ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ANALYTICAL

Adrenaline, Activity Ratio of, to Noradrenaline, in various Colour Reactions. T. Ozaki. (*Tohoku J. exp. Med.*, 1956, **63**, 225.) The activity ratio of adrenaline to noradrenaline, using such chemical methods as the permanganate, the corrosive sublimate, the iodine, the phosphotungstic and the arsenomolybdic estimations, was determined. The mean value of adrenaline to noradrenaline was 1·16:1 in the permanganate method, 1·31:1 in the corrosive sublimate method, 2·4:1 in the iodine method, 2·17:1 in the phosphotungstic method and 7·6:1 in the arsenomolybdic method. This variability in the ratio may be due to variations in the temperature and pH of the solutions. M. M.

Cardenolides, Dinitrobenzoic Acid Reaction of. A. L. O. M. Smithuis. (*Pharm. Weekbl.*, 1956, **91**, 253.) The colour reaction of 3:5-dinitrobenzoic acid with cardenolides does not give uniform results. Thus there is an increase in the extinction on boiling the glycosides and aglycones of strophanthus and digitalis with alcoholic acid, although g-strophanthin and 17-isocymarin do not show this phenomenon. On carrying out the reaction with some simpler butenolides, a difference in molecular extinctions was observed, showing that the structure of the β-compound linked to the butenolide group influences the stability and intensity of the colour. Examination of the ultra-violet spectra showed that boiling with alcoholic acid caused an increase in the absorption at 220 mμ due to destruction of the sugar part of the molecule, so that the aglycones show no increase or shift of wavelength. On boiling with alcoholic hydrochloric acid gitoxigenin shows an additional maximum at 338 mμ and the curve is identical with that of the compound $\triangle^{14,16}$-dianhydrogitoxigenin. It is to be supposed that digitoxin and digoxin will show a similar behaviour. The increase in the extinction after boiling the original glycosides or aglycones with alcoholic acid may be attributed to the formation of di-anhydro or mono-anhydro compounds, and the molar extinctions from the various cardenolides should have similar values. In the case of 17-isocymarin the butenolide group is in the transposition with respect to the C(14)hydroxyl, and the effect on the colour is eliminated. With g-strophanthin, this compound does not readily hydrolyse, nor does it easily form a 14-anhydro compound. The maximum colour intensity can only be obtained by using 4 milli-equivalents of sodium hydroxide. G. M.

Cardiac Glycosides containing Desoxy Sugars, Assay for. R. Dequeker. (*Bull. Soc. Pharm. Bordeaux*, 1955, **94**, 24.) The following method has been applied to preparations containing digitoxin, glycosides of *Digitalis purpurea*, digilanids A, B and C, ouabain and cymarin, with satisfactory results. Dissolve a quantity equivalent to 10–20 μg. of the sugar in 1 ml. of dry acetone in a 1·2 × 8-cm. test tube, add phosphoric acid to 5 ml., mix and heat at 35° C. for 15 minutes. Cool to 20° C. and measure the light absorption at 474 mμ, using as a blank a mixture of acetone and phosphoric acid treated in the same way. The quantity of the sugar is calculated from the light absorption, which follows the Lambert-Beer law with concentrations between 2 and 4 μg. of digitoxose per ml. The reaction is about 7 times more sensitive than the Keller-Kiliani test, the maximum intensity of colour is reached more rapidly and the colour is more stable and less dependent on the purity of the reagents. G. B.

Local Anaesthetics, Characterisation of. E. Hannig and W. Karau. (*Pharm. Zentralh.*, 1956, **95**, 187.) Local anaesthetics may be characterised by the formation of disulphimide derivatives which are prepared by simple mixing of equimolecular quantities of the substances in warm aqueous solutions. Melting points of the products are given in the Table below:

Disulphimide derivative	Falicaine	Procaine	Pantocaine	Xylocaine	Cocaine
4:4'-diaminodiphenyl disulphimide ..	163·5° C.	170·0° C.	142·0° C.	181·0° C.	—
4:4'-dichlorodiphenyl disulphimide ..	149·0° C.	141·0° C.	135·0° C.	151·0° C.	—
3:4:3':4'-tetrachlorodiphenylsulphimide ..	131·0° C.	114·0° C.	132·0° C.	162·0° C.	151·0° C.

G. M.

Morphine in Poppy Capsules, Estimation of. S. Pfeifer and W. Keller. (*Pharm. Zentralh.*, 1956, **95**, 189.) The polarographic determination of morphine cannot be applied directly to poppy capsules, but a modification described by the authors gives satisfactory results: 0·3 g. of the finely powdered capsules (dried at 75° C.) is rubbed down with 1 ml. of water and, after 15 minutes, mixed with "acid" alumina in portions until a dry powder is obtained (about 7–8 g.). The mixture is filled into a tube of 2 cm. diameter above a layer of 4 g. of alumina, and eluted with water. About 20 ml. of eluate is collected, and it is rinsed through with 3·5 ml. of hydrochloric acid (25 per cent.). The solution is made up to 25 ml. To 5 ml. of this solution is added 2 ml. of N sodium nitrite solution and, after exactly 5 minutes, 3 ml. of 20 per cent. potassium hydroxide and 7 drops of gelatine solution. Nitrogen is bubbled through, and the morphine is determined polarographically. G. M.

Pholcodine, Paper Chromatography of. F. Sabon and R. Monnet. (*Bull. Soc. Pharm. Bordeaux*, 1955, **94**, 41.) Preparations of pholcodine were submitted to descending paper chromatography using paper soaked in 0·5M potassium chloride and dried. Butanol containing 2 per cent. v/v of hydrochloric acid, saturated with water was used as the developing solvent. Acetic or tartaric iodobismuthate reagent was used to mark the position of the alkaloidal spots. The R_F value for pholcodine was 0·17. Using paper soaked in 0·2M potassium dihydrogen phosphate, with butanol saturated with water as solvent, the R_F value was 0·04. In either case pholcodine was clearly separated from morphine, codeine and ethylmorphine which have much higher R_F values. The method is applicable to the identification of commercial preparations of pholcodine phenylacetate but a preliminary extraction of the base is required.

G. B.

Quaternary Ammonium Compounds, Determination of. P. A. Lincoln and C. C. T. Chinnick. (*Analyst*, 1956, **81**, 100.) Surface-active quaternary ammonium compounds are shown to be quantitatively precipitated by phosphotungstic acid; by weighing the quaternary phosphotungstate after drying and again after ignition, it is possible to calculate the amount of quaternary cation in an unknown sample and also the ionic weight of the quaternary salt. The main disadvantage of the method is that ammonia and amines form insoluble phosphotungstates and must therefore either be removed or other allowance made; volatile amines may be removed by making alkaline and boiling. In a preferred method a solution of quaternary ammonium compound in *iso*amyl alcohol (0·1 to 0·5N) is freed from amine by washing with N hydrochloric acid.

R. E. S.

GLYCOSIDES, FERMENTS AND CARBOHYDRATES

***Digitalis purpurea*, Chromatographic Examination of.** C. Gunzel and F. Weiss. (*Pharmazie*, 1955, **10**, 725.) The composition of digitalis extracts was examined by means of inverse phase chromatography, using paper treated with silicone. Comparison of a chloroform extract with one made with chloroform-*iso*propanol showed that the larger proportion of the primary glycosides which determine the value of the drug are in the chloroform-*iso*propanol extract. Extracts made by the method of the D.A.B. VI, and also cold water extracts, contained the purpurea glycosides A and B, digitoxin, gitoxin, gitoxigenin, diginin and a saponin. The cold water extract contained, however, a larger proportion of secondary glycosides and correspondingly a smaller one of primary glycosides. This is due to the partial breakdown of the genuine glycosides to the digitoxin stage as the result of the activity of naturally occurring enzymes which are partially destroyed by hot water. An infusion is therefore to be preferred to a cold water extract. Comparison of fresh infusions with one 4 months old showed a greater proportion of digitoxin glycosides and a smaller one of primary ones in the older preparation. It is uncertain whether this is due to enzyme action or to hydrolysis under the influence of pH. G. M.

***Digitalis purpurea*, Detection of New Components in the Glycoside Complex of.** K. B. Jensen. (*Acta pharm. tox., Kbh.*, 1956, **12**, 11.) A paper chromatographic method for separation of digitalis glycosides has been developed, and used to detect the presence of the glycosides gitorin, strospeside and digitalinum verum in leaf extracts of *Digitalis purpurea*. *iso*Propanol has been shown to be a more suitable solvent than ethanol or methanol for the preparation of these extracts, the glycoside showing greater stability in *iso*propanol. Several unknown substances were detected by the use of a chloroform-acetone-formamide solvent system, and examination of the spots in trichloroacetic acid-fluorescence reactions. They are distinguished as A or B type substances according to whether they give digitoxigenin or gitoxigenin on hydrolysis. Substances A_1, A_2 and B_3 gave a green colour with the trichloroacetic acid reagent, whereas B_1 and B_2 gave no reaction. With *m*-dinitrobenzene-R, sodium nitroprusside-R or picric acid-R all five substances gave blue, red or orange colours respectively like the known cardiac glycosides. In all, five new A substances and nine new B substances were detected by the chromatographic technique. J. B. S.

***Digitalis purpurea*, Paper Chromatographic and Fluorimetric Method for Cardiac Glycosides and Aglycones of.** K. B. Jensen. (*Acta pharm. tox., Kbh.*, 1956, **12**, 27.) A method is described for determining the cardiac glycosides in digitalis leaves, based on previously published chromatographic and fluorimetric methods. The method includes purpurea glycosides A and B, digitoxin, gitoxin, digitalinum verum, gitorin, strospeside, digitoxigenin, gitoxigenin, and various unknown glycosides, transformable into known purpurea glycosides by hydrolysis with digipurpidase or by sodium bicarbonate in aqueous methanol. Experiments show that lead purification of glycoside extracts cause transformation similar to those observed with sodium bicarbonate. These transformations were even more marked with the use of lead subacetate. Stability tests with tinctures showed that within one year no other changes occurred other than a limited transformation of unknown to known glycosides. Glycoside extracts prepared by purification with lead subacetate were stable for at least four weeks with *iso*propanol as solvent, but not with methanol or ethanol. J. B. S.

ORGANIC CHEMISTRY

Cephalosporin C, Isolation of. G. G. F. Newton and E. P. Abraham. (*Biochem. J.*, 1956, **62**, 651.) Cephalosporin C, a Penicillin-like antibiotic containing D-α-aminoadipic acid, was separated from cephalosporin N penillic acid, formed by treating crude cephalosporin N at pH 3, by chromatography on Amberlite IR–4B in ammonium acetate buffer (pH 5·0). Cephalosporin N penillic acid was eluted first, cephalosporin C being isolated from the later fractions as its crystalline sodium salt. Separations effected on Amberlite IR–4B using pyridine acetate buffer were more satisfactory because of the greater ease with which the buffer could be removed. Countercurrent distribution with the solvent system, phenol-carbon tetrachloride-aqueous acetic acid was also used to effect the separation. Cephalosporin C has also been separated directly from cephalosporin N by chromatography on Amberlite IR–4B, using pyridine sulphate as buffer. Desalting was effected by addition of barium hydroxide, which precipitated sulphate leaving the barium salt of the antibiotic in aqueous pyridine, the latter being removed *in vacuo* without loss of antibacterial activity. Separation of cephalosporins by this technique was incomplete, and more satisfactory results were obtained by chromatography on buffered paper at pH 5·5 to 6·0. Cephalosporin C has been assigned a provisional formula, $C_{16}H_{21}O_8N_3S$. Electrometric titration shows two acidic groups (pK 3·1 and $< 2{\cdot}6$) and one basic group (pK 9·8) indicating a monoaminodicarboxylic acid structure. The ultra-violet absorption spectrum shows a maximum at 260 mμ ($\epsilon_{max.}$ 9000), whilst the infra-red shows bands at 2·94; 3·06; 5·61 (c.f. carbonyl of β-lactam-thiazolidine ring system); 5·77 (ester or lactone); 6·05 and 6·57 (monosubstituted amide carbonyl); 6·29 (carboxylate ion), and 7·17 and 7·36 μ (*iso*propyl group). Cephalosporin C is relatively stable to acid, but rapidly inactivated in alkaline solution above pH 11. Cephalosporin C showed activity equivalent to that of cephalosporin N against *E. coli*, but only one tenth of that of cephalosporin N against *Salm. typhi* and *Staph. aureus*. J. B. S.

Choline Esters of Monobasic Carbonic Acids, Syntheses of. L. E. Tammelin. (*Acta chem. scand.*, 1956, **10**, 145.) The synthesis of acetylcholine, propionylcholine and butyrylcholine in more than 90 per cent. of the theoretical yields is described by the action of the appropriate acid anhydride on β-dimethylaminoethanol, and treatment of the condensation product with methyl iodide. J. B. S.

Dihydrostreptomycin, Structure of a Naturally Occurring Antagonist of. J. W. Cornforth and A. T. James. (*Biochem. J.*, 1956, **63**, 124.) The examination of a dihydrostreptomycin antagonist, previously isolated from *Pseudomonas pyocyanea*, is described. Chemical investigation has shown the antagonist to be a mixture of closely related 2-alkyl-4-hydroxyquinoline-*N*-oxides. The principal constituents were separated by partition chromatography of the product obtained on reduction with zinc in acetic acid, using an ethylene glycol-benzene-*cyclo*hexane solvent system. They have been identified as 2-*n*-heptyl-4-hydroxyquinoline *N*-oxide and 2-*n*-nonyl-4-hydroxyquinoline *N*-oxide in the approximate proportion 2:1. A small concentration of 2-*n*-undecyl-4-hydroxyquinoline-*N*-oxide is also present, and possibly also 2-*n*-octyl-4-hydroxyquinoline-*N*-oxide. 2-*n*-Heptyl, 2-*n*-nonyl- and 2-*n*-undecyl-4-hydroxyquinoline-*N*-oxides have been synthesised and the *n*-nonyl compound shown to have the highest activity against dihydrostreptomycin. A plausible mode of biosynthesis is suggested. J. B. S.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Human Serum Albumin from Placental Extracts, Procedure for the Preparation of. H. L. Taylor, F. C. Bloom, K. B. McCall and L. A. Hyndman. (*J. Amer. chem. Soc.*, 1956, **78**, 1353.) An improved procedure is described for the separation and purification of albumin from human placental extracts (see Gordon and others, *J. Amer. chem. Soc.*, 1953, **75**, 5859 for earlier procedure). Many of the improvements described have made the original method more adaptable to the large-scale production of albumin. The albumin is separated from haemoglobin and other plasma proteins under controlled conditions of pH, ionic strength, ethanol and zinc concentration and temperature. A. H. B.

Hyperglycaemic Factor in Urine, Identification of. F. Moya, J. C. Szerb and M. MacIntosh. (*Canada J. Biochem. Physiol.*, 1956, **34**, 563.) The precipitate obtained by the addition of two volumes of ethanol to acidified human urine has been found to be hypotensive and hyperglycaemic when injected into rabbits. The activity appears to be due to kallikrein. In dogs 12 μg. per kg. caused a marked fall in blood pressure, which was not antagonised by atropine or antihistamine compounds. The material did not contract the guinea-pig ileum itself, but when incubated with serum for one minute the mixture did cause a contraction. This contractile action was not blocked by atropine or promethazine. Incubation with soya bean trypsin showed that the material was not fibrolysin. There was a loss of activity when it was boiled with water for one hour, and like kallikrein it was inactivated following prolonged incubation with human serum. The hyperglycaemic action in rabbits also appeared to be due to kallikrein. G. F. S.

BIOCHEMICAL ANALYSIS

Adrenaline and Noradrenaline in Plasma, Fluorimetric Determination of. J. A. Richardson, A. K. Richardson and O. J. Brodie. (*J. Lab. clin. Med.*, 1956, **47**, 832.) This method is a modification of that used by Weil-Malherbe and Bone; the main alteration being the adapting of the Beckman model DU spectrophotometer for use as a fluorimeter. By such a method it was found that when known amounts of adrenaline or noradrenaline were added to dog plasma, the mean recovery of adrenaline was 93·4 per cent. $\pm$ 11·5 and of noradrenaline was 90·3 per cent. $\pm$ 9·9. Determination of the adrenaline and noradrenaline content of arterial blood of conscious dogs subjected to thoracic surgery several days previously, showed that the plasma level of adrenaline was 0·65 μg. $\pm$ 0·43/litre and of noradrenaline was 1·30 μg. $\pm$ 0·76/litre. Using a 15 ml. blood sample, plasma levels as low as 0·25 μg. of adrenaline and 0·5 μg. of noradrenaline per litre of plasma may be determined with accuracy. M. M.

Adrenaline, Noradrenaline and Hydroxytyramine in Urine, Fluorimetric Estimation of. H. Weil-Malherbe. (*Biochem. J.*, 1956, **63**, 4P.) The method of Weil-Malherbe and Bone for the fluorimetric estimation of adrenaline and noradrenaline gives high results with acid-hydrolysed urine, due to the presence of hydroxytyramine, 3:4-dihydroxyphenylacetic acid and possibly other acidic catechols, which form fluorescent derivatives with ethylenediamine. Acid and basic catechols were separated by ion exchangers, after separation of the catechol

fraction from the urine by chromatography on alumina. The purified basic catechols were examined by paper chromatography and shown to be the only constituents giving rise to yellow-green fluorescence with ethylenediamine, and can be estimated in this way. Adrenaline and noradrenaline are estimated separately by the method of Lund, hydroxytyramine being obtained by difference. J. B. S.

Phenobarbitone and Diphenylhydantoin in Blood, Simultaneous Determination of. G. L. Plaa and C. H. Hine. (*J. Lab. clin. Med.*, 1956, **47**, 649.) A method is described for the simultaneous determination of the two drugs in the same blood specimen. To extract diphenylhydantoin, place 5 ml. of oxalated whole blood in a 50 ml. glass stoppered centrifuge tube containing 0·5 g. of sodium bicarbonate and 0·2 ml. of 10 per cent. sodium hydroxide. Add 20 ml. of *cyclo*hexane and 1 ml. of *n*-butanol. Shake for 5 minutes and centrifuge. Transfer the *cyclo*hexane phase to another tube containing 10 ml. of N hydrochloric acid (retain the buffered blood residue), shake for 5 minutes and centrifuge. Transfer 15 ml. of the *cyclo*hexane phase to another tube containing 5 ml. of carbonate buffer (0·1M sodium bicarbonate and 0·09M sodium hydroxide, pH 11), shake and centrifuge. Remove the *cyclo*hexane layer and retain the aqueous phase for estimation. To extract the phenobarbitone, acidify the buffered blood residue retained above with 2 ml. of 25 per cent. acetic acid, after removing any *cyclo*hexane remaining in the tube. When no more carbon dioxide is evolved add 35 ml. of chloroform, shake and centrifuge. Remove the aqueous phase from the clotted blood and transfer the chloroform through filter paper to a 75 ml. centrifuge tube. Add 30 ml. of 10N sulphuric acid, shake and centrifuge. Remove the acid layer. Add 25 ml. of the chloroform layer to 5 ml. of 0·3N sodium hydroxide, shake and centrifuge and save the aqueous layer for estimation. A reagent blank is prepared by running 5 ml. of distilled water through the above procedures. For estimation of the barbiturate, pipette 3 ml. 0·3N sodium hydroxide into a silica cell and read against reagent blank at 260, 250 and 240 mμ on a D.U. spectrophotometer. Add 0·5 ml. saturated potassium bicarbonate solution to each cell and read again. Multiply the second readings by 1·17 to correct for dilution and subtract from the first readings. A barbiturate is present if a maximum positive optical density (O.D.) difference occurs at 260 mμ, approaching a minimal difference at 250 and a maximum negative difference at 240 mμ. Determine the amount from the standard curve for phenobarbitone in 0·3N sodium hydroxide. (10 mcg./ml. = 0·205 optical density units.) For diphenylhydantoin, pipette 3 ml. of the carbonate buffer into a silica cell and read against reagent blank at 260, 250, 240 and 235 mμ. Add 0·5 ml. of 10 per cent. sodium hydroxide to each cell and read again. Multiply the second readings by 1·17 to correct for dilution and subtract from them the first readings. Calculate the absorption due to the phenobarbitone in carbonate buffer at 260 and 235 mμ as follows:

O.D. phenobarbitone at 260 = 0·668 O.D. difference at 260.
O.D. phenobarbitone at 235 = 2·12 O.D. difference at 260.

Subtract these calculated optical densities from those obtained in the first readings to give the true hydantoin readings at wavelengths 260 and 235. This difference bears a direct linear relationship to the amount of hydantoin present. Determine the amount present from the standard curve for diphenylhydantoin in carbonate buffer. (10 mcg./ml. = 0·196 optical density units.) The method is sensitive enough for clinical and toxicological determinations with a high degree of specificity. G. F. S.

CHEMOTHERAPY

Spiramycin, *In Vitro* Study of. S. Pinnert-Sindico and J. Pellerat. (*Thérapie*, 1956, **11**, 308.) In tests by the dilution method against a variety of organisms, spiramycin was shown to have an antibacterial spectrum closely resembling that of erythromycin and carbomycin. Inhibiting concentrations were generally higher for spiramycin *in vitro*, but of the same order as those of erythromycin and carbomycin *in vivo*. The activity of the substance was not affected by the presence of serum. A strain of *Staphylococcus* resistant to spiramycin was susceptible to other antibiotics, but showed slight resistance to erythromycin and carbomycin. Strains resistant to other antibiotics remained sensitive to spiramycin. Spiramycin was especially active against Gram-positive organisms. Its activity was influenced by the reaction of the medium, being a maximum in alkaline solutions. Different strains of *Staphylococcus* varied considerably in sensitivity to this antibiotic. G. B.

Streptonivicin and Cathomycin, Antibacterial Activity of. W. F. Jones, R. L. Nichols and M. Finland. (*J. Lab. clin. Med.*, 1956, **47**, 783.) Streptonivicin and cathomycin are new antibiotics produced by *Streptomyces niveus* and *Streptomyces spheroides* respectively. Data concerns the *in vitro* activity of the crystalline monosodium salts of these two substances against various species of aerobic bacteria. It was found that these two substances exhibited essentially the same antibacterial activity in all of the tests to which they were subjected. Many strains of a variety of bacterial species showed wide differences in their susceptibility to these two agents, but both were equally active against each strain. The addition of serum or blood to agar, or of various concentrations of serum in broth used in the sensitivity tests, resulted in a decrease of susceptibility of a strain of *M. aureus*, the extent of the decrease being directly related to the concentration of serum, and the effect being identical with both antibiotics. The minimum inhibiting concentrations of both streptomycin and cathomycin for *M. aureus* and proteus, when tested in broth, were decreased progressively and to the same degree by progressive decreases in the pH of the medium. Increases in the size of the inoculum, in tests employing broth, resulted in decreases in the *in vitro* activity to the same extent with both antibiotics against staphylococcus and proteus. The rate of development of resistance in strains of *M. aureus* was the same for both antibiotics. It is thus concluded that streptonivicin and cathomycin are either the same or very closely related substances. M. M.

PHARMACY

NOTES AND FORMULAE

Association Colloid Solutions, The Effect of Decanol-1 on the Viscosities of Some. K. Passinen and P. Ekwall. (*Acta chem. scand.*, 1956, **10**, 215.) The effect of the relatively long paraffin chain alcohol, decanol-1, on the viscosity of association colloid solutions, has been studied using solutions of sodium oleate, sodium lauryl sulphate and sodium myristyl sulphate. At low oleate concentrations (below 0·15M) the viscosity increases slowly as the amount of decanol is raised, and no marked change occurs at the turbidity point where a new phase composed of decanol, sodium oleate and water begins to separate. With oleate concentrations above 0·2M, viscosity rises rapidly as long as the decanol is solubilised in the micelles, but as soon as the system becomes heterogeneous, viscosity decreases with increasing decanol concentrations, passing

through a minimum and finally rapidly increases. The minimum in the viscosity curve appears at a decanol concentration of approximately 0·3 to 0·4 mole of decanol per mole of oleate and is in the vicinity of the turbidity maximum in the same system. The effect of *p*-xylene on the viscosity of sodium oleate solutions has also been studied. Increased viscosity at low oleate concentrations is explained on the assumption of an increase in micelle volume, and at higher concentrations large changes in the form and structure of micelles must be assumed. J. B. S.

Cyclobarbitone, Stability of. S. Åhlander. (*Svensk farm. Tidskr.*, 1956, **60**, 249.) On storage, cyclobarbitone undergoes decomposition with formation of peroxides, probably at the methylene groups which are in the α position to the double bonds. This decomposition is not revealed by direct titration with alkali, but the bromometric assay shows it clearly. A number of old samples were examined. All titrated 99 to 100 per cent. by alkali, whereas the actual contents ranged from 79 to 99 per cent. Values below 80 per cent. were shown by samples respectively 8, 6 and 4 years old. The loss in strength was in all cases proportional to the peroxide value. Cyclobarbitone-calcium and hexobarbitone do not decompose on storage. Tablets of cyclobarbitone showed a considerable loss in strength after storage for periods from 1 to 4 years.

G. M.

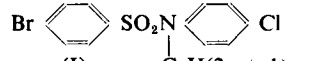
Soap Concentration where Interaction with Decanol-1 Begins and its Dependence on the Chain Length of the Soap. P. Ekwall, O. Söderberg and I. Danielsson. (*Acta chem. scand.*, 1956, **10**, 227.) Turbidity measurements show that the point at which interaction between decanol-1 and fatty acid soaps begins is dependent on the chain length of the soap. The soap concentration at which interaction begins decreases as the length of the hydrocarbon chain of the soap increases. This concentration lies very close to the lowest concentration at which hydrolysis in the soap solution leads to the formation of acid soap, or at which the soap forms acid soap when fatty acid is added. The variation of the upper limit of the first turbidity range with temperature is almost linear. The limiting association concentration lies considerably lower than the critical micelle concentration of the pure soap and below the concentration where micelle formation begins to increase rapidly in soap solutions that contain added alcohols. J. B. S.

Sodium Caprate Concentration where Interaction with Long-chain Alcohols Begins and its Dependence on the Chain Length of the Alcohol. P. Ekwall and C. F. Aminoff. (*Acta chem. scand.*, 1956, **10**, 237.) Turbidity measurements show that the interactions of hexanol-1, octanol-1, decanol-1 and dodecanol-1 with sodium caprate all begin at the same soap concentration and are independent of the chain length of the alcohol. The effect of temperature on the interaction between alcohol and soap is also independent of the nature of the alcohol. Higher molecular weight alcohols, tetradecanol-1, hexadecanol-1 and octadecanol-1 also show interaction at temperatures above their melting points, though interaction commences at slightly higher soap concentrations than with the shorter chain alcohols. It is shown that the association above the limiting concentration follows the law of mass action. It appears that the same forces that affect the association in pure soap solutions must take an active part also in the formation of soluble aggregates between soap and alcohols or fatty acids. Ion dipole interactions and hydrogen bond formation between carboxylate soap ions and alcoholic hydroxyl groups also contribute to the complex formation. J. B. S.

PHARMACOLOGY AND THERAPEUTICS

Benactyzine in Psychoneurosis. M. J. Raymond and C. J. Lucas. (*Brit. med. J.*, 1956, **1**, 952.) A pilot study carried out with benactyzine on 43 outpatients with various psychiatric disorders suggests that patients with a symptomatology in which anxiety and tension predominate respond favourably to the drug (of 18 cases, 8 were much improved and 4 improved), while those with depressive, hysterical and obsessive symptoms do not. About half the patients receiving 2 mg. three times a day experienced side-effects; these included a feeling of heaviness in the limbs, giddiness, ataxia and clumsiness, difficulty in reading small print, poor concentration, diarrhoea, increased anxiety, and drowsiness. On a dosage of 1 mg. three times a day side-effects did not occur and the higher dosage could be tolerated provided the increase was gradual. Most of the patients benefiting from the drug appeared first to notice an improvement towards the end of the first week of treatment. In 10 healthy volunteers given the drug subcutaneously subjective changes and EEG changes were noted. Changes in perception were predominant, and in half the subjects there was a marked diminution in the amount of alpha rhythm; this change is comparable to that following the administration of mescaline. S. L. W.

Dicophane, Substituted Benzenesulphonanilides as Synergists for. M. Neeman, A. Modiano, G. G. Mer and R. Cwilich. (*Nature, Lond.*, 1956, **177**, 800.) A series of 4-bromobenzenesulphon-4′chloroanilides (I) have been synthesised and examined for synergistic activity with dicophane (DDT) against dicophane-resistant houseflies. The compounds were tested together with dicophane by topical application of benzene solutions, and mortality observed after six hours. They were also tested in the form of residual deposits by the method of Mer and Davidovici. The proportional mortality values observed after topical application formed two statistically homogeneous groups of responses, significantly higher than the response to dicophane by itself, where $n = 1$ or 2, and where $n = 0$, 3, 4, 5, 6, 7 or 8 respectively. The proportional knock-down values observed after short duration contact with residual deposits formed three statistically homogeneous groups where $n = 6$, $n = 0$, 1, 2, 4, 5, 7, 8 and $n = 3$ respectively. A number of other synergists previously reported active were also examined. J. B. S.



(I)

Digitalis, Seasonal Variation in Response of the Pigeon to. R. A. Sachs, J. D. Highstrete and M. L. Pabst. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 248.) Examination of the data obtained over a 4-year period using the pigeon assay with the U.S.P. digitalis reference standard revealed a seasonal variation in the response of pigeons to digitalis. The animals were more resistant during the summer months, the maximum resistance occurring in August or September. On account of this seasonal variation it was found advisable to limit the interval between tests on the standard and the unknown to 30 days, when potency estimates were generally within the acceptable limits of error. Results outside the acceptable limits were more frequently encountered when the interval was increased to 60 days. G. B.

Meprobamate, Central Depressant and Anticonvulsant Activity of Compounds Isomeric with. F. M. Berger, C. D. Hendley, B. J. Ludwig and T. E. Lynes. (*J. Pharmacol.*, 1956, **116**, 337.) Meprobamate (Miltown, Equanil), an interneuronal blocking agent related to mephenesin, but with a longer duration of action, was compared for activity in mice with its seven isomers having the

basic 2-substituted trimethylene glycol dicarbamate structure, and with other structural isomers where alkyl substitution was made on one or more of the three carbons of the propanediol nucleus. All the compounds produced flaccid paralysis, either preceded or followed by excitement; meprobamate was the most potent of the series, being twice as effective as the next best compound. Against leptazol-induced convulsions and death, meprobamate gave most protection. The dicarbamates of 2-*n*-butyl-1:3-propanediol and of 2-*iso*butyl-1:3-propanediol afforded the same degree of protection against electroshock seizures as did meprobamate; taking the ratio between median paralysing dose and median seizure-modifying dose, meprobamate had the smallest ratio and 2-*n*-butyl-1:3-propanediol dicarbamate the greatest. The melting points of the compounds correlated well with paralysing potency and ability to protect against leptazol convulsions, but not with ability of the compounds to modify electroshock seizures. Clinically, meprobamate has been found to be of value in three types of condition: (1) anxiety states; (2) neurological and arthritic diseases involving muscle spasm; and (3) some forms of petit mal epilepsy. However, the closely related 2:2-diethyl-1:1:3-propanediol dicarbamate was of no value in anxiety states where beneficial results had previously been obtained with meprobamate. G. P.

Meratran, Clinical Trials with. W. G. A. Begg and A. A. Reid. (*Brit. med. J.*, 1956, **1**, 946.) This is a report on the use of a new stimulant drug meratran (α-(2-piperidyl) benzhydrol hydrochloride) in the treatment of over 200 psychiatric patients, the majority of whom were suffering from depression. In addition, 24 normal persons were given up to 3 mg. of the drug daily by mouth for periods of time up to a week. Two reported no change as a result of the drug, but the remainder reported an insidious elevation of mood (insufficient to be characterised as euphoria), with heightened confidence, greater ability to concentrate, and an increased work output. The effect of the drug lasted for 12 to 24 hours and there were no "hangover" effects. Some subjects reported interference with sleep. The drug was found to be most helpful in reactive depressions uncomplicated by anxiety, hysterical or obsessional traits. When obsessional features are present meratran tends to aggravate rather than relieve the condition; anxiety is also frequently increased by the drug. Of a group of 29 patients with the purer type of reactive depression 25 were helped by meratran, while of a group of 22 patients with reactive depression with hysterical features only 11 were improved. Dosage was started with a dose of 1 mg. three times daily and gradually increased to a maximum of 7·5 mg. a day in three doses; barbiturates were also given to counteract sleep disturbance. Patients with endogenous depressions were not so responsive to meratran as were the reactive depressives; of 65 patients suffering from severer depressions only 14 obtained any lasting benefit. Some of the patients in this group became worse during treatment with meratran and in some cases patients not previously showing obvious anxiety became acutely anxious, agitated, deeply depressed and even suicidal in the course of a day or two. The tendency of the drug to exacerbate pre-existing anxiety and produce unexpected aggravation of the mental state may often be successfully combated by combining each dose of meratran (2·5 mg.) with chlorpromazine hydrochloride 50 mg. or amylobarbitone sodium 100 mg. Meratran does not destroy appetite as the amphetamines do, but some patients may complain of nausea. No other serious side-effects were observed apart from the psychotic episodes mentioned (4 case reports are given). Unfortunately, owing to the lack of side-effects no warning of the imminence of

such episodes is given, and they can occur on minimal doses of the drug. Further clinical research is needed to ascertain more clearly the type of patient in whom these episodes are likely to occur. Promising results with meratran were obtained in 5 cases of spasmodic torticollis and in a number of patients suffering from post-leucotomy anergia. S. L. W.

Meratran in the Treatment of Schizophrenics. F. Houston. (*Brit. med. J.*, 1956, **1**, 949.) This is a study of group behaviour in chronic schizophrenics treated with the stimulant drug meratran. For the project a group of 20 male schizophrenics, the most deteriorated and withdrawn patients in a hospital of 900 patients, was selected. Their behaviour was studied under the headings of feeding, letter writing, mutual aid, conversation, washing and dressing. After 6 weeks preliminary charting, 10 of the patients were given meratran (2 tablets three times daily) and 10 were given placebo tablets, of similar appearance and flavour, for 4 weeks. The nursing staff did not know which were the placebo tablets. After a 2-weeks interval the meratran and placebo order was reversed and administered for a further 4 weeks. The results in the fourth weeks of the two courses of treatment with meratran and placebo were compared and were found not to differ significantly. The results in the second week of the project were compared with the results in the final week, and a significant improvement in reading, washing and dressing was noted. This was attributable to increased nursing enthusiasm. Such a control experiment had not previously been carried out in the hospital, and it was the focus of considerable discussion, feeling and approval. The author concludes that caution and adequate control procedures are essential before any therapy or drug is accepted as beneficial in chronic psychotics, and that statistical analysis of results is essential, since in this particular group it showed that meratran was no more effective than placebo tablets yet an improvement in the behaviour of the patients occurred that would otherwise have been attributed to meratran. S. L. W.

Methitural, a New Intravenous Anaesthetic: Comparison with Thiopentone. S. Irwin, R. D. Stagg, E. Dunbar and W. M. Govier. (*J. Pharmacol.*, 1956, **116**, 317.) Methitural, sodium 5-(2′-methylthioethyl)-5-(1-methylbutyl)-2-thiobarbiturate, had about two-thirds of the anaesthetic potency of thiopentone in the cat, dog and monkey. With equivalent anaesthetic doses recovery from anaesthesia was more rapid with the methitural than with thiopentone. Cumulative action was also considerably less with methitural than with either thiopentone or thioamylal. The more rapid recovery from anaesthesia and low cumulative effects were due to a higher rate of destruction of the drug by the liver. Affinity of methitural for the fat depots of the body was the same as for thiopentone. In unanaesthetized dogs both thiopentone and methitural caused a transient hypotension, cardiac acceleration and reversible ectopic beats and bigeminy. Induction apnoea with thiopentone in dogs and cats was more often encountered than with methitural; also, intercostal respiration in the monkey and the dog was depressed more with thiopentone. Muscle relaxation was the same with both drugs. The incidence of side effects was slightly greater with methitural, more salivation and spontaneous coughing being noted in the cat. Atropine abolished salivation and reduced the incidence of coughing and cardiac arrhythmias; depth and duration of surgical anaesthesia also appeared to be prolonged. Morphine also prolonged, and leptazol partly reversed, anaesthesia with methitural. With continued administration of methitural or thiopentone to dogs, liver damage was considerably more frequent with the thiopentone. G. P.

3-(α-Naphthyl)-4-hydroxycoumarin, a New Synthetic Anticoagulant. J. Moraux. (*Thérapie*, 1956, **11**, 104.) Synthetic anticoagulants derived from coumarin were differentiated chemically into symmetrical and asymmetrical compounds: the former were twinned molecules, the single molecule being Vitamin K-like (e.g., 3-methyl-4-hydroxycoumarin) whilst the twinned molecule (e.g., dicoumarol) was anticoagulant. Symmetrical compounds were twinned at ring position 3, whilst the asymmetric were substituted at that position, giving such compounds as 3-(α-naphthyl)-4-hydroxycoumarin, which possessed marked antivitamin K properties. Pharmacologically, these anticoagulants have either short (ethyl biscoumacetate, phenylindanedione) or long (dicoumarol) duration of action. 3-(α-Naphthyl)-4-hydroxycoumarin is without many of the drawbacks of the other derivatives, being long-acting, of low toxicity, well tolerated, active at doses close to those of dicoumarol, and acting on at least three coagulation factors: prothrombin, factor VII (prothrombin conversion) and factor X (thromboplastinogenesis). It is without action on factor V (prothrombin activator) and is antagonized by the K vitamins. G. P.

3-[α-(4-Nitrophenyl)-β-acetylethyl]-4-hydroxycoumarin (Coumarin G. 23.350), Properties of. M. Leroux and B. Jamain. (*Thérapie*, 1956, **11**, 85.) Coumarin G.23.350 (Sintrom), an asymmetrical derivative of coumarin obtained synthetically by substituting a *p*-NO_2 into the phenyl group of the side-chain of Warfarin [3-(α-phenyl-β-acetylethyl)-4-hydroxycoumarin], was a potent anticoagulant. Sintrom contrasted with the closely related compounds Warfarin and Marcoumar in having a short duration of action closely similar to phenylindanedione and ethyl biscoumacetate. Sintrom differed from ethyl biscoumacetate in that maximum activity, when reached, remained steady for 12–24 hours, and then declined rapidly. Anticoagulant effectiveness in man, in order of diminishing potency was Sintrom (1); Marcoumar (2/3); Warfarin (2/5); phenylindanedione (1/5); dicoumarol (1/15); 3-(α-naphthyl)-4-hydroxycoumarin (1/20); ethyl biscoumacetate (1/45). Sintrom was an indirect anticoagulant, inactive *in vitro*, but active *in vivo*, inhibiting liver synthesis of proconvertin, prothrombin and factor X; vitamin K_1 was a rapid antidote. The toxicity of Sintrom in mice was less than with ethyl biscoumacetate, Marcoumar and phenylindanedione. Sintrom was tested clinically in 53 patients with no untoward effects; the initial dose was at most 20 mg. the first day and 16 mg. the second; maintenance doses (2 to 8 mg. a day) depended on the results of blood tests. The drug appeared therapeutically useful and presented some advantages over ethyl biscoumacetate. G. P.

Novobiocin: A Laboratory Investigation. G. Lubash, J. van der Meulen, C. Berntsen and R. Tompsett. (*Antibiotic Med.*, 1956, **2**, 233.) Novobiocin was found to be highly active *in vitro* on all strains of *Staph. aureus* tested, including strains highly resistant to all other commonly used antibiotics; it was also found active *in vitro* against other Gram-positive cocci, including certain strains of pneumococci and haemolytic streptococci. In general it was found relatively inactive against most Gram-negative bacilli with the exception of certain strains of *P. vulgaris*. The *in vitro* activity is markedly inhibited by human serum, probably because of its high degree of binding by serum albumin. It is well absorbed when administered orally and reaches high concentrations in the blood. It was not found, however, in cerebrospinal fluid or pleural fluid, but was demonstrated in bile. Novobiocin was administered to 30 patients in a dosage of 2 g./day in adults, given in 4 equal doses for periods up to

(ABSTRACTS *continued on p. 1000.*)

activity is a function of solution structure. I suggest that on these lines an explanation of the mode of antibacterial action, with a stronger theoretical background, could be developed.

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REFERENCES

1. Berry, Cook and Wills, *J. Pharm. Pharmacol.*, 195 **8**, 425.
2. Ekwall, *Kolloid-Z.*, 1954, **136**, 37.
3. Ekwall, *J. colloid. Sc.*, Supplement 1, 1954, 66.
4. Brudney and Saunders, *J. chem. Soc.*, 1955, 2916.
5. Brudney and Saunders, *J. Pharm. Pharmacol.*, 1955, **7**, 1012.
6. Brudney and Saunders, *J. chem. Soc.*, 1956, 2978.
7. Hartley, *Trans. Farad. Soc.*, 1939, **35**, 1109.

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5 days. In 6 cases with uncomplicated pneumococcal pneumonia the clinical outcome was satisfactory; in a seventh patient the condition deteriorated on novobiocin and he was changed to penicillin therapy after 24 hours. Fourteen patients were treated for infections of the genito-urinary tract; cultures of urine prior to treatment all revealed *P. vulgaris*. Five of the patients were improved by novobiocin, though in 3 of these the cultures remained positive for *P. vulgaris*. Three patients derived no benefit, and in 6 the outcome was indeterminate. Proteus could be cultured from the urine of 8 of the 14 patients at the termination of therapy. The only side effects observed in this series of patients were mild skin eruptions which occurred in 2 cases; in one of these a second course of novobiocin did not cause a recurrence of the eruption. S. L. W.

Nystatin in Mycotic Infections. G. T. Stewart. (*Brit. med. J.*, 1956, **1**, 658.) Nystatin (Mycostatin) is an antibiotic prepared from *Streptomyces noursei*. It is an amphoteric crystalline polyene with the probable empirical formula $C_{46}H_{77}NO_{19}$, insoluble in water, but soluble in various alcohols and ethers. It is available as a pale-yellow lyophilised powder which is rapidly inactivated by heat, light and oxygen; tablets containing 500,000 units of the substance are prepared for clinical use. *In vitro* experiments show that nystatin inhibits cell-division and mycelial growth of candida and saccharomyces, including pathogenic strains isolated from a variety of human lesions. This effect is fairly complete against *C. albicans* at concentrations of 5–20 units/ml. Its mode of action is complex but highly specific. The presence of a chain of CH_2 groups, as in the alcohols, favours activity, while CHOH and CHO groups, as in various sugars, are antagonistic. Glycols, with combination of both, show intermediate properties. A series of 12 bronchitic patients with fungal hyphae demonstrable in direct examination of films made from sputum, and cultures positive for *C. albicans*, were treated with three to four daily oral doses of 500,000 units for 7 days. The moniliasis in these patients had developed as a sequel to antibiotic therapy. As a result of the treatment with nystatin 9 out of the 12 patients were rapidly and completely cleared of the mycotic infection. A similar result was obtained in 7 out of 8 cases of stomatitis. Apart from transient nausea no toxic effects were observed. Nystatin and antibacterial agents showed no mutual interference *in vitro* but when given prophylactically nystatin was not wholly successful in preventing mycotic superinfection in patients receiving antibacterial therapy. Resistance was not found to develop in strains after passage *in vitro* or on re-isolation during and after treatment. S. L. W.