric ions). When extracted with acetone for 4 hours, it yields not more than 2·5 per cent. of acetone–soluble extractive, dried at 105° C. for 2 hours. When dried at 105° C. for four hours, it loses not more than 5·0 per cent. of its weight; it yields not more than 0·05 per cent. of sulphated ash. It contains 39·8 to 43·1 per cent. of Hg, equivalent to 95·0 to 103·0 per cent. of mercumallylic acid, when assayed by the thiocyanate method. The solution of mercumatilin sodium must comply with an additional identity test for theophylline and with the test for absence of mercuric ions. It contains 94·0 to 106·0 per cent. of the labelled amount of mercumatilin sodium, determined by the assay for mercury described above, and 94·0 to 106·0 per cent. of the labelled amount of theophylline. Mercumatilin sodium is used as a diuretic. G. R. K.

PHARMACOLOGY AND THERAPEUTICS

p-Acetamidobenzaldehyde Thiosemicarbazone in the Treatment of Leprosy. J. Lowe. (*Lancet*, 1952, 262, 436.) This drug has been administered daily in tablets of 50 mg. to 71 patients over periods varying from 5 to 17 months. Three types of cases were under treatment: a group of lepromatous type previously untreated, a group of tuberculoid type also previously untreated, and a group of lepromatous type previously treated with sulphones but with resulting complications. Apart from 1 case of acute agranulocytosis no serious toxic effects were observed. The drug was well tolerated and complications few and usually not severe. Clinical and bacteriological response was satisfactory. Compared with sulphones, allergy is rare, but apart from this the drug has no obvious advantage over sulphone treatment in non-lepromatous cases. In more severe lepromatous cases the complications are fewer and less severe. However, administration is more difficult, and the drug more expensive. It is suggested that if agranulocytosis is rare the drug will be a valuable alternative to the sulphone treatment. J. R. F.

Analgesic Drugs, Assay of, on Man. C. A. Keele. (*Analyst*, 1952, **77**, 111.) A review is made of the techniques available for the quantitative assessment of the value of drugs given to patients suffering pain. The effects of dithienyl analgesics on ischæmic muscle pain have been studied in two ways: (*a*) by observing the effects on maintained ischæmic pain, the drug being injected intravenously, and (*b*) by observing the effects on the number of muscular contractions required to produce ischæmic muscle pain, the drug being injected intramuscularly. The first method yielded useful results and the estimate of the analgesic potency of the dithienyl compounds places them somewhat between morphine and amidone, on the one hand, and pethidine on the other; subsequent work on patients confirmed this estimate of the relative potency of new compounds. The second method, using muscular contractions producing ischæmic muscle pain, was less reliable and an analysis of the results suggested that the figures gave more information about the subject than about the analgesic potency of the drugs used. Results are given of the frequency of side effects observed, including drowsiness, euphoria, dizziness, nausea and vomiting. Work on normal persons and on selected patients showed that the dithienylbutylamines had an analgesic action, usually associated with a definite hypnotic effect. Such properties would be most useful in treating post-operative pain or in helping to procure sleep in patients kept awake by pain during the night; an investigation on patients is being carried out. R. E. S.

Analgesic Potencies, Estimation of. A. Tye and B. V. Christensen. (*J. Amer. pharm. Ass., Sci. Ed.*, 1952, **41**, 75.) Analgesic potencies of a number of drugs were estimated in rats. The criterion of analgesia was the failure of the rat to move its tail when a radiation stimulus was applied from a modified Hardy-Wolff-Goodell pain threshold apparatus. Satisfactory estimates of the strengths of morphine sulphate solutions were obtained by a comparison of the AD50 for the solutions with that of pure morphine sulphate. There was no statistical difference in the results for AD50 whether or not litter mates were used in the test. Pentobarbitone and acetylsalicylic acid showed no activity when tested by this method, and pentobarbitone did not potentiate the action of codeine. Diethylaminoethanol, a hydrolytic fragment to which the analgesic effect of intravenous procaine has been attributed, produced analgesia only when administered in toxic doses. G. B.

Aureomycin, Intrathecal Administration in Meningitis. K. M. S. Ainley-Walker and F. D. Bosanquet. (*Lancet*, 1952, **262**, 433.) Systemic administration to 14 out of 15 patients did not produce therapeutic levels of the antibiotic in the cerebrospinal fluid. A fall in blood pressure in hypertensive patients and a fall of cerebrospinal fluid pressure in both normal and hypertensive patients were observed. An intrathecal preparation was used in an attempt to achieve sufficient concentration. This was administered to 3 patients with advanced penicillin- and streptomycin-resistant types of meningitis. Therapeutic levels were produced without untoward reactions and an improvement in their condition was seen although recovery was not achieved. Intraventricular or cisternal injection is considered essential to obtain a satisfactory concentration. The solution used was prepared by dissolving 100 mg. of aureomycin hydrochloride in 10 ml. of sterile water giving a *p*H of 2·6. This, when frozen solid, keeps for a minimum of 6 weeks. Immediately before use, 1 ml. is added to 9 ml. of a buffer consisting of 9 ml. of 2 per cent. glycine in water and 0·175 ml. of 0·2N sodium hydroxide solution, giving a final *p*H of 7·2 to 7·4. The solution contains 1 mg. of aureomycin per ml. and is active for 1 hour. A slight precipitation may occur. The buffer may be made in bulk and distributed in 9 ml. quantities into vaccine bottles and autoclaved. The contents will keep for at least 6 weeks. J. R. F.

Barbiturate Poisoning, Conservative Treatment of. S. Locket and J. Angus. (*Lancet*, 1952, **262**, 580.) On admission the patient receives gastric lavage with 2 pints of normal saline or tap water. This is followed by penicillin, 500,000 units 6-hourly by intramuscular injection as a prophylactic against broncho-pneumonia, until the patient has been conscious for 48 hours. Oxygen is given at the rate of at least 10 l./minute until respiration is normal, cyanosis has permanently disappeared, and consciousness is fully restored. In the event of coma lasting more than 24 hours, fluid loss is made up by giving intravenous 5 per cent. glucose saline, 1 l. in 24 hours. Catheterisation of the bladder is necessary in unconscious and some stuporose patients. Prolonged laryngeal intubation, which may occasionally produce fatal laryngeal œdema, is unjustified. The use of sympathomimetics to raise blood pressure may produce renal vasoconstriction and interfere with clearance of barbiturates with a prolonged action. In a series of 64 consecutive cases of barbiturate poisoning given this conservative treatment there were only 2 deaths. No analeptics were used and drainage by lumbar puncture was never attempted. No chest-thumping is practised, but during the entire period of coma great care is taken to ensure an adequate airway by careful attention to the tongue and mouth. S. L. W.

Cardiac Glycosides, Absorption Rate of Orally Administered. W. F. White and O. Gisvold. (*J. Amer. pharm. Ass., Sci. Ed.*, 1952, **41**, 42.) Doses of digitoxin, digoxin, acetyldigoxin and lanatoside C were administered orally to unanæsthetised cats and the time of death was observed so that the survival time could be used as a measure of the absorption rate for the drug. Using solid forms (tablets of digitoxin, digoxin and lanatoside C, and capsules of acetyldigoxin) digitoxin and acetyldigoxin were absorbed fairly rapidly, but digoxin and lanatoside C were absorbed much more slowly. When the drugs were administered as solutions in aqueous ethanol, in aqueous solution with Tween 80 or in a solution of low ethanol content with Tween 80, all the glycosides were more rapidly absorbed than from the solid. Digoxin administered in this way was comparable with digitoxin and acetyldigoxin. Thus if absorption in cats and human beings is comparable the maintenance dose of 0·5 mg. of

digoxin in tablets might be reduced to one-fifth by administration of the substance in capsules containing a Tween 80 solution. Lanatoside C was slowly and incompletely absorbed even from solutions. It is suggested that acetyldigoxin in tablets should be tried clinically. G. B.

Chloramphenicol, Local Use in Wound Infections. M. H. Flint, H. Gillies and D. A. C. Reid. (*Lancet*, 1952, **1**, 541.) 30 cases of wound infection (infected burns, gravitational ulcers, pedicle flaps, grafts and abscess cavities) were treated with chloramphenicol applied as a 5 per cent. dilution in lactose or a 5 per cent. solution in propylene glycol. The majority of infections were due to penicillin-resistant organisms (*Staphylococcus aureus*, *Pseudomonas pyocyanea*, *Proteus vulgaris* and coliform bacilli) and had not responded to penicillin, aureomycin or chloramphenicol administered systemically. Bacterial clearance was obtained in an average of 4 or 5 days and improved wound healing occurred during treatment. None of the organisms showed any tendency to become more resistant to chloramphenicol. The propylene glycol solution, irrigated into the cavities or applied on wicks or gauze pads appeared to be preferable to the powder. G. B.

Citrinin, Therapeutic Tests on. L. Leusch. (*J. Pharm., Belg.*, 1952, **7**, 77.) Ointments containing 0·5 per cent. of citrinin, an antibiotic obtained from *Penicillinum citrinum* Thom. were very effective in cases of streptococcal and staphylococcal skin infections, whereas ointments prepared with sodium citrinate were ineffective. In the treatment of tropical ulcers the initial effect of the ointment was good, but after the first week, progress was slow. Treatment of the tropical ulcers with gauze dressings impregnated with a 0·5 per cent. suspension of citrinin in water, followed at a later stage by the application of a powder containing 0·5 per cent. of citrinin in boric acid, cleared the infection and the curative action continued without delay until healing was complete. 25 cases of ulcers infected with fusiform bacteria and borrelia were successfully treated by this method, the average time of hospitalisation in this series, which included cases complicated by œdema etc., being 18 days. Simple cases were cured in 12 to 15 days. G. B.

Daraprim, a New Antimalarial; Trials in Human Volunteers. L. G. Goodwin. (*Brit. med. J.*, 1952, **1**, 732.) In a group of 13 volunteers, daraprim (2:4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine) in doses of 50 mg. twice weekly for 3 months produced no significant effects on the blood counts, sedimentation rate or urine. Slight gastro-intestinal upset was observed in 2 persons. In one individual, daily doses of 5 mg. administered continuously for one year produced no toxic symptoms and no abnormalities in the blood and bone-marrow or urine. This dose was an effective suppressant of *P. falciparum* malaria infections. G. B.

Daraprim in Treatment of Malaria. I. A. McGregor and D. A. Smith. (*Brit. med. J.*, 1952, **1**, 730.) 25 children and 4 adults infected with *P. falciparum* and 3 children with *P. malariæ* were treated with daraprim (2:4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine), a tasteless substance administered in a single oral dose of 0·25 to 0·5 mg./kg. in the form of a suspension or a syrup. The blood was freed from asexual parasites within 96 hours for *P. malariæ* infection and in 72 hours in all but 2 cases of *P. falciparum* infection. The drug was equally effective in patients without or with a considerable immunity. No skin rashes, toxic renal damage or depression of hæmopoiesis were observed, but

vomiting occurred in 2 children. The drug appears to act mainly during schizogony at the stage of plasmodial development when the chromatin is in active division, but, after a single dose, the blood concentration remains high enough to be lethal to all asexual forms even if some do not reach the vulnerable phase for 72 hours after the drug has been administered. G. B.

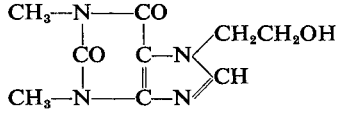
Dinitro-*ortho*-cresol Poisoning, Prevention of. P. L. Bidstrup, J. A. L. Bonnell and D. G. Harvey. (*Lancet*, 1952, **262**, 794.) The estimation of blood levels in workmen subjected to the risk of absorbing dangerous amounts of this substance would prove a valuable additional measure in the prevention of acute poisoning. This should be done at least at weekly intervals and the man should not return to work with this substance until the results are known. If the level in blood taken 8 hours after the last exposure is 20 μg./g. or above, the workman should be removed from further contact with the substance for at least 6 weeks. At this level the only symptom is an exaggerated feeling of well-being, but at levels of 40 μg./g. or more symptoms of headache, lassitude and general malaise occur. Where the blood level is 10 to 20 μg./g. strict supervision is necessary to ensure that all the recommendations for safe handling are observed, and if it has risen further after 2 days the man should be removed from contact with the compound. With levels below 10 μg./g. no extra precautions are necessary. The main route of absorption is by inhalation, and respirators should be worn, especially by spray operators and others concerned in the spraying of cereal crops. Determination of dinitro-*o*-cresol in the urine is unlikely to prove a reliable test of absorption when the blood level is about 20 μg./g. S. L. W.

Fungistatic Powers of Phenindamine and Asterol Dihydrochloride. E. E. Seale. (*Canad. med. Ass. J.*, 1951, **65**, 582.) *In vitro* studies on fungistatic properties are reported on the antihistamic drug phenindamine (thephorin) and a new compound, asterol dihydrochloride, 2-dimethylamino-6-(β-diethylamino-ethoxy-benzothiazole). Three methods were used in the investigation, namely, the mycophil broth sensitivity test, the agar plate technique to establish the critical fungistatic dilution, and the penicillin cylinder assay method. The results obtained suggest that both substances possess *in vitro* fungistatic properties for pathogenic fungi. Using the mycophil broth sensitivity test, asterol dihydrochloride in a concentration of 0·3215 mg./ml. inhibited the growth of the dermatophytes, the effective inhibitory concentration of phenindamine varying with the species. Both compounds showed fungistatic properties with the penicillin cylinder assay technique using *Tricophyton mentagrophytes*. With the agar plate method resistance to asterol dihydrochloride developed in cultures of *Microsporon audouini* isolated from ringworm of the scalp, when treatment with the compound had been continued for 6 to 7 weeks. S. L. W.

Hydrocortisone (Free Alcohol), Hydrocortisone Acetate and Cortisone (Free Alcohol) Antirheumatic Effects of, Compared with Cortisone Acetate. E. W. Boland. (*Brit. med. J.*, 1952, **1**, 559.) The compounds were administered orally to patients with rheumatoid arthritis and results assessed by observing the response to large suppressive doses, and by comparing equivalent maintenance doses. Cortisone (free alcohol) and cortisone acetate were equally effective. Hydrocortisone (free alcohol), i.e., 17-hydroxycorticosterone, in initial suppressive doses acted more rapidly and lowered the erythrocyte sedimentation rate more quickly. By comparison of maintenance doses, this

compound was 50 per cent. more active than cortisone. The smaller maintenance doses of hydrocortisone (free alcohol) induced fewer side effects than the cortisone treatment. Hydrocortisone acetate was much less active, possibly because its lower solubility may lessen alimentary absorption. G. B.

Hydroxyethyltheophylline, Clinical Experience with. O. W. Lürmann and W. Böres. (*Dtsch. med. Wschr.*, 1952, 77, 15.) As an alternative to the present method of increasing the solubility of theophylline by the addition of amines, soluble derivatives of theophylline have been tried. One such product is 7-(β-hydroxyethyl)theophylline



Clinical experience with this compound, in a large number of cases, has shown that its action is somewhat less than that of the other preparations, probably owing to the absence of the additional effect of the amine on the heart and circulation. It is, however, more readily tolerated. G. M.

Insulins, Comparison of Duration of Action of Different Forms of. F. Gerritzen. (*Brit. med. J.*, 1952, **1**, 249.) The duration of action of 10 different products was investigated on young healthy student volunteers. They were administered, in equal doses of 20 units, to groups varying in numbers from 4 to 12, with a control group of 6 who did not receive insulin. In the control group no significant deviation was found between the average blood sugar values at different times over 24 hours. The other groups responded as follows:—Regular insulin; blood sugar reaches its lowest point after 1 hour and returns to its starting-point in 8 hours. Protamine zinc insulin; duration of action 18 hours, lowest point reached in 5 to 8 hours. Di-insulin; duration of action 16 hours, greatest decrease in blood sugar during first 3 hours. Iso-insulin; duration of action 16 hours, rapid decrease in the first hour. Globin insulin; action identical with that of di-insulin. N.P.H. 50 (two samples); duration of action 11 hours, lowest point after 3 (or 4) hours. Insulin mixtures (proprietary); duration of action would appear to depend on the regular insulin content only so far as the decrease during the first 3 hours is greatest with the mixture containing most regular insulin (a 3:1 mixture) and that thereafter the blood sugar takes longer to come back to the starting-point than with 2:1 and 1:1 mixtures. S. L. W.

Kemadrin in Postencephalitic Parkinsonism. E. Montuschi, J. Phillips. F. Prescott and A. F. Green. (*Lancet*, 1952, **262**, 583.) Kemadrin (1-*cyclo*hexyl-1-phenyl-3-pyrrolidino-propan-1-ol) is a spasmolytic chemically related to artane. A trial of the drug in 50 cases of postencephalitic parkinsonism showed that it is of considerable value in relieving some of the symptoms of the disease, particularly the rigidity, depressed emotional tone, and lack of expression. It was administered for periods varying from 3 to 11 months in doses of 5 to 20 mg. 3 times daily, the average dose being 15 mg. 3 times daily. Side-effects (giddiness) occurred in only 3 of the patients, and was relieved by reduction of the dose; one patient complained of visual disturbance. In no case did toxic effects necessitate withdrawal of the drug. There would appear to be no significant difference in the therapeutic actions of kemadrin and artane, and it was found possible to change patients from one drug to the other without

causing any apparent change in their clinical condition. No contra-indications to the use of the drug were found; in particular, hypertension is not a contra-indication. As kemadrin has no greater mydriatic effect than artane it is likely that, with due care, it can be used in patients with glaucoma. S. L. W.

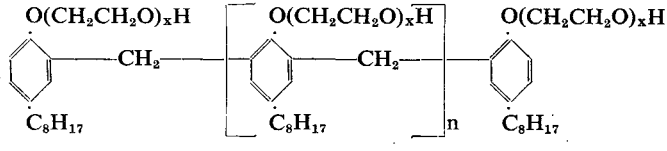
Methonium Compounds: Oral Use in the Treatment of Hypertension. A. J. M. Campbell, J. G. Graham and R. D. H. Maxwell. (*Brit. med. J.*, 1952, **1**, 251.) The authors have used methonium compounds for almost 2 years in the treatment of hypertension, and the treatment of an unselected group of 35 patients with severe symptoms, whose ages ranged from 29 to 67 years, is described. Tablets of comparable methonium content were used, that is, a 250 mg. tablet of hexamethonium bromide, which is equivalent to a 350 mg. tablet of the bitartrate and to 125 mg. of M. and B. 1863 bromide (a homologue of hexamethonium). Oral dosage began with a single tablet, followed by a progressive increase in frequency and quantity to a maximum of 12 to 16 tablets a day. At no time was more than 4 g. of hexamethonium bromide given daily. In 23 of the 35 patients there was a good symptomatic improvement with regression of the signs. Hexamethonium also produced a symptomatic improvement in 5 patients with severe chronic nephritis and 2 with malignant hypertension. S. L. W.

1-Methyl-2-mercaptoimidazole, Treatment of Thyrotoxicosis with. R. L. Kendrick, K. Balls and E. Rose. (*Arch. intern. Med.*, 1952, **89**, 368.) A mixed group of 17 patients was treated with 1-methyl-2-mercaptoimidazole with the object of inducing remission of thyrotoxicosis without operation, and a group of 15 women was treated pre-operatively. A daily dose of 30 mg. for adults and 15 mg. for children was given initially and reduced as thyrotoxicosis subsided. Responses were good in 26 cases, fair in 5 and poor in 1. In 15 patients on prolonged therapy with complete remission, the minimum time required to induce complete remission of symptoms was 4, the maximum 12 and the average 7 weeks. The only untoward effects were sensitivity reactions (vesicular skin eruptions, urticaria and pruritus) in 3 patients. G. B.

Morphine, Liberation from Codeine in the Rat. T. K. Alder and F. H. Shaw. (*J. Pharmacol.*, 1952, **104**, 1.) Rat-liver slices were incubated at 38° C. in Krebs–Ringer bicarbonate solution containing 1 to 2 mg. of codeine, nitrogen or oxygen, with 5 per cent. of carbon dioxide, being passed in and the preparations agitated. The solution after precipitation of protein with trichloracetic acid and extraction with chloroform under acid and alkaline conditions to remove codeine, etc., was saturated with sodium bicarbonate and the phenolic metabolite extracted with ethanol–chloroform mixture. The product was identified as morphine by spectrophotometer and by the X-ray diffraction pattern and ultra-violet spectrum of the derivative formed with 2:4-dinitrochlorobenzene. Codeine in the metabolites was estimated by a modification of a method depending on the opacity produced after adding silicotungstic acid. Under ærobic conditions about 40 per cent. of the codeine disappeared and the morphine formed was equivalent to less than half this quantity. Under anærobic conditions about 6 per cent. only of the codeine was destroyed and no morphine could be detected. The morphine was shown to undergo conjugation which could be inhibited by M/50 sodium fluoride or M/1500 monoiodoacetic acid, but the latter compound interfered with the metabolism of the codeine. G. B.

Mysoline in the Treatment of Epilepsy. R. Handley and A. S. R. Stewart. (*Lancet*, 1952, **262**, 742.) Mysoline, an anti-convulsant drug closely related to phenobarbitone, is 5-phenyl-5-ethyl-hexahydropyrimidine-4: 6-dione. It is a white, crystalline substance, practically tasteless, chemically stable, and sparingly soluble in water. It has an extremely low toxicity, both acute and chronic, in all species of laboratory animals tested, and has no hypnotic action in doses many times that required to protect animals against electrically-induced convulsions. Of 40 patients suffering from major epilepsy, 32 (80 per cent.) were improved and 12 (30 per cent.) were completely freed from all types of attacks, under mysoline therapy. The optimum daily dosage rarely exceeds 1·6 g., and this dosage produces only very mild and transient side-effects and does not make the patients sleepy. Hypertrophy of the gums and abnormal blood changes did not occur in this series. The change from old to new treatment was uneventful; the previous drug should be withdrawn gradually over 2 weeks. 0·25 g. of mysoline twice daily should be added for 3 days and then increased by 0·25 g. every 3 days to a daily total of 1 g., with further increases to a daily total of 1·6 g. if necessary. Withdrawal of previous treatment should begin on the 4th day and be complete by the end of the second week. S. L. W.

Surface-active Agents, Anti-tuberculous, Depression of Tuberculin Sensitivity in Guinea-pigs by. P. D'Arcy Hart, D. A. Long and R. J. W. Rees. (*Brit. med. J.*, 1952, **1**, 680.) Surface-active polyoxyethylene ethers of low toxicity were prepared by polymerisation of ethylene oxide with condensation products of formaldehyde with *p-tert.*-octylphenol. They had the general formula given below.



The following were chemotherapeutically active in the tuberculous mouse:— (1) a mixture in which $n = 0$ upwards, $x = 20$ (average value); (2) a similar mixture with a smaller proportion of lower members of the series and (3) as for (1), but $x = 10$ (average value). An isolated $n = 1$ compound and a mixture with $x = 60$ (average value) were inactive. Single subcutaneous or intravenous injections of the chemotherapeutically active compounds, but not the inactive ones, decreased the sensitivity of BCG-sensitised guinea-pigs to tuberculin, in a degree comparable to that for cortisone. The desensitising action, unlike that of cortisone, was independent of dietary factors and thyroid activity. It is suggested that (1) for these surface active compounds the mechanism of chemotherapeutic action and depression of sensitivity are interlinked, although there is little evidence that the antituberculous effect is due to desensitisation and (2) for cortisone the mechanism of desensitisation is different, being related to diet etc., and the cortisone-induced mesenchymal depression equals or outweighs the benefits of desensitisation, since cortisone has no anti-tuberculous action. G. B.

Terramycin in Infections in Infants and Children. B. Wolman and A. Holzel. (*Brit. med. J.*, 1952, **1**, 419.) Cases of pneumonia responded rapidly, fever disappearing in 24 to 72 hours. Of 35 patients, only 3 showed no response

to the drug. Good results were also obtained in upper respiratory tract infections and in tonsilitis. Treatment with terramycin was effective in pyuria where sulphonamides, streptomycin and chloramphenicol had given only temporary improvement. In newborn infants with purulent conjunctivitis, terramycin was useful when the infecting organism had become resistant to penicillin or streptomycin. No toxic reactions were observed. The drug was conveniently administered to children in a dose of 50 mg./kg., as a palatable elixir, and a solution with sodium chloride and sodium borate in distilled water was used for ophthalmic cases, G. B.

Triethylene Melamine in Neoplastic Diseases. J. C. Wright, A. Prigot, L. T. Wright and I. Arons. (*Arch. Intern. Med.*, 1952, **89**, 387.) 42 patients with neoplastic diseases were treated with triethylene melamine, administered orally in an average dose of 5 mg. daily for 3 days. When an initial course produced no toxic effects and no therapeutic effect after 15 days, the treatment was repeated. Pyridoxine (50 mg.) was administered orally at the same time as the drug to reduce the incidence of nausea and vomiting. Citrovorum factor was used in 2 cases to correct leucopenia after the treatment. Improvement occurred in 18 patients and was marked in lymphosarcoma, Hodgkin's disease, chronic myelogenous leukæmia and chronic lymphatic leukæmia, and moderate in fibrosarcoma, reticulum-cell sarcoma and mycosis fungoides. No improvement occurred in cases of carcinoma. When triethylene melamine showed marked inhibition of a patient's tumour in tissue culture, the drug was also active *in vivo*. G. B.

Vitamin B_{12}, Side-effects of a Preparation of. P. D. Bedford. (*Brit. med. J.*, 1952, **1**, 690.) The following preparations were tested for skin reaction following intradermal injection and for side-effects following deep intramuscular injection:—(1) a commercial solution of vitamin B_{12} factors obtained by extraction from *Streptomyces griseus* fermentation liquors, (2) a preparation of vitamin B_{12} (cyanocobalamin) derived from liver and (3) a solution of vitamin B_{12c} obtained from streptomyces cultures but highly purified by crystallisation. Of 100 patients, 14 had a positive skin reaction to (1), 2 to (3) and none to (2), 6 showed side effects to (1) and none showed side effects to (2) and (3). Both cutaneous reactions and side-effects to intramuscular injection were twice as common in patients who had previously been treated with antibiotics. Attention is drawn to the fact that as non-specific hypersensitivity to fungi or mould products may cause a significant proportion of unusual responses to antibiotic therapy, the use of impure vitamin B_{12} preparations derived from mould cultures is liable to induce idiosyncrasy to antibiotics. G. B.

BACTERIOLOGY AND CLINICAL TESTS

Alkaloids, Toxicity to Bacteria. C. C. Johnson, G. Johnson and C. F. Poe. (*Acta pharmacol. Toxicol.*, 1952, **8**, 71.) Various species of *Escherichia* and *Aerobacter* were incubated at 37° C. for 72 hours in media containing various concentrations of berberine, sanguinarine, and physostigmine, and the volume of gas produced after 24, 48 and 72 hours was compared with that produced in controls. Berberine and sanguinarine were more toxic for *Escherichia* than for *Aerobacter*, although the difference was not sufficient to allow separation of the genera by growth in media containing the alkaloids. In media containing 1 in 900 of berberine, no gas was formed during 48 hours by cultures of *Escherichia*; cultures of *Aerobacter* required a concentration of 1 in 400 to produce

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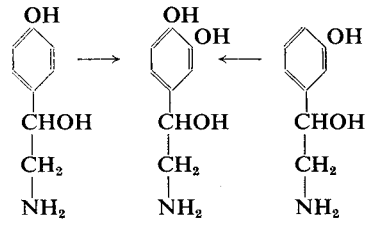

p-Norsynephrine Noradrenaline *m*-Norsynephrine

We have now shown that both the *p*- and the *m*-norsynephrine can form noradrenaline under such conditions. The irradiation was carried out using a Hanovia Fluorescence Lamp, Model 11, and the best yields were obtained after two hours irradiation at *p*H 5 with a 1 in 10,000 solution of the amine. Proof that noradrenaline was in fact the material formed was obtained by running concurrently chromatograms of the irradiated solutions and of noradrenaline. Further chromatograms allowed of elution of the corresponding areas and biological examination of the eluates on the blood pressure of a spinal cat and the isolated rabbit intestine.[2]

In the biosynthesis of noradrenaline, therefore, *p*- or *m*-norsynephrine may be formed at an intermediate stage, and it may be possible to identify one or other of these substances in extracts of mammalian suprarenal glands. Their formation from tyrosine or tyramine is conceivable, a step not requiring the production of dihydroxyphenylalanine or hydroxytyramine. Further work on this approach to the synthesis of adrenaline is in progress.

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July 11, 1952.

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ABSTRACTS (*Continued from page* 670)

inactivation. Of the three alkaloids, sanguinarine was the most toxic to the bacteria studied, and physostigmine the least. Berberine at a dilution of 1 in 10,000 showed some stimulation of growth. In media containing berberine and sanguinarine, gas was produced in a number of experiments after an inactive period of as much as 10 days, confirming evidence of bacteriostasis. Experiments designed to test the germicidal activity of the alkaloids in relation to that of phenol showed that media saturated with salts of the alkaloids did not inhibit the growth of *E. typhi* and *Staph. aureus* after 15 minutes exposure, and that *Staph. aureus* was not inhibited by the following concentrations until after the times stated: berberine hydrochloride (saturated), 43 minutes; physostigmine hydrochloride (1 in 11), 10 minutes; and sanguinarine sulphate (1 in 40), 24 minutes. G. R. K.