ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ANALYTICAL

Dienoestrol and Diethylstiboestrol, Colorimetric Determination of. G. Tokár and I. Simonyi. (*Magyar Kémiai Folyóirat.*, 1956, **62**, 320. *Hung. Tech. Abstr.*, 1957, **9**, 111.) A colorimetric method for determining dienoestrol, dienoestrol diacetate and diethylstilboestrol dipropionate is based on the fact that nitration products of the compounds produce intense colour reactions with alkali solutions. The coloured solutions obey the Beer-Lambert law, and thus they are suitable for the quantitative determination of the two hormones.

Reserpine, Determination of, in Non-aqueous Media. J. Bayer. (*Magyar Kémiai Folyóirat.*, 1956, **62**, 355. *Hung. Tech. Abstr.*, 1957, **9**, 110.) Reserpine can best be dissolved in glacial acetic acid and in chloroform. The base content of crystalline reserpine dissolved in anhydride-free acetic acid can be determined by means of a 0·1N acetic acid solution of perchloric acid, in the presence of a solution of crystal violet indicator in acetic acid: error of the determination is less than $\pm 0{\cdot}3$ per cent. The microdetermination of reserpine includes the titration of the chloroform solution of the crystalline material by means of a 0·005N chloroform solution of *p*-toluenesulphonic acid, in the presence of *p*-aminoazobenzene indicator dissolved in chloroform: error of the procedure is less than $\pm 0{\cdot}6$ per cent. The accuracy of both procedures considerably surpasses that of previous methods (± 2 to 6 per cent).

Reserpine, Reserpic Acid and Yohimbine, Paper Chromatographic Separation of. F. Machovičová. (*Československ. Farm.*, 1957, **6**, 310.) Reserpine is separated from reserpic acid and yohimbine on paper saturated with a 40 per cent methanolic solution of formamide, with benzene + chloroform (1 : 1) saturated with formamide as the mobile phase at 18°. Reserpine has an R_F value of 0·40 but reserpic acid and yohimbine remain stationary. The method is suitable for the identification of reserpine in tablets. For the separation of reserpic acid from yohimbine, the system *n*-butanol-pyridine-water (4 : 1 : 5), or ethyl acetate-pyridine-water (2 : 1 : 2), is used with the same paper. The three alkaloids can be separated by a combination of the two methods. The spots are detected by observing the paper in ultra-violet light. E. H.

Tropic and Mandelic Acids and their Esters, Colorimetric Determination of. I. Simonyi and G. Tokár. (*Magyar Kémiai Folyóirat.*, 1956, **62**, 348. *Hung. Tech. Abstr.*, 1957, **9**, 110.) A colorimetric method has been evolved for determining tropic acid, mandelic acid and their esters (atropine, scopolamine, homatropine). The principle of the procedure is that the nitrated products of tropic acid and mandelic acid give intense colour reactions with hot alkali solutions. The coloured solutions obey the Beer-Lambert law, thus the reaction is suitable for the quantitative determination of the above compounds.

ORGANIC CHEMISTRY

Central Nervous System Depressants, A New Class of. B. M. Bloom, J. F. Gardocki, D. E. Hutcheon and G. D. Laubach. (*J. Amer. chem. Soc.*, 1957, **79**, 5072.) 2(1-Naphthylamino)-2-oxazoline, a new structural type of central nervous system depressant has been synthesised as the hydrobromide from β-bromoethylamine, by condensation with α-naphthyl isocyanate to yield 1-(1-naphthyl)-3-(2-bromoethyl)-urea, and intramolecular cyclization of the latter in boiling water. Treatment of an aqueous solution with ammonium hydroxide gave the free base. The latter with dry hydrogen chloride in methylene chloride gave the corresponding hydrochloride, which reverted to 1-(1-naphthyl)3-(2-chloroethyl)-urea in boiling 2-propanol. Marked quieting and muscle relaxation followed oral or parenteral administration of the oxazoline in cats, dogs and monkeys. It is also more potent than either reserpine or chlorpromazine in potentiating anaesthesia by 21-hydroxypregnanedione sodium succinate. J. B. S.

BIOCHEMISTRY

BIOCHEMICAL ANALYSIS

Carbutamide, Estimation of, in Blood. R. H. Thompson. (*J. clin. Path.*, 1957, **10**, 369.) An accurate method is described for the measurement of blood levels of carbutamide in blood. Add 0·1 ml. of blood to 7·9 ml. of water, add 2 ml. of 15 per cent trichloroacetic acid, mix and centrifuge or filter after a few minutes. Transfer 5 ml. of the filtrate to a test-tube, add 0·5 ml. of 0·1 per cent sodium nitrite solution, shake and stand for five minutes. To the mixture add 0·5 ml. of 0·5 per cent ammonium sulphamate solution, mix, allow to stand for two minutes, then add 1 ml. of a 0·5 per cent solution of *N*-(naphthyl) ethylenediamine solution and mix again. After 15 minutes compare the colour in a colorimeter against a standard prepared by taking 5 ml. of a solution of carbutamide containing 1 mg./ml. Correct for a reagent blank of 4 ml. of distilled water and 1 ml. of 15 per cent trichloroacetic acid through the diazotisation and coupling procedure. G. F. S.

Carbutamide and Sulphonamides, Estimation of, in Blood. D. G. Moss. (*J. clin. Path.*, 1957, **10**, 371.) A method is described for the simultaneous estimation of sugar and sulphonamides in blood. Wash 0·2 ml. of blood into 3·5 ml. of isotonic sodium sulphate/copper sulphate solution (a mixture of 320 ml. of 3 per cent sodium sulphate and 30 ml. of 7 per cent copper sulphate), add 0·3 ml. of a 10 per cent sodium tungstate solution and centrifuge. Use 1 ml. of the supernatant for estimation of the blood sugar by the modified Schaffer–Hartman method. Use a further ml. for estimation of the hypoglycaemic sulphonamide carbutamide as follows. To 1 ml. add 0·2 ml. of N hydrochloric acid and 0·1 ml. of a 0·1 per cent solution of sodium nitrite. Mix well and add 2 ml. of a 1 per cent solution of *N*-sulphatoethyl-*m*-toluidine. A standard for comparison is prepared by taking 1 ml. of a diluted stock standard solution to contain 15 mg. of carbutamide in water. The orange colour formed is measured after 15 minutes in a spectrophotometer on a colorimeter. The method may be used as a routine method for the estimation of other sulphonamides. G. F. S.

Adrenaline and Noradrenaline, Fluorimetric Estimation of, in Plasma. H. Weil-Malherbe and A. D. Bone. (*Biochem. J.*, 1957, **67**, 65.) A further investigation is made into the specificity of the fluorimetric estimation of adrenaline and noradrenaline, based on the condensation of these amines with ethylenediamine, as applied to plasma. Also a comparison is made between this method and the fluorimetric method of Lund which depends on the formation of 3:5:6-trihydroxyindoles. The catechol compounds were extracted from bovine and human plasma by passage through columns of alumina and elution with dilute acid. The eluates were separated into basic and non-basic fractions by passage through cation exchange resins. The purified basic fraction was studied by paper chromatography, paper electrophoresis or bioassay. At every stage of the procedure samples were analysed by the two fluorimetric methods. It was found that the basic fraction accounted for the catechol compounds present in the alumina eluates. The estimates of adrenaline and noradrenaline obtained by direct fluorimetric assay agreed with results obtained by electrophoresis and by chromatography. No 3-hydroxytyramine was detected. A high degree of correlation was found consistently, at every stage of the procedure, between the two fluorimetric methods. The biological estimation of noradrenaline, using the ascending colon of the rat, was inconclusive since the concentration, as determined by the fluorimetric analysis, was on the threshold of the sensitivity of this preparation. Little biological activity was found in the test for adrenaline, using the isolated uterus of the rat, despite the chemical evidence for the presence of this amine. Possible reasons for this discrepancy are discussed. M. M.

Parathion, Paraoxon and *p*-Nitrophenol in Organic Tissue Material, Determination of. O. Karlog. (*Acta pharm. tox. Kbh.*, 1957, **14**, 92.) The method described is intended for use in forensic chemistry and for determining the concentration of residues on vegetables. Grind 100 g. of tissue in a Waring blender and transfer to centrifuge tubes, add 2 N sulphuric acid until acid, 75 ml. of ethanol and 50 ml. of ether. Shake for 5 minutes and centrifuge in a refrigerated centrifuge. Extract the residue twice more and transfer the pooled extract to a separating funnel and add 5 ml. of 2 N sulphuric acid with 100 ml. of water. Shake and separate. Shake the ether phase twice more with ether, wash the pooled ether extract three times with 100 ml. of water to which 5 ml. of 2 N sulphuric acid has been added. Dry the ether extract with anhydrous sodium sulphate and evaporate to dryness at a temperature below 70°. To the residue add 5 ml. of acetonitrile and heat to 70°. Add 6 ml. of water, cool, filter and centrifuge. The residue is treated twice more. The acetonitrile extract is purified by column chromatography as described by Erwin and others (*J. Agric. Food Chem.*, 1955, **3**, 676) using 40 per cent acetonitrile as the developing liquid. The eluate is extracted with ether after adding an equal volume of water. Then 5 ml. of 2 N sulphuric acid is added and the mixture shaken three times with 50 ml. of ether. Wash the total ether extract twice with 25 ml. of water containing 5 ml. of 2 N sulphuric acid. Dry the ether extract with anhydrous sodium sulphate and evaporate at not more than 70°. Dissolve the purified residue in a suitable amount of ether and apply to paper strips using a Carlsberg pipette. Carry out descending paper chromatography with a mixture of water and acetonitrile as the stationary phase and light petroleum saturated with water and acetonitrile as the moving phase. The paper hangs for at least 12 hours in the vessel before the chromatogram is developed. After reading the R_F values the individual spots are eluted by washing three times with 50 per cent ethanol, and the amount of *p*-nitrophenol is determined spectrophotometrically. G. F. S.

CHEMOTHERAPY

1-*iso*Nicotinylamido-2 : 5-dimethylpyrrol (G.144), Tuberculostatic Activity of. J.-M. Gazave, N.-P. Buu-Hoi and N.-D. Xuong (*Thérapie*, 1957, **12**, 486.) When tested *in vitro* against *Mycobacterium tuberculosis* strain H37RVD, *iso*nicotinylamido-2 : 5-dimethylpyrrol (G.144), a structural analogue of isoniazid, appeared to be only slightly less active than isoniazid. The LD50 determined by oral administration to mice was three times greater for G.144 than for isoniazid. G.144 is less soluble than isoniazid, and might be expected to have a more prolonged effect. G. B.

PHARMACY

Lissapol-Cirrasol Cleansing of Blankets. B. R. Frisby. (*Brit. med. J.*, 1957, **2**, 506.) Hospital blankets, unless specially laundered, are bacteriologically contaminated and potentially dangerous, particularly from their harbouring of penicillin-resistant strains of *Staph. aureus*, which are not removed by ordinary laundering. Provided they can be washed frequently, e.g., after every patient, the lissapol-cirrasol technique (Blowers and Wallace, *Lancet*, 1955, **1**, 1250) is adequate to keep ordinary woollen blankets clean. Many hospital laundries may not be equipped, however, to deal with the increased washing required for this technique. Blankets made of terylene may help in the solution of this problem. These may be boiled like sheets and the resulting counts of the clean blankets are under 20 per plate, with no *Staph. aureus*. They produce very little fluff, are light and warm, and have stood up very well to an average of 14 boilings. There must still, however, be adequate facilities for providing each patient with a clean set of blankets. S. L. W.

Tablet Making, Influence of Physical and Mechanical Factors in. P. L. Seth. (D.Sc. (Nat.) Thesis, Zurich, 1956.) This printed thesis describes work done under Prof. Munzel. The author analyses the tabletting process and selects certain aspects for investigation. He extends the work of Munzel and Kagi in separating tabletting additives into two classes—"lubricants" (materials facilitating the smooth ejection of the formed tablet by reducing the tendency to stick to the die) and "glidants" (materials improving the flow properties of the granules). Several types of natural and treated starches are assessed empirically for their glidant properties by measuring the improvement of flow of a standard lactose granulation to which varying proportions of the material under test have been added. Using the flow rate of the standard granule as a reference, the glidant properties of the starches are found to be twice as effective as those of talc. Of the starches and their derivatives the best results are obtained with potato starch, but as a general group they are found to possess little or no lubricating properties. A modified Brinell press is used to measure the influence of increasing compacting pressure on the corresponding ejection force and a linear relation is obtained over the small range considered. The mechanism of the action of the lubricant is discussed. Using the same press and two granule formulations ((*a*) starch/lactose, (*b*) phenacetin) the effects of increasing compacting pressure and increasing moisture content of the granules on tablet strength (Monsanto "hardness") and disintegration times are reported. Some attempt to investigate the effect of storage condition is also made. Studies are made of the conditions for preparing tablets of lactose which meet the requirements of homeopathic specifications; of the difference in properties of tablets compressed with eccentric and rotary types of tablet machines and of the effect of altering tablet shape and size on the strength and disintegration times. D. T.

PHARMACOLOGY AND THERAPEUTICS

5-Hydroxytryptamine, Release of, by Benzoquinolizine Derivatives with Sedative Action. A. Pletscher. (*Science*, 1957, **126**, 507.) It is known that reserpine causes a release of 5-hydroxytryptamine (5-HT) from the brain, intestine and platelets. After one large dose of reserpine the 5-HT content of these tissues decreases to approximately one tenth of the normal level and remains low for several days. Among the rauwolfia alkaloids, only those with a tranquillising action show this effect. It has now been found that various benzoquinolizine derivatives also release 5-HT. In mice and rabbits, these compounds produce sedation without hypnosis. Among the derivatives examined, 2-oxo-3-*iso*butyl-9 : 10-dimethoxy-1 : 2 : 3 : 4 : 6 : 7-hexahydro-11bH-benzo[a]quinolizine (compound I) showed the most marked sedative and 5-HT-releasing activity. After injection of 40 mg. of compound I per kg. the maximum depletion of brain 5-HT occurred within 30 minutes. During the 4 hours after the injection of compound I there was a considerable increase in the urinary excretion of 5-hydroxyindoleacetic acid, the major metabolite of 5-HT. Pretreatment with *iso*propyl*iso*nicotinic acid hydrazide prevented this depletion of 5-HT. Despite these similarities between compound I and reserpine there were some differences; chiefly in the time required to reach a maximum depletion of brain 5-HT, in the maximum degree of depletion obtainable, and in the time necessary for recovery of the 5-HT levels. These benzoquinolizine derivatives are thus a second group of substances which, like the centrally acting rauwolfia alkaloids, cause both sedation and 5-HT depletion of the brain. Further investigation may lead to an explanation of the role of 5-HT in brain function. M. M.

Morphine and Amiphenazole, Antagonism Between. J. Mercier and F. H. Shaw (*Thérapie*, 1957, **12**, 493.) Experiments were carried out in unanaesthetised rabbits to determine the effect of amiphenazole on the motor and respiratory depression induced by doses of 10 mg. or more of morphine per kg. body weight. In all cases amiphenazole was shown to antagonise the action of morphine on the respiration. The main effect of amiphenazole was on the respiratory rhythm, although in about half the rabbits the amplitude was also increased. Electroencephalographic studies in dogs showed that amiphenazole eliminates the slowing of the trace due to morphine, and antagonises its depressant effect on the reactivation of the reticular system. G. B.

Novobiocin and Erythromycin in the Treatment of Burns. E. J. L. Lowbury. (*Lancet*, 1957, **2**, 305.) This is an investigation carried out over a period of 3 months to assess the therapeutic value of concurrent systemic administration of novobiocin and erythromycin in patients whose burns were colonised by *Staphylococcus aureus* sensitive to these antibiotics, and to test the effect of using this mixture of antibiotics on the incidence and emergence of staphylococci resistant to either or both of them. Adult dosage was erythromycin 300 mg. six-hourly, novobiocin 500 mg. 12-hourly. The majority of patients were treated by the "closed" method, penicillin cream being applied at every change of dressings, until the time of skin-grafting or until the burn was healed. The "exposure" method was used on some burns, with repeated local insufflation of penicillin-lactose powder. The results showed that *Staph. aureus* was cleared

from a higher proportion of covered burns treated with the combined antibiotics (34 out of 49, 68 per cent) than from comparable burns receiving no chemotherapy (3 out of 31, 10 per cent). The therapeutic effect of the mixture was significantly greater than that of either of the two drugs used alone. Patients treated by the exposure method usually did not lose their staphylococci when receiving erythromycin and novobiocin. The incidence of erythromycin-resistant staphylococci fell during the first 4 weeks of a period when the two drugs were being used in combination. Some degrees of resistance began to appear to novobiocin in the second week, and there was a gradual increase in the numbers of staphylococci resistant to erythromycin and slightly resistant to novobiocin from the 5th week onwards. In several trials which showed a selective prophylactic or therapeutic action against *Staph. aureus* the results of skin-grafting were better in treated patients than in the controls. The local pathogenicity of *Staph. aureus*, however, is insufficient to warrant routine chemotherapy against the organism in burns. S. L. W.

Oximes and Atropine in Sarin Poisoning. B. M. Askew. (*Brit. J. Pharmacol.*, 1957, **12**, 340.) It has been shown previously that two oximes, mono*iso*nitrosoacetone (MINA) and diacetylmonoxime (DAM), exert a marked protective effect in rats poisoned with *iso*propyl methylphosphonofluoridate (sarin). Although less active in other species, it seemed possible that they might be effective in sarin poisoning when administered in conjunction with atropine. A third oxime, pyridine-2-aldoxime methiodide (PAM) has also been studied. It was found that when treatment commenced 15 minutes before the administration of the sarin, atropine enhanced the protective effect of MINA and DAM 2 to 3 times and of PAM 9 to 10 times, in mice and rats. In mice, rats and guinea pigs, atropine doubled the protective effect of all 3 oximes when given 30 seconds after sarin. Atropine given to monkeys 1 minute after sarin raised the LD50 approximately 3 times. When given in conjunction with MINA or DAM, the LD50 of sarin was raised 7 to 14 times. DAM is less toxic than either MINA or PAM and can therefore be given in somewhat higher doses. However, it is only a poor reactivator of cholinesterase inhibited by sarin; a property of considerable importance in anticholinesterase poisoning. It is therefore likely to be of less importance than MINA or PAM as an antidote in anticholinesterase poisoning. M. M.

Pethidine-Levallorphan Mixtures, Analgesic Action of. A Herxheimer and C. Sanger. (*Brit. med. J.*, 1957, **2**, 802.) A comparison was made between the analgesia produced by intravenous injections of (*a*) pethidine 22·5 mg., (*b*) pethidine 22·5 mg. + levallorphan 0·075 mg. (dose ratio 300:1), (*c*) pethidine 22·5 mg. + levallorphan 0·15 mg. (dose ratio 300:2), and (*d*) physiological saline solution. The effects of these drugs on ischaemic muscle pain and on the thermal pain threshold were measured in 5 normal men. The pethidine-levallorphan mixtures produced no less analgesia than did pethidine; the mixture containing the smaller amount of levallorphan (*b*) produced significantly greater analgesia than did pethidine. This might be due to the fact that the lower dose of levallorphan might cause vasodilatation and/or sweating, and so raise the threshold, while with the higher dose the antagonism for pethidine becomes manifest. On the other hand there is some indication that levallorphan is a weak analgesic, and the rise in threshold may be due to an analgesic action added to that of pethidine. S. L. W.

5-Phenylthiazolidine-2:4-dione (2:4-Dihydroxy-5-phenylthiazole), Pharmacology of. A. Shulman. (*Aust. J. exp. Biol. med. Sci.*, 1957, **35**, 289.) The object of this paper is to consider the hypnotic properties of 5-phenylthiazolidine-2:4-dione (P.T.D.) and to present evidence suggesting its possible value as an antiepileptiform agent and to indicate that its associated administration will both antagonise and potentiate selected pharmacological actions of its parent substance, 2:4-diamino-5-phenylthiazole hydrochloride (amiphenazole). Evidence is also presented from both *in vivo* and *in vitro* experiments which indicates that amiphenazole may be metabolised to P.T.D., possibly through the intermediate substance 2-amino-4-hydroxy-5-phenylthiazole. It was found that P.T.D. produces narcosis in mice which is reversed by the barbiturate antagonist bemegride. It also potentiates the hypnotic action of pentobarbitone sodium in mice. P.T.D. protects mice against the convulsant action of leptazol. Further, it antagonises the respiratory stimulant and convulsive properties of its parent substance amiphenazole, in mice. This is followed by an increased depth of narcosis and an increased incidence and rapidity of death, thus indicating that the latter substances may be metabolised to the former during this process of antagonism. A similar interaction between convulsant and hypnotic barbiturates has been noted. As there appears to be a possibility that amiphenazole may be metabolised in the body to yield P.T.D., which has been shown to potentiate barbiturate narcosis, it would be advisable to be more cautious in the use of amiphenazole in the treatment of barbiturate overdosage. Nevertheless very large doses of amiphenazole have been given in combination with bemegride in the treatment of barbiturate intoxication without harmful effects. M. M.

Piperazine in the Treatment of Ascariasis. L. G. Goodwin and O. D. Standen. (*Brit. med. J.*, 1958, **1**, 131.) Various piperazine salts were given as a single large oral dose in the treatment of 770 cases of ascariasis in the Gambia. With piperazine citrate, adipate and phosphate a dose equivalent to 3 g. of piperazine hexahydrate gave complete clearance in 76 per cent of cases: a 4-g. equivalent gave complete clearance in 82 to 89 per cent of cases. Piperazine sebacate and stearate gave clearance in 86 per cent of cases given a 3-g. equivalent, but were objectionable on grounds of taste or bulk. It was concluded that the efficiency of piperazine preparations is directly related to the content of base and is little influenced by the nature of the salt. Piperazine citrate syrup was found to be stable at high temperatures, to be as effective as solid citrate, adipate or phosphate, and to be of more practical value than tablet preparations in mass treatment owing to rapidity of dosage, rigidity of control, and palatability. No toxic side-effects were observed after a single dose of 4 g. of piperazine. S. L. W.

Piperazine in the Treatment of Hookworm. L. G. Goodwin and O. D. Standen. (*Brit. med. J.*, 1958, **1**, 135.) Of 2 children, aged 8 and 11 respectively, infected with hookworm, one was treated with 900 mg. of piperazine adipate three times daily for 7 days, and the other with 1 g. of piperazine phosphate three times daily for 7 days. Neither patient showed any significant decrease in egg count at the end of the course of treatment, but on subsequent treatment with a single dose of 2 ml. of tetrachlorethylene egg counts were reduced to nil in both cases in 24 hours. A third child aged 6 months, not given piperazine treatment, was also cleared of ova after a single dose of 0·25 ml. of tetrachlorethylene. S. L. W.

Piperazine in the Treatment of Tapeworms. L. G. Goodwin and O. D. Standen. (*Brit. med. J.*, 1958, **1**, 133.) One group of 15 patients in Tanganyika harbouring *T. saginata* was given a dose of piperazine citrate equivalent to 3 g. of hexahydrate, and on the following morning were given 5·3 ml. of extract of male fern, followed 2 hours later by 2 oz. of magnesium sulphate. A second group of 15 patients was treated with extract of male fern and purge alone. The number in which tapeworm heads were found in the stools was greater in the first group but the difference was not statistically significant. Piperazine used alone was found to be inefficient. It would be of advantage to investigate the effect of giving the dose of piperazine only 5 to 6 hours before giving the male fern. A systematic method of examining stools for tapeworm heads is described.

S. L. W.

Preludin, Euphoriant Effects of. J. B. Randall. (*Brit. med. J.*, 1957, **2**, 508.) A clinical trial of Preludin in 147 patients suffering from mild depressive and psychoneurotic conditions showed that it has effects similar to those of amphetamine. It appeared that a dose of 25 mg. twice daily produced euphoriant and stimulant effects more powerful than those produced by 5 mg. of amphetamine twice daily. Of the 147 patients, 87 appeared to be improved, 17 were unchanged, and 43 complained of symptoms indicating that the drug had an adverse effect. Fifty-four out of 84 cases of depression were significantly improved, as were 17 of 33 cases suffering from hysteria, 9 out of 13 obsessional states, 4 out of 6 personality disorders, and 3 out of 8 anxiety states. In addition to anorexia, some patients complained of insomnia, excitement, palpitations, trembling, dryness of the mouth, abdominal pain, and sensations of increased energy. Mild depersonalisation also occurred, and elevation of mood, increased mental activity and concentration were reported. In 2 cases appetite was increased, 2 further patients reported symptoms of hunger, and in 1 case there was a definite increase in weight. Weight reduction was not a significant finding as there was very little voluntary reduction of food intake. There is no doubt that the drug is pharmacologically active, and it would appear that it should be classified under the same pharmaceutical schedule as the amphetamines. S. L. W.

Propoxyphene Hydrochloride, Comparison of, with Codeine as an Analgesic. C. M. Gruber. (*J. Amer. med. Ass.*, 1957, **164**, 966.) Propoxyphene hydrochloride (α-(+)-2-propionoxy-4-dimethylamino-1 : 2-diphenyl-3-methyl butane hydrochloride) was compared for its effectiveness as an analgesic with codeine phosphate in 101 patients suffering from chronic pain due to arthritis, malignancy, neuritis, fractures or peripheral vascular disease. Five medicaments in identical capsules were administered orally 4 to 6 times daily; the capsules contained (1) a placebo, (2) 32·5 mg. of codeine, (3) 32·5 mg. of propoxyphene, (4) 65 mg. of codeine, and (5) 65 mg. of propoxyphene. Each medicament was given for 3 consecutive days, the placebo being given on the middle 3 days (7th, 8th and 9th). In equal doses by weight propoxyphene hydrochloride and codeine phosphate were equally effective in reducing pain and discomfort: both drugs were more effective in doses of 65 mg. than in doses of 32·5 mg., and both drugs were appreciably more effective than the placebo. Codeine in doses of 65 mg. produced a significant number of gastrointestinal side-effects; these reactions were much less frequent with the same dose of propoxyphene. In comparison with the placebo, codeine and propoxyphene produced comparable increases in the number of central nervous system side-effects. S. L. W.

Tolbutamide, Clinical Experience with. G. Walker, J. D. H. Slater, E. K. Westlake and J. D. N. Nabarro. (*Brit. med. J.*, 1957, **2**, 323.) This paper presents the results of a trial of tolbutamide in 72 diabetic out-patients observed for up to one year. The patients were not grossly obese and had "mild" diabetes that could not be satisfactorily controlled by diet alone. Their age varied between 22 and 78 (mean 53 years) and the duration of the diabetes between 1 and 30 years (mean 6·6 years). Of the 72 patients, 41 had previously been treated by diet alone, 19 were transferred from carbutamide, and 12 from insulin. Patients transferred from carbutamide were initially given the same dose of tolbutamide. Those who had been taking insulin were given reduced doses for a few days and were then started on tolbutamide. Patients who had had neither carbutamide nor insulin were observed on a strict diet for a month and if their mid-morning blood sugar remained above 200 mg./100 ml. they were given tolbutamide: the starting-dose for these patients and for those transferred from insulin was 0·5 g. two or three times daily, taken with the main meals. The dose was subsequently adjusted to a maximum of 4 g. daily according to the blood sugar response. Ketonuria was regarded as an indication for stopping the drug and resuming insulin. Nineteen of the patients stopped treatment for the following reasons; resistance (requiring insulin), 2; failure to respond, 6; rash, 2; abdominal symptoms, 4; not required, 1; irregular attendance, 2; returned to insulin at own request, 2. Of the 53 patients who had not been treated with carbutamide, 7 showed no response, 33 showed an immediate response and 13 a delayed response: 20 of the patients (61 per cent) who showed the immediate response and 9 (69 per cent) who showed the delayed response appear to be satisfactorily controlled by tolbutamide. All patients who had responded to carbutamide did so to tolbutamide but one became resistant to it. Of 26 patients complaining of diabetic symptoms (thirst, polyuria, and pruritus vulvae), 23 responded to tolbutamide and their symptoms were relieved as the blood sugar fell. In 22 of the 53 still taking tolbutamide control is unsatisfactory as judged by the mid-morning sugar. The authors conclude that about 50 per cent of patients with "mild" diabetes that cannot be controlled by diet alone will benefit from the drug, but that as its mode of action and possible long-term ill-effects are not yet known it should be used cautiously. S. L. W.

Tolbutamide in the Treatment of Diabetes. W. J. H. Butterfield, I. K. Fry, C. Hardwick and H. E. Holling. (*Brit. med. J.*, 1957, **2**, 325.) There is no single test which will serve to distinguish which patient will ultimately be satisfactorily controlled by tolbutamide, and a therapeutic trial is necessary for each patient. (Details are given of a scheme which has been found useful in testing the response of various types of patient to tolbutamide.) The rapidity of response to tolbutamide varies from patient to patient, so that a therapeutic trial should last for 3 weeks and should be cut short only if it appears the diabetes is getting out of control. Tolbutamide is less likely than insulin to produce a hypoglycaemic attack as its full effect takes place about 4 hours after administration, by which time the next meal is due. If satisfactory control is achieved the patient may be maintained indefinitely on up to 3 g. of tolbutamide daily. There should be no relaxation of dietary restrictions. Side-effects are few, skin rashes being the most common complication. Blood dyscrasias are rarely seen, and renal damage has not been encountered. It is not possible at present to assess the value of tolbutamide in the prevention of diabetic complications such as arterial disease, retinitis, neuritis, and renal disease, but it seems unlikely

that it will be more effective than insulin. It will not prevent ketosis or the exacerbation of the diabetic state associated with infection or trauma. S. L. W.

Voacamine, an Alkaloid from *Voacanca africana*, Pharmacology of. A. Quevauviller and O. Blanpin. (*Thérapie*, 1957, **12**, 635.) The cardiotonic action of voacamine is due to a direct action on the heart muscle. Its toxicity (determined in animal experiments) is 100 to 250 times less than that of digitoxin, and it kills by causing respiratory failure. The camphorsulphonate is about half as toxic as the equivalent amount of sulphate. Voacamine has a depressant effect on the central nervous system. It has a hypotensive action due to a parasympathomimetic and sympatholytic effect, and causes contraction of the smooth muscle of the blood vessels and intestine. The action of voacamine resembles that of the total alkaloids of *Voacanca africana*, with the exception of certain digitoxin-like effects, which may be due to the presence of voacorine. G. B.

APPLIED BACTERIOLOGY

Antimycotic, 2:2-Dihydroxy-5:5-dichlorodiphenylsulphide, Evaluation of. L.-G. Allgrén and Å. Frisk (*Svensk farm. Tidskr.*, 1957, **61**, 637.) The fungistatic effect of 2:2′-dihydroxy-5:5′-dichlorodiphenylsulphide was determined by a serial dilution method, using *Candida albicans* and *C. tropicalis* as test organisms. The substance showed a satisfactory fungistatic action. Doses of 1·0–1·5 mg./g. injected subcutaneously in the form of an oily suspension were lethal to mice. Rabbits received 0·25 g./kg. or more intramuscularly without untoward effect. In clinical investigations, uncoated tablets gave rise to gastric upset, especially when taken on an empty stomach. Intramuscular injections (in oil) caused local pain, and suppositories caused considerable anal irritation and pain. A slight improvement was observed in 5 of 17 cases, mainly of bronchial infections, treated with the drug. The best result was obtained in a case of *Candida* cystitis. The determination of 2:2′-dihydroxy-5:5′-dichlorodiphenylsulphide in serum was carried out by extracting with ether and purifying the extract. The difference in optical density at 323 mμ between acid and alkaline solutions was measured and the concentration calculated. Recovery on extraction was 90–100 per cent, and the determination was reasonably accurate with concentrations above 1 mg./ml. G. B.

Bacteria in Droplets, Action of Disinfectants on, as Compared with Large Volumes. R. C. Valentine. (*J. gen. Microbiol.*, 1957, **17**, 474.) Most work on disinfectant actions of chemicals has been restricted to the use of relatively large volumes of bacterial suspensions; little work has been done on bacteria suspended in droplets because most methods of determining viability are not applicable to such small samples. The urea method of Valentine and Bradfield (*J. gen. Microbiol.*, 1954, 11, 349) provided a suitable method of estimating viability in droplets. The organism used was a paracolon bacterium and test suspensions were prepared from 18 hour growths. Droplets were formed in a platinum loop, which was then held just above the suspension from which the droplet had been taken, the end of the tube having been closed. It was found that the bactericidal action of low concentrations of copper sulphate was much less in the drops than in the bulk suspension, provided the suspension was unwashed. The difference in killing in droplets and in bulk became smaller when suspensions were washed and became negligible when the washing was repeated several times. Phenol was found to be equally toxic to washed or

unwashed suspensions. At phenol concentrations of 0·1 and 0·2 per cent, there was markedly more killing in the drops than in the bulk suspension, but this effect was not observed at higher phenol concentrations. The results with copper sulphate were explained by the concentration of protein at the surface of droplets of unwashed suspensions. This protein decreases the toxicity of copper ions. Phenol, however, itself lowers surface tension and becomes concentrated at the surface of the droplet. From a calculation of the time required for half the bacterial population of a droplet to pass to, and be held in, the surface layer it is suggested that the organism used, although it is non-flagellate, appears to move about five times faster than would be expected from Brownian movement alone. B. A. W.

Nystatin Sensitivity of *Candida* Strains. R. F. Jennison and P. Stenton. (*J. clin. Path.*, 1957, **10**, 219.) In view of reports of the use of nystatin in the treatment of clinical conditions and in prophylaxis of *Candida* infections in patients treated with broad-spectrum antibiotics and cortisone, it was desirable to develop a rapid routine test for sensitivity to this antibiotic. Two methods were studied: a serial dilution technique and a blotting paper disc method. Serial dilutions of nystatin were made in a broth containing 3 per cent glucose and Andrade's indicator at pH 7·2. Penicillin and streptomycin were included in order to inhibit growth of any bacterial contaminants. Development of turbidity was taken as the first indication of growth. Although pH 7·2 is high for growth of *C. albicans*, the use of a solution of acid reaction was precluded by the instability of nystatin. An inoculum of 0·02 ml. of a 48 hour broth culture was added to 5 ml. volumes of broth which were incubated at 37°. Results of turbidity and change of indicator colour were read after 2, 3 and 5 days. The paper disc method employed 8 mm. diameter discs (Ford Mill 428) impregnated with differing amounts of nystatin (*iso*propanol solution) and dried. Blood or nutrient agar plates were seeded with 6 hour *Candida* culture and incubated overnight at 37° after introduction of the discs. Zones of inhibition were difficult to measure except by matching against reference white circles painted on black cards. Results are given for the sensitivity of 76 strains of *C. albicans* and for 14 strains of other species of *Candida*; some of these were stock strains and others had been isolated from cases of vaginal infection. All strains were sensitive to nystatin, the mean inhibitory concentration at 48 hours in broth being 3·2 μg./ml. It was found that paper discs impregnated with 12·5 μg./ml. were stable on refrigeration for several months and gave an average zone of inhibition of 16 mm., which was not dependent upon the type of culture medium used. B. A. W.