ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

Berberine and Cotarnine, Isomerisation in the Presence of Alkali. B. Skinner. (*J. chem. Soc.*, 1950, 823.) The absorption spectra of cotarnine hydrochloride in aqueous and alcoholic solutions have been re-investigated and the results confirm the earlier suggestion (Dobbie *et al*, *J. chem. Soc.*, 1903, **83**, 598) that quarternary cotarninium hydroxide is converted into the ψ base in the presence of excess of alkali hydroxide. Cotarnine shows two types of absorption spectrum: the first in simple aqueous or alcoholic solution with two well-marked absorption bands at 3278 and 2500 Å and the second in strongly alkaline solution (aqueous or alcoholic) with less general absorption and an ill-defined maximum at 2857Å. In weakly alkaline solutions, curves intermediate between the two types were obtained. The transition from the yellow to the colourless form (alkali) is almost instantaneous and is immediately reversed on the addition of a slight excess of dilute acid. Potentiometric titrations and conductivity measurements confirm that ψ cotarnine behaves as a typical strong base, which in solution in the absence of alkali is stable as a quaternary ion ($R.CH=\overset{+}{N}=R'$, CH). Alkali catalyses its conversion to the colourless carbinol form (R.CHOH-N=R'). Parallel effects are observed in the ultra-violet absorption spectra of berberine hydroxide; this base is more stable than cotarnine in both aqueous and alcoholic solution and can actually be isolated in a solid form, which remains stable for some days. The various types of system covered by the term ψ base (Hantzsch and Kalb, *Ber. dtsch. chem. Ges.* 1899, **32**, 3109) are discussed.

J. B. S.

ANALYTICAL

Digitalis, A Spectrophotometric Method of Assay of. R. E. Abrams and M. S. Dunn. (*Amer. J. Pharm.*, 1950, **122**, 337.) This is an investigation to ascertain whether a method based on a modification of the original Baljet reaction (production of a red-orange colour by active digitalis glycosides when treated with alkaline picrate solution), and the use of a narrow band spectrophotometer, can be shown to give a practical, efficient and easily reproducible chemical assay. The authors conclude that for a workable spectrophotometric assay of digitalis and its preparations, the following conditions must be rigidly adhered to, (a) the colour produced by the Baljet reaction should be read at the conclusion of 30 rather than 20 minutes; (b) a narrow band spectrophotometer employing a wave-length of 495 mμ should be used; (c) if the concentration of the digitalis glycosides is kept at the level necessary to have all the readings fall somewhere between 32 and 65 per cent. transmission, the Lambert-Beer law is followed. Under these conditions the method (which is described) is shown to be accurate to well within 5 per cent. and the reproducibility is also very high, the

calculated error being within 2 per cent. The authors recommend a further study of the method with possible consideration of its adoption as an official assay. S. L. W.

Hydroxy Compounds in Amine Mixtures, Determination of. S. Siggia and I. R. Kervenski. (*Anal. Chem.*, 1951, **23**, 117.) The following method depends on acetylation of a mixture of amines and alcohols, and saponification of the esters without affecting the amides. A sample (about 0·01 mole of hydroxyl) is acetylated by heating in a glass stoppered flask on a steam-bath for 45 minutes, with 10 ml. of a mixture of 3 parts of pyridine and 1 part of acetic anhydride. The solution is cooled, diluted with water, neutralised to a mixed cresol red/thymol blue indicator, and the esters saponified by boiling with 0·5 N methanolic sodium hydroxide for 2 hours. The excess of alkali is titrated with 0·5 N sulphuric acid. The hydroxyl content is calculated from the quantity of alkali used in the saponification. The total primary and secondary amine content may be calculated from the quantity of acetic anhydride used for acetylation, allowing for the amount which reacts with the hydroxyl groups; a blank test on the acetylating reagent is required. The method used is of use in following the course of the alkylation of amines and alcohols. G. B.

Iodoform Reaction. K. J. Morgan, J. Bardwell and C. F. Cullis. (*J. chem. Soc.*, 1950, 3190.) The iodoform reaction applied to acetone is recognised to take place through the following stages. (a) Conversion of the ketone into the enolate ion $CH_3.CO.CH_3 + B \rightarrow [CH_2.CO.CH_3] + BH^+$ (where B is the basic catalyst, usually the hydroxyl ion). This is the rate-determining stage. (b) Progressive iodination of this ion to form tri-iodoacetone. (c) Hydrolysis of tri-iodoacetone by the following base catalysed reaction, $CH_3.CO.CI_3 + H.OH \rightarrow CH_3.COOH + CHI_3$. The investigation described was conducted to increase the reliability of Messinger's volumetric procedure (*Ber., dtsch. chem. Ges.*, 1888, **21**, 3366) for the determination of methyl ketones by the iodoform reaction, because low results are obtained unless the order, rate of addition and the concentrations of the reagents are properly adjusted. A systematic examination of these factors was made. The inaccuracy encountered, when the recommended analytical procedure is not closely followed, may be ascribed, in part, to the competing reaction: $3IO' \rightarrow IO_3' + 2I'$. It was found that, in order to obtain quantitative yields of iodoform, the experimental conditions should be adjusted as follows. 1. The acetone and alkali should be "premixed" and the iodine added slowly with constant agitation. 2. A large excess of alkali, preferably 20 times that required according to the stoichiometric equation, must be used. 3. A moderate excess of iodine (about 1·5 × stoichiometric) should be employed. 4. The reactants should be set aside for at least 20 minutes (at 25°C.) before acidification, to ensure completion of the reaction. A. H. B.

Iron, Colour Reaction of, with Hydroxyquinoline. R. Castagnou and G. Gaucher. (*Bull. Trav. Soc. Pharm. Bordeaux.* 1950, **88**, 98.) A colorimetric study was made of the green colour given by ferric salts with hydroxyquinoline. The reaction was found to be unsuitable for the colorimetric determination of iron as, except within a narrow range of concentration, turbidities and precipitates are formed. This does not happen when the reaction is used for the determination of hydroxyquinoline, for which purpose

the reaction must be neutral, and a concentration of 0·2 g. of iron per litre gives the most satisfactory results. G. M.

ESSENTIAL OILS

Rosemary Oil, Tanganyika. E. Brown, T. J. Coombes and H. T. Islip. (*Colon. Plant Anim. Prod.*, 1950, **1**, 114.) This oil conformed to the requirements of the B.P. except the weight per ml. which was slightly lower. The characters fell within the ranges for Spanish rosemary oil apart from a rather higher total alcohols figure. It was considered that the oil had been contaminated with geranium oil which prevented a true assessment of odour value. The characters were wt. per ml. at 20°C., 0·8925; $\alpha_D^{20°C.}$ −4·06°; $n_D^{20°C.}$ 1·4699; acid value, 1·2; ester value, 18·9 (equivalent to 6·6 per cent. bornyl acetate); ester value after acetylation, 59·5 (equivalent to 17·1 per cent. borneol); free alcohols as borneol, 11·7 per cent.; apparent cineole content, 21·0 per cent.; solubility in alcohol (80 per cent.) at 15·5°C., soluble in 10 volumes with slight turbidity; solubility in alcohol (90 per cent.) at 15·5°C. soluble in 0·5 volume. G. R. A. S.

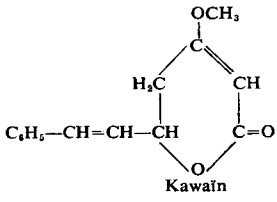
ORGANIC CHEMISTRY

Adsorption Colours and their Significance for Tautomeric and Thermochromic Effects. A. Schönberg and W. Asker. (*Science*, 1951, **113**, 56.) A solution of β-dinaphthaspiropyran in a cold inert solvent is colourless, whereas a hot solution is intensely violet. That this is due to the formation of a heteropolar molecule is supported by the observation that activated alumina added to a cold colourless solution in xylene immediately becomes bluish-green. Using a column of activated alumina, the adsorbed material can be eluted with methyl alcohol. Similarly, the colourless triarylmethyl halides and related substances were adsorbed with a colour similar to that of the corresponding cation. For example, triphenylmethyl chloride gives the yellow colour of the triphenylmethyl cation, and the base $[(CH_3)_2N.C_6H_4]_3C.OH$ is adsorbed with the violet colour of the corresponding cation. In benzene, 1:3-diketohydrindene gives a colourless solution. The addition of activated alumina immediately produces a violet colour, which appears to be due to the enol form. G. R. K.

9-Anthraldehyde, Reactions with. A. Mustafa. (*Science*, 1950, **112**, 440.) The following compounds have been obtained by condensation of 9-anthraldehyde with substances containing a reactive methylene group:— 9-anthrylidene acetone and di-9-anthrylidene acetone (from acetone), 9-anthrylidenepinacolone (from pinacolone), 9-(9′anthrylidene)fluorene (from fluorene), and 9-anthrylidene nitroanilines (from *o*-, *m*-, and *p*-nitroanilines), α-(9-anthrylidene)-β-(2′pyridyl)ethylene may be prepared from α-picoline, or from α-picoline methiodide, by thermal decomposition of the methiodide produced. Direct fusion of indane-1:3-dione with 9-anthraldehyde yields 9-anthrylidene-indane-1:3-dione, which condenses with ethyl 2-aminocrotonate in glacial acetic acid to produce ethyl-1-anthryl-3-methyl-1:4-dihydro-4-azofluorenone-2-carboxylate. On oxidation with chromic acid in acetic acid this compound yields ethyl-1-anthryl-3-methyl-4-azofluorenone-2-carboxylate. G. B.

Hydrazine Carbamate. E. Staal and C. Faurholt. (*Dansk Tidsskr. Farm.*, 1951, **25**, 1.) Hydrazine carbamate is formed when carbon dioxide is passed into a solution of hydrazine in sodium hydroxide, the carbonate being also formed. The velocity constant for the reaction is $10^{5\cdot51}$ at 18°C. By the action of carbon dioxide on a concentrated solution of hydrazine at 0°C., the carbamate may be prepared in solid form. In water, or in strongly acid solution, it is decomposed very rapidly to carbonate, but in weak alkali an equilibrium is set up, and the equilibrium constant was found to be 0·013. In strong alkali the conversion to carbonate, though slow, is ultimately complete. The compound is produced from 1 molecule of hydrazine and 1 molecule of carbon dioxide. G. M.

Kawaïn, Synthesis of. D. G. F. R. Kostermans. (*Rec. Trav. chim. Pays-Bas.*, 1951, **70**, 79.)



Kawaïn

Kawaïn was synthesised by a Reformatzky reaction, using ethyl γ bromo-β-methoxycrotonate and cinnamic aldehyde. The ethyl-γ-bromo-β-methoxycrotonate, dissolved in dry benzene was warmed with zinc wool and the aldehyde, the product being separated by adding ammonium chloride solution and extracting with ether. The product was identical with the kawaïn previously isolated from *Piper methysticum* exception for the higher melting-point of the synthetic substance (145°C. compared with 106°C.) Details of the preparation of ethyl-γ-bromo-β-methoxycrotonate and of the degradation of kawaïn to kawaïc acid are given. G. B.

Sodium Salicylate and Bicarbonate, Oxidation of Solutions of. P. Mesnard and J. Marzat. (*Bull. Trav. Soc. Pharm. Bordeaux.* 1950, **88**, 136, 140.) Solutions containing sodium salicylate with bicarbonate rapidly become brown, and give a black precipitate. This is due to oxidation, catalysed by traces of iron in the bicarbonate, although the *p*H of the mixture is too high for the iron to give the usual violet colour with the salicylate. The precipitate itself contains iron. After removal of this precipitate, the remaining solution gave reactions of gentisic acid, present in the proportion of about 20 per cent. of the salicylic acid. This compound, when mixed with salicylic acid, gives a greenish colour which may be shaken out into ether. G. M.

DL-Thyroxine, Preparation of Derivatives of. J. C. Clayton and B. A. Hems. (*J. chem. Soc.*, 1950, 840.) The preparation of the following derivatives of thyroxine is recorded (solubilities and physiological activities are given in brackets): DL-thyroxine monosodium salt (<0·001, 1·0), thyroxine methyl ester (0·017, 0·65), thyroxine ethyl ester (0·002, 0·5) *N*-formylthyroxine (0·16, 0·3), *N*-phthaloylthyroxine (>0·02, inactive), *N*-β-carboxypropionyl thyroxine (0·95, 0·07), *N*-oxalothyroxine (0·14, 0·3), *O*-carboxymethylthyroxine (0·03, 0·1, *N*-carbamylthyroxine sodium salt (0·6, inactive) thyroxine methyl ether (< 0·008, 0·5). A new method of iodination of 3:5-diiodothyronine and several of its derivatives is described, which avoids the possible formation of explosive nitrogen iodides sometimes encountered during iodination in strong aqueous ammonia (Harington and Barger, *Biochem. J.* 1927, **21**, 169). The use of tertiary organic bases in place of ammonia met with no success, but aqueous or alcoholic solutions of primary and secondary

aliphatic bases gave rapid condensation and production of thyroxine in 90 per cent. yield. J. B. S.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Adrenal Cortical Hormones, Synthetic Analogues of. W. H. Linnell, D. W. Mathieson and G. Williams. (*Nature*, 1951, **167**, 237.) The following substances which have significant physiological activity have been synthesised from the corresponding carboxylic acids by the method of Steiger and Reichstein. The figures for comparison with deoxycortone acetate are from life prolongation tests (survival under cold stress of bilaterally adrenalectomised young rats). Corresponding acetoxymethyl

Substance	Melting-range	No. of molecules equivalent to one molecule of deoxycortone acetate
Indan-1-hydroxymethylketone	(Boiling-range, 101° to 102°C. at 0·1 mm)	16
Hexahydroindan-1-hydroxymethylketone	99°C.	10·7
5-phenylindan-1-hydroxymethylketone	36°C.	6·6*
5-*p*-methoxyphenylindan-1-hydroxymethylketone	84°C.	2·9*
p-acetoxy-*p'*-(ω-hydroxy) acetonyldiphenyl	93°C. to 94°C.	2·9*

* Preliminary results only.

compounds were inactive. The first two compounds had no influence on the liver glycogen of adrenalectomised fasting mice, nor on the sodium/potassium metabolism in the rat. G. B.

Adrenaline and Noradrenaline, Paper Chromatography of. U. Hamberg and U. S. v. Euler. (*Acta chem. scand.*, 1950, **4**, 1185.) A report is given of the results obtained by paper chromatography using *n*-butanol saturated with N-hydrochloric acid; a good separation of adrenaline and noradrenaline was obtained after 20 to 40 hours in descending runs, and in longer runs the separation of other related compounds such as dihydroxyphenylalanine and hydroxytyramine was achieved. Practical details of the chromatographic procedures are given, together with photographs of the chromatograms obtained from cattle suprarenal extracts. Partition chromatography of adrenaline and noradrenaline on starch columns was also attempted using *n*-butanol saturated with 0·1N hydrochloric acid to which one half volume of 10 N acetic acid and 0·1 per cent. of ascorbic acid had been added. The total yield of adrenaline from the partition chromatograms of cattle suprarenal extracts was 83 to 90 per cent. R. E. S.

Adrenocorticotrophic Nonprotein Preparations. I. I. Geschwind, G. P. Hess, P. G. Condliffe, H. M. Evans and M. E. Simpson. (*Science*, 1950, **112**, 436.) The following process yielded an activity equivalent to 360 mg. of an adrenocorticotrophic protein (ascorbic acid depletion test) from each kg. of fresh sheep pituitary glands. The glands (250 g.) were ground with 175 ml. of water at 5°C., stirred with 375 ml. of 10 per cent. trichloracetic acid and allowed to stand. After centrifuging, the supernatant

liquid was extracted repeatedly with ether to remove trichloracetic acid, and from the solution, 2·9 g. of the extract was obtained as a brown hygroscopic powder, containing 10 per cent. of nitrogen of which 10 per cent. consisted of ammonia and amide nitrogen, and 43 per cent. of amino-nitrogen. When the extract was subjected to paper chromatography using phenol-water as solvent, the greater part of the activity was contained in a fluorescent area (R_F value, 0·95). The extracts also contained the follicle-stimulating hormone, which could be separated from the adrenocorticotrophic activity by dialysis. G. B.

Amino-acids, Paper Chromatography of, Effect of *p*H. A. J. Landua, R. Fuerst and J. Awapara. (*Anal. Chem.*, 1951, **23**, 162.) The effective separation of mixtures of amino-acids by paper chromatography depends upon the *p*H to which the sample has been adjusted. R_F values and spot sizes are given for over 20 amino-acids and for ethanolamine adjusted to a wide range of *p*H values, using the following solvents, saturated with water in each case:—phenol, 2:4-lutidine, and 1-butanol. Several amino-acids (for example arginine in phenol and glutathione in phenol and lutidine) give multiple spots at certain *p*H values. At some *p*H values, all pure amino-acids give a single compact spot, but variability of R_F value and spot size were observed about the isoelectric point of most of the substances studied. The chromatograms are affected by the presence of inorganic salts and of other amino acids if in sufficient concentration. The *p*H effects in cresol are similar to those in phenol, in collidines similar to those in lutidine, and in alcohols similar to those in butanol. G. B.

***p*-Aminobenzoic Acid Derivatives, Paper Chromatography of.** E. Lelemen, B. Tanos and D. Halmagyi. (*Biochem. J.*, 1950, **47**, 138.) Determinations of *p*-aminobenzoic acid derivatives were carried out by means of paper-partition chromatography using the upward-running method. Urine (2·5 to 20 μl.) was applied directly to the paper, the solvent being *n*-butanol saturated with water, and the colouring agent Ehrlich reagent (2 g. of *p*-dimethylaminobenzaldehyde in 100 ml. of 20 per cent. w/v aqueous HCl); ochre-yellow spots developed suddenly on spraying, even at room temperature, results being read before the paper dried. R_F values obtained were *p*-aminobenzoic acid 0·68 to 0·72; *p*-aminohippuric acid 0·07 to 0·10; and *p*-aminosalicylic acid 0·26 to 0·30. The sensitivity of the reaction allowed detection of 1 μg. of each of the 3 compounds and normal variations in *p*H and salt concentration of the urines used caused little alteration in R_F values. Using parallel strips with less than 20 μg. of the substance, measurement of the area of spot can be used for quantitative comparisons, the error being 5 to 12 per cent. On administering *p*-aminobenzoic acid orally or intravenously to healthy persons, resulting plasma levels lay in the range of 1·5 to 24 mg./100 ml. 3 spots due to *p*-aminobenzoic acid, *p*-aminohippuric acid, and urea were obtained in the chromatograms of urine from patients receiving *p*-aminobenzoic acid. At plasma levels around 2 mg./100 ml. the spot of *p*-aminobenzoic acid mostly failed to appear in the urine, the chromatogram indicating excretion mainly as *p*-aminohippuric acid. The spot of *p*-aminobenzoic acid always appeared at more elevated serum levels, but the amount of *p*-aminohippuric acid remained or even increased markedly in intensity. R. E. S.

β-Amino*iso*butyric (α-Methyl-β-alanine): A New Amino-acid from Human Urine. H. R. Crumpler, C. E. Dent, H. Harris and R. G. Westall. (*Nature*, 1951, **167**, 307.) In 2-dimensional paper chromatograms of human

urine, using phenol and collidine-lutidine as solvents, a ninhydrin-reacting substance appears in the position occupied by methionine sulphoxide. The substance is a neutral amino-acid and may be isolated from urine by fractionation on a "Zeo-Karb215" cation-exchange column, removal of polypeptides by acid hydrolysis, further fractionation, and final fractionation on a "Dowex 2" anion-exchange column to remove creatinine. The substance appears to be (-)β-amino*iso*butyric acid, and, after racemisation it is identical with synthetic β-amino*iso*butyric acid. In 4·8 per cent. of the individuals tested, the urine contained an abnormally high concentration of the substance, although the blood level was normal. There is some evidence that this phenomenon is genetically determined. G. B.

Autosynthesis in Bacteria. P. C. Caldwell and Sir Cyril Hinshelwood. (*J. chem. Soc.*, 1950, 3156.) Certain characteristics of the autosynthetic processes occurring in cells are considered with reference to proteins, ribose nucleic acid and deoxyribose nucleic acid. Analogies between autosynthesis and the formation of polymerised material and crystal growth are discussed. The hypothesis is advanced that autosynthesis depends essentially upon a co-ordination of the following kind. In the synthesis of protein, the nucleic acid, by a process analogous to crystallation, guides the order in which the various amino-acids are laid down; in the formation of nucleic acid the converse holds, the protein molecule governing the order in which the different nucleotide units are arranged. These ideas are formulated mathematically and discussed in relation to various experimental findings.

A. H. B.

Vitamin B_{12}. Identification as a Cyano-Cobalt Coordination Complex. N. G. Brink, F. A. Kuehl Jr. and K. Folkers. (*Science*, 1950, **112**, 354.) Hydrogen cyanide is evolved from vitamin B_{12}, but not from vitamin B_{12a}, on heating with oxalic acid or hydrochloric acid. Using oxalic acid, 0·96 mole of hydrogen cyanide is obtained from each mole of vitamin B_{12}. It is suggested that a cyano group is held in the molecule in a coordination complex from which it can be displaced by anions having a strong coordination tendency. Sulphuric acid does not displace hydrogen cyanide under the same conditions as oxalic or hydrochloric acids, but sulphate shows only a slight tendency to enter coordination complexes with cobalt. The extreme lack of toxicity of vitamin B_{12} suggests that the cyano group is tightly bound within the complex. An absorption band at 4·69 μ may be ascribed to a C=N. bond in vitamin B_{12}. This band is absent from the infra-red spectrum of Vitamin B_{12a} which is apparently the same as vitamin B_{12b}. G. B.

Vitamin B_{12}. Reactions of Cyanocobalamin and Related Compounds. E. A. Kaczka, D. E. Wolf, F. A. Kuehl Jr. and K. Folkers. (*Science*, 1950, **112**, 354.) On treatment of vitamin B_{12a} with potassium cyanide and extraction with phenol-carbon tetrachloride at *p*H 5 to 6, vitamin B_{12}, which may be purified and identified by its absorption spectrum, is obtained. Vitamin B_{12a} is weakly basic and appears to contain a hydroxo group in place of a cyano group present in vitamin B_{12}. Crystalline compounds are obtained by reaction of vitamin B_{12} with sulphurous acid, chloride ions or hydrogen sulphide. Physical and microbiological data for these compounds are given. The compounds can be reconverted into vitamin B_{12} by reaction with cyanide ions. The spectra of the compounds are exemplified by the spectrum of vitamin B_{12a} with *p*H change. A nomenclature is suggested in which all the vitamin B_{12} molecule, except the cyano

group is called "cobalamin", and the compounds are known as cyano-cobalamin (vitamin B_{12}), hydroxo-cobalamin (vitamin B_{12a}, identical with vitamin B_{12b}), sulphato-cobalamin and chloro-cobalamin. G. B.

Vitamins B_{12} and B_{12b}, Magnetic Susceptibility of. J. C. Wallmann, B. B. Cunningham and M. Calvin. (*Science*, 1951, **113**, 55.) Magnetic measurements on 6 samples of vitamin B_{12} showed that 3 were clearly diamagnetic and were unquestionably covalent cobaltic complexes with octahedral d^2sp^3 bonding. A fourth sample exhibited both diamagnetic and paramagnetic behaviour, but the paramagnetism was attributed to the presence of an impurity. The remaining 2 samples were paramagnetic. One of these had been charred in sealing the tube and was therefore probably contaminated with carbon and strongly paramagnetic cobaltous phosphate. The other, however, appeared to be homogeneous and gave consistent results on repeated measurements. Despite this and the additional fact that the susceptibility was consistent with that expected for an ionic cobaltous compound, it was suspected that the result was due to uniform contamination with a strongly paramagnetic or ferromagnetic impurity. Of 3 samples of vitamin B_{12b} investigated, one was diamagnetic and therefore a hexa-coordinated covalent cobaltic complex, the second exhibited weak paramagnetism due probably to the presence of a paramagnetic or ferromagnetic impurity, whereas the third had also been charred in sealing and was therefore not significant. G. R. K.

BIOCHEMICAL ANALYSIS

***p*-Aminosalicylic Acid, Elimination and Estimation of.** R. Fleury. (*Bull. Trav. Soc. Pharm. Bordeaux*, 1950, **88**, 68.) The estimation was made colorimetrically, depending on the violet colour produced with ferric chloride solution. A single injection was given of 30 ml. of a 30 per cent. solution of sodium *p*-aminosalicylate at the level of the abscess. For the estimation of *p*-aminosalicylic acid in pus, dilution with saline and centrifuging was used, followed by the addition of a drop of 10 per cent. ferric chloride solution and the spectrophotometric measurement of the resulting violet colour; urine after appropriate dilution was acidified with hydrochloric acid to about *p*H 3 and the colour measured after the addition of ferric chloride. The determination was estimated to have an error of ± 2 per cent. and to be more precise than diazotisation processes. It was found that *p*-aminosalicylic acid disappeared from the urine, after about 36 hours, in two distinct phases.

R. E. S.

17-Ketosteroids, Neutral, in Urine, Determination of. W. T. Beher and O. H. Gaebler. (*Anal. Chem.*, 1951, **112**, 118.) Urine is boiled under reflux with hydrochloric acid, extracted with ether and the ether extract washed with sodium hydroxide solution to remove acidic impurities, œstrogens and other phenols. The ether solution is evaporated, a colour produced by heating at 25°C. with alcoholic *m*-dinitrobenzene solution and aqueous potassium hydroxide, and the absorbances determined photo-electrically at 515 mμ and 440 mμ. The quantity of ketonic substance (expressed as μg. of standard steroid) is given by

$$\frac{A_s^{515} - KA_s^{440}}{k^{515} - Kk^{440}}$$

where A_s is the absorbance of the test solution, k is the absorbance of the colour produced per μg. by the standard steroid (dehydro*iso*androsterone or androsterone) and K is the ratio of absorbances at 515 mμ and 440 mμ for

the non-ketonic material. The procedure for separation of ketonic and non-ketonic material is described. The effects due to the method of hydrolysis used, the presence of bile salts, protein, glucose and urea, and to the use of aqueous or alcoholic potassium hydroxide, are discussed. G. B.

Methonium Compounds, Isolation from Urine and Photometric Determination. E. J. Zaimis. (*Brit. J. Pharmacol.*, 1950, **5**, 424.) The urine of animals, including man, after intravenous administration of methonium compounds, possessed marked biological activity. The active substances were precipitated by addition of ammonium reineckate and the reineckate was converted to the iodides or the picrates. The compounds obtained after injection of hexamethonium di-iodide were found to be the hexamethonium compounds, and the methonium compounds all appear to pass unchanged through the body. About 60 per cent. of the amount of hexamethonium iodide injected into rats was recovered unchanged during the first 24 hours after injection. A further 10 per cent. was recovered from the second day's urine. No evidence of the excretion of any demethylated compound was obtained and if any of the injected material undergoes change in the body the amount is small. The formation of insoluble reineckates can be used for assaying methonium compounds in urine. The precipitated reineckate is washed free from ammonium reineckate, and dissolved in acetone. The optical density of the acetone solution is then determined by means of a Hilger Biochem Absorptiometer and a Chance green (OG_1) filter, the comparison being made against a standard obtained from a solution of hexamethonium iodide in the urine of the appropriate animal. Maximum absorption occurs at 525 mμ. H. T. B.

Methylthiouracil, Colour Reaction for. R. A. McAllister. (*Nature*, 1950, **166**, 789.) It has been found that when small amounts of 2-thiouracil and 4-methyl-2-thiouracil in a borate buffer (*p*H 8·0) are treated with a solution of 2:6-dichloroquinone-chloroimide in ethanol, soluble yellow products are obtained. Uric acid, thiourea, creatinine, and a number of other urinary solutes also gave coloured products in the reaction; the yellow-coloured products obtained with thiouracil and methylthiouracil however were readily soluble in chloroform, whereas those due to uric acid, creatinine, and the majority of urinary solutes were completely insoluble. The colour produced by thiouracil and methylthiouracil was thus made specific and using this reaction, it was possible to determine methylthiouracil in urine, the sensitivity being of the order of 10 μg.; the reaction also is applicable to the determination of methylthiouracil in plasma. R. E. S.

Trichloroacetic Acid in Urine, Determination of. R. Frant and J. Westendorp. (*Analyst*, 1950, **75**, 462.) Two methods are described for the estimation of trichloroacetic acid in urine, a semi-quantitative method with a possible error of about 25 per cent., and a more quantitative method with an average deviation of 5 per cent. In the semi-quantitative method the urine is made alkaline with a strong solution of sodium hydroxide and the mixture is poured on to pyridine contained in a test-tube which can be closed and connected to an absorption apparatus containing potassium hydroxide. After heating to 70°C for exactly 5 minutes and cooling rapidly the red-orange coloration of the pyridine layer is compared with a previously standardised series of coloured papers. Traces of trichloroacetic acid too small for determination by this means may be detected by passing a stream of carbon dioxide through the pyridine layer. A colour change from orange to yellow

may then be perceived at a concentration of 1 mg. of trichloroacetic acid per l. In the quantitative method an acetone extract of the alkaline urine is made and an aliquot part of this is mixed with an aqueous alkaline pyridine solution before heating; immediately after cooling, the coloured solution is transferred to a 5 mm. cell and its extinction is measured at 540 mμ. Variations of the conditions were studied and details are given which can be used for the determination of trichloroacetic acid concentrations ranging from 10μg. to 600 μg./ml. R. E. S.

Urea; Determination in Blood and Urine. A. C Kebrick and S. Skupp. (*Proc. Soc. exp. Biol., N.Y.*, 1950, **73**, 432.) Place 2 ml. of protein-free filtrate from plasma or serum, or 2 ml. of diluted ammonia-free urine, in test-tubes graduated at 10 ml. Add 0·5 ml. of M phosphoric acid and cover the mouths of the tubes with tin foil. Heat for 60 minutes in a pressure cooker at 20 lb. pressure or for 90 minutes at 15 lb. pressure. After cooling add 1 ml. of M sodium hydroxide and dilute the solutions to 10 ml. Add 1 ml. of Koch-McMeekin Nessler's solution and allow to stand for 10 minutes. Measure the colour in a colorimeter; a blank tube containing water and acid is heated with each series, and a standard tube, containing 0·03 mg. of nitrogen as ammonium sulphate, is prepared for comparison. The method was tested in a series of samples of plasma and of urine in which urea nitrogen was also determined by incubation with urease, aeration into standard acid, and titration with 0·01N sodium hydroxide, the proposed method showed good agreement of values. S. L. W.

CHEMOTHERAPY

4-Alkoxy-α-naphthamidines as Local Anæsthetics. Emil Lorz and Richard Baltzly. (*J. Amer. chem. Soc.*, 1951, **73**, 93.) A series of *N,N*-disubstituted 4-alkoxy-α-naphthamidines was prepared by the addition of the appropriate bromomagnesium dialkylamides to 4-alkoxy-α-naphthonitriles. The *N*-*N*-dialkyl amidines having *N*-alkyl groups of four to five carbon atoms showed a high local anæsthetic potency—more than 20 times that of cocaine, and a toxicity between 2 and 4 times that of cocaine. The pK_A values of some of the compounds were determined. A. H. B.

Antimalarials, Chemistry of Synthetic. Some Pyrimidine Derivatives. J. S. Moffatt. (*J. chem. Soc.*, 1950, 1603.) *p*-Chlorobenzamidine was condensed with ethyl malonate, in the presence of sodium ethoxide, to give 4:6-dihydroxy-2-*p*-chlorophenylpyrimidine, which was converted into the corresponding 4:6 dichloro derivative by treatment with phosphoryl chloride and dimethylaniline. The 6-chloro group was replaced by 6-methoxy, 6-amino and 6-(4-diethylamino-1-methylbutylamino) groups, and the 4-chloro group in these compounds replaced by the 4-(4-diethylamino-1-methylbutylamino) group. The resulting compounds were inactive against *P. gallinaceum* in chicks. The compound, 4-(4-diethylamino-1-methylbutylamino)-2-*p*-chlorophenylpyrimidine, possessing a low order of activity, was prepared by the interaction of equimolecular amounts of *p*-chlorobenzamidine and ethyl sodioformylacetate to produce 4-hydroxy-2-*p*-chlorophenylpyrimidine, followed by the replacement of the 4-hydroxyl group with the 4-chloro group and reaction with 4-diethylamino-1-methylbutylamine. A. H. B.

Monoalkylcarbamates as Local Anæsthetics, A Study of. D. A. Schlichting, G. E. Awalina and G. L. Jenkins. (*J. Amer. pharm. Ass. Sci. Ed.*, 1950, **39**, 575.) A series of 21 monoalkylcarbamic

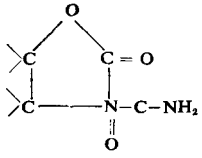
esters of tertiary-amino alcohols was prepared by the following reactions. $RCO_2H \xrightarrow{SO_2Cl} ROCl \xrightarrow{NaN_3} RCON_3 \xrightarrow{heat} RNCO$; $RNCO + HOR' \longrightarrow RNHCOOR'$. R = butyl, pentyl, hexyl, octyl, nonyl, 9-decenyl, 3-pentenyl or 2:4:4-trimethylpentyl and R′ = 2-diethylaminoethyl or 3-diethylaminopropyl. 3-piperidino-1:2-propanediol monononylcarbamate was also prepared. The compounds were tested by the rabbit cornea, guinea-pig wheal and Rider frog methods, and some of these substances appeared to be local anæsthetics.

G. B.

Nitrogen Mustards, Some Related Compounds. A. R. Kon and J. Roberts. (*J. chem. Soc.*, 1950, 978.) A number of compounds related to the aromatic nitrogen compounds have been prepared in order to test conclusions, previously established, relating chemical structure to biological activity. Anilino-alcohols ($PhNH(CH_2)_nOH$) were condensed with ethylene chlorhydrin to yield compounds of the type $PhN(CH_2CH_2OH).(CH_2)_nOH$ where n was 2, 3, 4 and 5 and these converted to the corresponding di(halogenoalkyl)arylamines ($PhN(CH_2CH_2Cl).(CH_2)_nCl$). The latter are inactive, in agreement with the earlier conclusions of Ross (*J. chem. Soc.*, 1949, **183,** 1972). That the inactivity of these compounds is not due to steric factors is illustrated by the synthesis of a second series of compounds of the general type $ArN.(CH_2)_nX.(CH_2)_m\ NAr(CH_2)_nX$ showing that reactivity depends upon the position of the halogen with reference to the activating group (nitrogen). Compounds of this type where n = m = 2 are some of the most active yet tested and several analogues, in which Ar and the side chain are varied, are also described. Aliphatic analogues are also active. Derivatives of propylenediamine (m = 3) are also biologically active but this activity falls off as m increases. As in the first series, lengthening of the halogenoalkyl side chain results in complete loss of activity. The hydrolysis of representative compounds in boiling 50 per cent. acetone-water has been examined and the results are in harmony with the recorded biological activities. Two methods are described for the preparation of the second series of compounds, (a) the condensation of anilino-alcohols (2 mols) with the appropriate alkylene dibromide (1 mol.) and (b) the condensation of an α-ω-dianilinoalkanes with ethylene oxide or a chlorhydrin. Chlorination of the resulting hydroxy compounds affords the corresponding chloro compound. The condensation of anilino-alcohols with formaldehyde give rise to *N*-aryloxazolidines.

J. B. S.

2-Oxazolidones as Anticonvulsant Drugs. W. J. Close. (*J. Amer. chem. Soc.*, 1951, **73,** 95.) Some 2-oxazolidone derivatives were prepared, principally by heating β-amino alcohols or their hydrochlorides with urea. When the requisite amino alcohols were not readily available, the oxazolidones were obtained from β-hydroxy esters by means of the Curtins reaction. Because allophanic esters showed anticonvulsant activity, similarly constituted molecules of type (I) were prepared by converting the oxazolidine to its sodium derivative and then treating with excess of phosgene, followed by ammonia. *N*-acyl derivatives of the oxazolidones were also prepared. Approximately one-third of the compounds exhibited anticonvulsant action. The 3-carbamyl and 5-phenyl groups were particularly effective in this connection. It is of interest that 3:5:5-trimethyl-2-oxazolidone, the 4-desoxy analogue of tridione was completely inactive.



(I)

A. H. B.

Thiosemicarbazides, Thiosemicarbazones, and Related Compounds in Tuberculosis. R. Donovick, F. Pansy, G. Stryker and J. Bernstein. (*J. Bact.* 1950, **59,** 67.) The *in vitro* activities of a number of thiosemicarbazones and related compounds are compared against the B.C.G. strain of *M. tuberculosis* in a modified Kirchner medium. Certain correlations between chemical structure and *in vitro* tuberculostatic activity have been established. Aryl thiosemicarbazides (RCO NH NHCS NH_2) are inactive (inhibitory concentrations 10 μg./ml.) with the exception of thiocarbamylthiosemicarbazides (R NHCS NH NH CS NH_2) which show definite activity. Thiosemicarbazide itself and it *N*- and *S*- alkyl derivatives are active, though, with the exception of the parent substance and *S*-methylthiosemicarbazide, derived thiosemicarbazones are inactive. Thiosemicarbazones of aromatic ketones and heterocylic aldehydes are somewhat less active than aldehyde thiosemicarbazones; aliphatic carbonyl compounds give rise to inactive thiosemicarbazones. The effect of substituents in the aromatic ring of aldehyde thiosemicarbazones upon activity is also studied. Positional isomerism is important and in general para-substituted compounds are the most active, though the presence of ortho-hydroxy groups markedly increases activity. J. B. S.

PHARMACY

GALENICAL PHARMACY

Tablets, Disintegration of. R. V. Evanson and H. G. DeKay. (*Bull. Nat. Form. Comm.*, 1950, **18,** 45.) A modified form of the test described by Sperandio, Evanson and DeKay (*J. Amer. pharm. Ass.*, 1948, **37,** 71) was compared with the methods of Calamari and Roth and Gershberg and Stoll, and found to produce more consistent results. The modified method consists in rotating a wire-mesh drum containing the tablets six times per minute in water maintained at a temperature of 37°C. The mesh is big enough to allow normal granules to pass through but not granule clumps, and the slow revolution of the drum simulates the natural wave motion of the stomach. The use of artificial gastric juice instead of water did not make any significant difference to the results. 9 samples were examined for the effects of storage for one year on the disintegration time. Of these, 77 per cent. varied less than 25 per cent. of their original disintegration time and remained within the limits of their class, whereas 23 per cent., all of which were tablets of aspirin compound, varied over 24 per cent. of their original time. The disintegration properties of 9 different tablets obtained from 17 sources were examined by the three methods. Only one type of tablet, amidopyrin, 5 gr., showed unsatisfactory results in that 5 of the 7 samples tested did not break up within 30 minutes. All aspirin tablets disintegrated in 5 to 96 seconds, all except one sample of phenobarbitone tablets disintegrated in 8 to 831 seconds and all but 2 samples of sulphathiazole tablets disintegrated in 27 to 1428 seconds. The remainder of the samples, which included tablets of sodium bicarbonate, ascorbic acid, and thiamine hydrochloride and antacid tablets were well under the 30-minute limit which was set as the stopping-point. G. R. K.

NOTES AND FORMULÆ

Ethyl Iodophenylundecylate (Pantopaque). (*New and Nonofficial Remedies; J. Amer. med. Ass.*, 1950, **144,** 1464.) Ethyl iodophenylundecylate is a mixture of the K and ω isomers; the proportions are unknown but the

principal isomer is thought to be the *K*. It occurs as a colourless to pale yellow, odourless, viscous liquid, specific gravity 1·240 to 1·263, refractive index 1·5230 to 1·5280, freely soluble in alcohol, benzene, chloroform and ether, and very slightly soluble in water. When treated with sodium dichromate and sulphuric acid and heated under a reflux condenser for 2 hours, it yields a precipitate of *p*-iodobenzoic acid, which melts at 263° to 265°C. The saponification equivalent determined by heating with alcoholic potassium hydroxide, and titrating the excess of alkali with hydrochloric acid is 395 to 420. A solution of 1 ml. in chloroform containing phenolphthalein becomes red on the addition of 0·3 ml. of 0·1N alkali (absence of free acids). When treated with potassium iodide and starch mucilage, no blue colour is produced (absence of free iodine). Ethyl iodophenylundecylate yields not more than 0·1 per cent. of ash, and contains 29·0 to 30·5 per cent. of iodine, equivalent to 95 to 100 per cent. of ethyl iodophenylundecylate. It is assayed by fusion with halogen-free sodium peroxide and lactose in a Parr bomb and gravimetric estimation of the sodium iodide formed by precipitation with silver nitrate. Ethyl iodophenylundecylate is injected intrathecally for myelography of the lumbar region. G. R. K.

Methylbenzethonium Chloride (Diaparene Chloride). (*New and Non-official Remedies; J. Amer. med. Ass.*, 1950, **144,** 548.) Methylbenzethonium chloride is benzyldimethyl 2-(2-[*p*-1 : 1 : 3 : 3-tetramethylbutylcresoxyethoxy)-ethyl ammonium chloride, $C_{28}H_{44}ClNO_2,H_2O$. It occurs as colourless, odourless crystals with a bitter taste, melting on the hot stage of a microscope at 161° to 163°C., and soluble in water, alcohol, chloroform, ethoxyethanol and hot benzene, insoluble in ether and carbon tetrachloride. It gives an orange-red solution and possibly a brown precipitate when treated as follows: heat with sulphuric acid and sodium nitrate on a steam-bath for 3 minutes, dilute with water, add granulated zinc and warm for 10 minutes, cool, add sodium nitrite to the clear liquid and mix with a solution of G salt (sodium 2-naphthol-6 : 8-disulphonate) in ammonia solution. Methylbenzethonium chloride loses 3·5 to 4·2 per cent. of its weight when dried in a platinum dish at 105°C. to constant weight and yields not more than 0·1 per cent. of ash. It contains 7·6 to 8·0 per cent. of chloride (determined by adding an excess of silver nitrate, filtering and titrating with ammonium thiocyanate), 2·7 to 3·2 per cent. of nitrogen (determined by the Kjeldahl method), and 97 to 103 per cent. of methylbenzethonium chloride, determined by adding a known volume of potassium ferricyanide solution to a buffered solution, filtering and estimating the excess of ferricyanide iodimetrically. Methylbenzethonium chloride is a cationic detergent. G. R. K.

Methylhexamine. (*New and Nonofficial Remedies, J. Amer. med. Ass.*, 1950, **143,** 1156.) Methylhexamine is 1 : 3 dimethylamylamine, and contains not less than 99 per cent. and not more than the equivalent of 101 per cent. of $C_2H_5.CH(CH_3).CH_2.CH(CH_3)NH_2$. It is not a derivative of hexamine B.P. It is a colourless to pale yellow liquid; odour ammoniacal; b.pt. between 130° and 135°C. Readily soluble in alcohol, chloroform, ether, and dilute mineral acids; very slighly soluble in water. Refractive index, 1·4150 to 1·4175; s.g. 0·7620 to 0·7655. Residue on evaporation for 1 hour not more than 0·2 per cent. No turbidity is produced on dissolving in liquid paraffin. On dissolving 1 ml. in 5 ml. of dilute sulphuric acid and 20 ml. of water, adding about 1 g. of potassium cyanate, heating on a steam-bath for 1 hour, cooling and filtering, and crystallising and recrystallising from boiling water, white crystals melting between 118° and 121°C. are obtained. A

colourless, odourless gas is evolved when 1 ml. of 10 per cent. sodium nitrite solution is added to 5 drops of methylhexamine dissolved in 2 ml. of dilute hydrochloric acid. For the assay, 1 ml. of methylhexamine accurately weighed is dissolved in 25 ml. of 0·5N sulphuric acid, and the excess of acid is back-titrated with 0·5N sodium hydroxide using methyl red as indicator; each ml. of 0·5N sulphuric acid is equivalent to 0·0576 g. of $C_7H_{17}N$. It is used as a volatile sympathomimetic inhalant and an assay for the inhaler is described. L. H. P.

Sodium Acetrizoate (Urokon Sodium). (*New and Nonofficial Remedies; J. Amer. med. Ass.*, 1950, **144,** 623.) Sodium acetrizoate is sodium 3-acetylamino-2:4:6-triiodobenzoate and is prepared by dissolving the acid in dilute sodium hydroxide. It is not isolated, and is used as a 30 per cent. aqueous solution for excretory urography and retrograde pyelography. Acetrizoic acid is a white, odourless powder m.pt., with decomposition, at 278° to 283°C. It is soluble in alcohol, slightly soluble in ether, chloroform and water, and insoluble in benzene. When heated, it melts to a dark brown liquid and evolves iodine. It contains not more than 20 p.p.m. of heavy metals and yields not more than 0·1 per cent. of sulphated ash. When dried at 105°C. for 24 hours, it loses not more than 0·1 per cent. of its weight. It is assayed by solution in alcohol, dilution with an equal volume of water, and titration with sodium hydroxide, using phenolphthalein as indicator; a blank determination is also carried out. The amount of acetrizoic acid present is 99·0 to 101·0 per cent. It contains 67·0 to 68·5 per cent. of iodine, which is estimated by dissolving in sodium hydroxide solution, adding potassium permanganate and heating under a reflux condenser. When cool the solution is diluted with water, treated with sulphuric acid and sodium metabisulphite, and shaken until a clear solution is obtained. The excess of sodium metabisulphite is removed with potassium permanganate, starch solution is added, and the solution titrated with silver nitrate until the green precipitate formed just changes to bright canary yellow. A 30 per cent. sterile solution is clear and practically colourless; specific gravity about 1·2, *p*H 4·8 to 5·2. G. R. K.

PHARMACOGNOSY

Pepper, Adulteration of. H. Hadorn and R. Jungkunz. (*Pharm. Acta Helvet.* 1951, **26,** 25.) A war-time substitute for pepper is known as Congo pepper or Congo cubebs. Botanically the fruits are derived from *Piper guineese,* Schumann. A comparative examination showed a considerable difference in essential oil content: 10·6 per cent. for *Piper guineense* against 1·3 per cent. for white pepper, 1·77 per cent. for black pepper, and about 10 per cent. for true cubebs. Pepper (black or white) contains 5 per cent. of piperine, while the substitute has only 0·3 per cent. Resin is 2·3 per cent. against 0·6 per cent. for pepper and 3·7 per cent. for cubebs. Congo pepper has a relatively low content of crude fibre (4·2 per cent.), owing to the absence of sclereids. G. M.

Solanaceous Drugs, Cultivation Studies of *Atropa belladonna* and *Hyoscyamus niger*. W. R. Brewer and L. D. Hiner. (*J. Amer. pharm. Ass. Sci. Ed.*, 1950, **39,** 586.) Plants were grown in a 12 in. by 12 in. spacing, in soils having a high and a low content of nitrate, phosphate and potassium, and a high and a low *p*H value. It is concluded that for highest belladonna production a high nitrogen fertiliser (ammonium nitrate) alone is best, but calcium phosphate with lime is almost

as good. The highest alkaloidal yield is obtained by the use of high nitrogen and potassium (ammonium nitrate and potassium chloride). None of the fertilisers significantly increases hyoscyamus production, but ammonium nitrate used with calcium phosphate increases the alkaloidal yield. G. B.

PHARMACOLOGY AND THERAPEUTICS

Adrenocorticotrophic Hormone (ACTH) Release, Effect of Eserine and Atropine on. F. Dordoni and C. Fortier. (*Proc. Soc. exp. Biol., N.Y.*, 1950, **75**, 815.) The mechanism controlling the release of adrenocorticotrophic hormone from the pituitary is not known and an investigation was carried out to ascertain whether acetylcholine is responsible. As an index of corticotrophic function the authors used Sayer's test which depends on the adrenal ascorbic acid response. The substances used were eserine as a drug having a parasympathomimetic action and atropine as an anticholinergic agent. 120 male rats in groups of 8 were employed for the test. The doses given were 0·03 mg./100 g. of eserine salicylate and 20 mg./100 g. of atropine sulphate, by subcutaneous injection, the two drugs being tested both independently and simultaneously. At intervals after the injections the animals were killed and the adrenal ascorbic acid determined. With eserine, maximal ascorbic acid depletion was observed one hour after administration, the level thereafter returning gradually to normal. Atropine, on the contrary, increased the depletion significantly when both drugs were given, and by itself was responsible for an intense discharge. Atropine after hypophysectomy had no effect on the release showing that the drug did not act directly on the adrenal. The results seem to preclude the possibility of a cholinergic control of ACTH release. H. T. B.

Aminopterin, Treatment of Acute Leukæmia with. J. F. Wilkinson and C. Gardikas. (*Lancet*, 1951, **260**, 325.) In 21 patients with acute myeloid, lymphatic or monocytic leukæmia, treatment with aminopterin produced no response in 15, partial remissions in 4 and complete remission (i.e., clinical improvement and remission of the hæmatological condition) in 2 cases, for relatively short periods. In a further 6 patients severe leucopenia developed or death occurred. A number of toxic symptoms were observed. A case in which two complete remissions occurred, is reported in detail. G. B.

Barbiturate Poisoning, Treatment of. J. Riishede (*Lancet*, 1950, **259**, 789.) The object of this study was to compare the value of nikethamide and of amphetamine as cerebral and circulatory stimulants in the treatment of acute barbiturate poisoning. The first 61 patients were treated with nikethamide 2 to 5 g. per hour and the next 132 patients were treated with amphetamine, generally 50 mg. per hour. Apart from this the two series were treated similarly, namely, by aspiration of the stomach and gastric lavage with 10 g. of medicinal charcoal in 250 ml. of water, followed by instillation of 30 g. of medicinal charcoal and 15 g. of magnesium sulphate in 500 ml. of water, stimulation of peristalsis with neostigmine 1 mg. 4-hourly, prophylactic treatment against pneumonia, and, when considered necessary, the administration of parenteral fluid and anti-shock treatment. Of the 61 patients in the nikethamide series 27 (44 per cent.) died; the mortality for the 43 "severe" cases was 63 per cent. Of the 132 cases in the amphetamine series 12 (9 per cent.) died; the mortality for the 58 "severe" cases was 21 per cent. In the amphetamine-treated cases the course was less

eventful and the condition of the patients far better than in the nikethamide-treated cases, and untoward effects were fewer and of little importance. The author concludes that in the treatment of acute barbiturate poisoning amphetamine is far more effective than nikethamide. S. L. W.

Cortisone, Administered Orally. R. H. Freyburg, C. T. Treager, C. H. Adams, T. Kuscu, H. Wainerdi and I. Bonomo. (*Science*, 1950, **112**, 429.) Cortisone was effective when administered orally to 4 patients with rheumatoid arthritis. Used in a dosage of 300 mg. on the first day, 200 mg. on the second day, followed by 100 mg. daily (increased in the case of 2 patients to 200 mg. daily), the clinical effects were comparable with those of cortisone given parenterally, or of adrenocorticotrophic hormone.

G. B.

3-Hydroxy-*N*-methylmorphinan, Pharmacological Action of. K. Fromherz. (*Arch. int. pharmacodyn*, 1951, **85**, 387.) This compound has in general a similar action to that of morphine, differing considerably in different species. Thus with cats and mice central stimulating effects predominate, in rats, and generally, rabbits, it is purely paralysing. Conclusions regarding the therapeutic effect on man should only be drawn from animals which react in a similar manner, e.g. rats. In this case the analgesic action is stronger and more lasting than that of morphine, while the lethal doses are generally smaller than for morphine. The lævo isomer shows the same toxicity but higher analgesic action than the racemic compound, while the dextro isomer has a lower toxicity and no analgesic effect. Of two structural isomers, recovered from the mother liquors, one showed a slightly weaker action, the other had no analgesic effect. G. M.

Insulin: Effect on Rabbits of Implantation of Tablets. I. C. Gilliland and M. M. Martin. (*Lancet*, 1951, **260**, 143.) Observations were made of the effect of four types of insulin tablets implanted subcutaneously in 39 normal and 25 alloxan-diabetic rabbits. The types of tablets were (1) tablets of equal quantities of protamine zinc insulin and cholesterol, estimated to contain 500 and 1000 units of protamine zinc insulin; (2) tablets of protamine zinc insulin with calcium carbonate (20 mg. of specially dried protamine zinc insulin powder, the whole from a solution of 400 unit strength, was used for each tablet, mixed with 100 mg. of calcium carbonate); (3) tablets of neutral protamine zinc insulin estimated to contain 500 and 1000 units of insulin; (4) tablets of equal quantities of neutral protamine zinc insulin and cholesterol, estimated to contain 1000 units of insulin each. The tablets were implanted in the flanks of the rabbits. No metabolic effects were noted from the protamine zinc insulin and cholesterol tablets, whose weight had not altered 3 months after implantation. Some insulin action, lasting up to 4 days, was observed after implantation of protamine zinc insulin tablets containing 400 units, but the action was less than that obtained from the daily injection of 2·5 units of protamine zinc insulin. Insulin action lasting for only about 2 days was observed from implanted tablets of neutral protamine zinc insulin either alone or mixed with an equal quantity of cholesterol. Histological examination of the removed tablets showed encapsulation by a tissue reaction which probably accounted for the short duration of their effects.

S. L. W

Lead Poisoning, Sodium Citrate in. D. O. Shiels, W. C. Thomas and G. R. Palmer. (*Med. J. Aust.*, 1950, **2**, 886.) This paper describes the results obtained in the oral treatment by sodium citrate of 10 patients suffering from industrial lead poisoning. In the assessment of the therapeutic

value the criteria considered were the feeling of well-being of the patient, the effects on symptoms, and the results of the following laboratory tests:— the stippled cell count per million red cells, the ratio of large lymphocytes and monocytes to small lymphocytes, the concentration of lead in the urine, and in some cases the concentration of lead in the blood. The dose of sodium citrate was 4 or 5 g. in an ounce or two of water three times daily. The effects of the treatment on the symptoms were prompt, improvement being noticed in some cases as early as the day following its institution. Abdominal pain was promptly relieved, nausea disappeared, appetite improved, muscular strength improved, muscular pain diminished, and there was a great improvement in the feeling of well-being. Within a day or two of commencing treatment there was increased elimination of lead in the urine without exacerbation of symptoms, and there was a prompt rise in the cell ratio. S. L. W.

Neomycin, Clinical Trials with. G. G. Duncan, C. F. Clancy, J. R. Wolgamot, B. Beidleman. (*J. Amer. med. Ass.* 1951, **145,** 75.) This is a report of ten cases of urinary tract infection in which neomycin therapy was employed. Each patient had a bacterial infection due to one or more pathogenic organisms which were completely or moderately resistant to penicillin, aureomycin, chloramphenicol and streptomycin. The neomycin was given intramuscularly, in doses varying from 4,498 units (to an infant) to 100,000 units at 6-hour intervals, the duration of therapy varying from 3 to 9 days. In infections due to a sensitive organism, 100,000 units at 6-hour intervals of 4 doses and then 50,000 to 100,000 units at 12-hour intervals for 5 to 7 days appeared adequate, but dosage required regulation in accordance with the desired blood and urine concentrations of neomycin (assays in serum and urine were conducted by inoculation of graded serial dilutions of the fluids with a test strain of *Klebsiella pneumoniæ* and comparison of the ensuing degree of inhibition with that obtained with the test strain in known concentrates of neomycin). After adequate therapeutic levels had been achieved, usually after 48 to 72 hours of therapy the serum and urine levels remained relatively stable on either a 6- or 12-hour dosage scheme. The maximum serum levels varied from 4 to 10 units per ml., and maximum urine levels varied from 26 to 410 units per ml. Neomycin was dramatically effective in eradicating organisms sensitive to it from the blood and urinary tract and the original observations of Waksman and Leckevalier on the bactericidal properties of the drug were confirmed. Most strains of *Proteus,* however, and more especially the *Pseudomonas* cultures, exhibited properties suggesting potential development of resistance to neomycin. Evidence of toxicity was confined to one patient. Neomycin is an extremely effective agent in the treatment of clinical infections, particularly those of the urinary tract. S. L. W.

Œstrogens, Toxicity of. T. Nicol and I. D. Helmy. (*Nature,* 1951, **167,** 321.) Double-ovariectomised mature guinea-pigs were used for the tests. Trypan blue, injected subcutaneously was definitely toxic, but a combination of trypan blue and œstrogen was more toxic than either alone. Synthetic œstrogens (stilbœstrol, dienœstrol and αα-di(*p*-ethoxyphenyl)-β-phenylbromoethylene) were more toxic than the naturally occurring œstrone and œstradiol benzoate. 0·1 mg. of œstrone daily was more toxic than the same dose of œstradiol benzoate, and 1·0 mg. daily of œstradiol benzoate was more toxic than 0·1 mg. Stilbœstrol, the most toxic œstrogen used, was more toxic by mouth than by intramuscular injection. 5 mg. of dienœstrol daily for 3

days, followed by 5 mg. of stilbœstrol daily for 3 days was less toxic than either substance used alone. For dienœstrol by mouth the toxicity may possibly be reduced by using ethyl lactate as solvent instead of arachis oil. Synthetic œstrogens were more toxic in small than in large daily doses, and possibly resistance to the toxic action of œstrogens can be acquired by overdosage. G. B.

***Veratrum viride* preparations, Bio-assay of.** L. Maison and J. W. Stuszman. (*Arch. int. pharmacodyn.* 1951, **85**, 357.) Proposed methods for the bio-assay of veratrum derivatives have not been successful, since they do not in general measure the effect for which the drug is used. The authors propose a method using the hypotensive effect on anæsthesised dogs, the material being administered by intravenous infusion lasting 10 minutes. The unknown material is compared with that of a standard preparation giving the same effect, this standard being prepared by pooling a number of batches of an extract of the drug. The accuracy of the method is ±25 per cent. of the potency of a reference standard preparation having an activity approximately 50 times that of the dried root. G. M.

BACTERIOLOGY AND CLINICAL TESTS

Aureomycin, Effect on Liver Function Tests. J. Galt and R. B. Hunter. (*Amer. J. med. Sci.*, 1950, **220**, 508.) After 3 days treatment with aureomycin, 0·5 g. twice daily, 4 out of 5 normal subjects gave stools containing no urobilinogen while the fifth gave a negative response after a further day's treatment. The urinary urobilinogen remained constant at normal levels. Tests for fæcal bilirubin became positive at the same time as tests for urobilinogen became negative. Serum bilirubin was unaffected. It is suggested that the antibiotic destroys the bacteria responsible for the conversion of bilirubin to urobilinogen. H. T. B.

Ribose Nucleic Acid Content and Cell Growth of *Bacterium lactis aerogenes*. P. C. Caldwell, E. L. Mackor and Sir Cyril Hinshelwood. (*J. chem. Soc.* 1950, 3151.) The work described is an attempt to correlate the ribose nucleic acid content of cells of *Bact. lactis aerogenes*, grown under widely differing conditions, with the corresponding rate of growth. The study is in three parts: (a) cells of a normal strain were examined after growth in different media, or in the presence of drugs; (b) slow growing " mutants ", produced by irradiation of the calls with ultraviolet light, were investigated; (c) the rate of exchange of the nucleic acid phosphorus with the medium under different conditions was investigated, using radioactive phosphorus. The results indicate that (a) the ribose nucleic acid content of the cells is approximately proportional to the rate at which they had actually been growing in the culture from which they were taken; (b) while nucleic acid is actually participating in the synthesis of protein, little of its phosphorus undergoes exchange with the medium, which means that the molecules probably remain polymerised during the process. During the stationary phase, however, a considerable loss of the active phosphorus takes place from the cells. The results, combined with those previously published (*J. chem. Soc.*, 1950, 1415) led to the following conclusions. 1. The deoxyribose nucleic acid forms an approximately constant component of the cell and probably causes the onset of division. 2. The ribose nucleic acid content of the cells is approximately proportional to the rate at which they are growing and is probably closely concerned in autosynthesis. A. H. B.