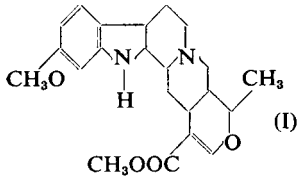
ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

3-Epi-α-yohimbine, A New Rauwolfia Alkaloid. F. E. Bader, D. F. Dickel, C. F. Huebner, R. A. Lucas and E. Schlittler. (*J. Amer. chem. Soc.*, 1955, **77**, 3547.) The isolation from *Rauwolfia serpentina* of a new alkaloid isomeric with yohimbine and identified as 3-epi-α-yohimbine is reported. It is demonstrated by degradative and synthetic evidence that 3-epi-α-yohimbine has the 3-epialloyohimbane configuration and represents the first recognition of this ring system in a natural product. The structure is confirmed by the isomerisation to α-yohimbine. Neither the alkaloid itself nor any of its synthetic esters resembled reserpine in general pharmacological activity. A. H. B.

Tetraphyllin and Tetraphyllicine, New Alkaloids from *Rauwolfia tetraphylla* L. C. Djerassi and J. Fishman. (*Chem. and Ind.*, 1955, 627.) Four alkaloids were obtained in a pure state from extracts of the roots of *Rauwolfia tetraphylla* L. The presence of additional ones is indicated by paper chromatography. Reserpine (*ca.* 0·03 per cent. yield) was separated easily by virtue of the chloroform solubility of its acetate. Chromatography of the remaining alkaloids on alumina gives 3 alkaloids which were eluted in the following order. Elution with benzene followed by crystallisation from methanol led to colourless plates of a new alkaloid named *tetraphyllin*, $C_{22}H_{26}O_4N_2$ m.pt. 220 to 223° C. (decomp.) $[\alpha]_D^{28}$ − 73° (chloroform) − 35° (pyridine). The ultra-violet absorption spectrum was essentially superimposable with that of reserpinine. Infra-red and other evidence suggests that tetraphyllin has the structure (I), and is thus a stereoisomer of reserpinine and *iso*reserpinine. With increasing polar solvents (benzene/chloroform 7:3) there was eluted another new alkaloid *tetraphyllicine*, $C_{20}H_{26}N_2$, which crystallised from acetone as needles, m.pt. 320 to 322° C. $[\alpha]_D^{27}$ + 21° (pyridine), pKa 8·5. The ultra-violet absorption spectrum is completely superimposable with that of ajmaline, and the infra-red spectra of the two alkaloids is similar. The most polar alkaloid obtained crystallised from methanol as bright yellow needles m.pt. *ca.* 270° $\lambda_{max.}$ in chloroform 5·84 and 6·18 μ. It was shown to be identical with serpentinine.



(I)

A. H. B.

***Veratrum viride*, New Hypotensive Ester Alkaloids of.** G. S. Myers, P. Morozovitch, W. L. Glen, R. Barber, G. Papineau-Couture and G. A. Grant. (*J. Amer. chem. Soc.*, 1955, **77**, 3348.) The isolation of the five hypotensive ester alkaloids *iso*germidine, germbudine, neogermbudine, desacetylneoprotoveratrine and veratetrine (neoprotoveratrine) from commercial *Veratrum viride* is described. *iso*Germidine is germine monoacetate-mono-α-methyl-butyrate. Germbudine is a diester of germine which gives germine, α-methylbutyric acid and the high melting diastereoisomer of αβ-dihydroxy-α-methylbutyric acid upon hydrolysis. Desacetylneoprotoveratrine is a known triester of protoverine which gives one mole each of acetic acid, α-methylbutyric

acid and the high melting isomer of αβ-dihydroxy-α-methylbutyric acid on hydrolysis. Veratetrine is shown to be a tetraester of protoverine and to be identical with the alkaloid neoprotoveratrine. All five ester alkaloids are powerful antihypertensive agents. In comparison with a mixed alkaloidal preparation from *Veratrum viride* Deravine which produced a 30 per cent. fall in the mean arterial blood pressure of the anæsthetised dog at a dose of 2 μg. per kg., administered intravenously over a 10 minute period, the relative activities of germbudine, neogermbudine, *iso*germidine, veratetrine and deacetylneoprotoveratrine are 0·8, 1·0, 0·1, 1·5 and 0·4, respectively. The infra-red spectra of the alkaloids are recorded. A. H. B.

ANALYTICAL

Hyoscine Hydrobromide in a Tablet Mixture, Determination of. R. B. Scott, E. J. Schoeb and J. M. Vanderbelt. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 377.) By the use of the following method it is possible to determine hyoscine hydrobromide with a mean recovery of about 97 per cent. from material containing only 0·25 per cent. of the alkaloidal salt admixed with diphenhydramine hydrochloride. The determination depends upon the infra-red absorption band of hyoscine at 11·82 μ. Interference due to the absorption by diphenhydramine (maximum at 11·58 μ) is minimised by the use of a selective solvent and corrected by a geometric procedure. After a preliminary extraction of a sample of about 1·25 g. of tablet material with dehydrated ethanol, the residue is dried in a vacuum oven at 75° C. for 4 hours to remove the ethanol. The dry material is extracted with dimethylacetamide at 50° C., the excess of solid being separated by centrifuging. The solution is examined in an infra-red spectrophotometer between 11 and 12 μ, against a solvent blank. A tangent is drawn to the absorption minima at 11·02 and 11·82 μ and the distance from this to the maximum at 11·61 μ is a measure of the hyoscine hydrobromide content. The dimethylacetamide used must be saturated with sodium chloride and kept dry to avoid attack on the spectrophotometer cells. The method is applicable only to uncoated tablets; coated tablets give low results. G. B.

Morphine, Elution from Ion Exchange Resins. C. H. Van Etten. (*Analyt. Chem.*, 1955, **27**, 954.) Experiments were made to find conditions under which morphine could be quantitatively removed from strong anion and cation exchange resins using micro ion exchange columns and samples of about 10 mg., and results are reported which show the effect of the degree of cross linkage of the exchange resin on the elution of morphine, and the effect of *p*H and ionic concentration of the elutriant. Dowex 50 (a strong, sulphonic acid, cation exchange resin) and Dowex 1 (a strong, quaternary ammonium anion exchange resin) of different degrees of cross linkage were used and complete elution was obtained from the 1, 2, and 4 per cent. cross-linked cation resins with either ammonium or sodium hydroxide, but incomplete elution was obtained with 8 and 16 per cent. cross-linking. Conditions for complete elution from the anion resin were more restricted, quantitative elution being obtained only for the 1 per cent. cross-linked resin with acetic acid as the elutriant. The elution of codeine and narcotine also was incomplete from resins having more than a certain degree of cross linkage. Factors affecting elution were the degree of cross linkage of the resin and the size of the ion, the *p*H of the elutriant especially in case of ampholytes, and the effect of the ionic concentration of the elutriant on volume changes of the exchange resin. Both lysine and aneurine were, however, incompletely eluted under all conditions examined. R. E. S.

Neomycin, Turbidimetric Assay of. J. Dony and J. Conter. (*J. Pharm. Belg.*, 1955, **10**, 104.) Solutions are prepared in phosphate buffer solution, *p*H 8, containing 6, 9, 12, and 15 μg. of a standard preparation of neomycin. To 1 ml. of each solution is added 9 ml. of a nutrient broth medium (*p*H 7), inoculated with *Klebsiella pneumoniæ*. Six tubes are prepared for each concentration. The tubes are incubated for 3 to 3·5 hours at 37° C., after which growth is stopped by the addition of 2 drops of solution of formaldehyde. The turbidity of each suspension is measured photoelectrically and a standard curve is prepared. The same procedure is carried out with samples of the neomycin under test containing the equivalent of about 11 μg. of neomycin base per ml. in phosphate buffer, *p*H 8. The potency is calculated by reference to the standard curve. Reproducible results have been obtained with samples of neomycin sulphate, neomycin ointment and ointment of neomycin sulphate with bacitracin. G. B.

Nitro-Nitrogen, Determination of. P. R. W. Baker. (*Analyst*, 1955, **80**, 481.) It was found that the sealed tube micro-Kjeldahl method of White and Long (*Analyt. Chem.*, 1951, **23**, 363) could be used for the reduction of nitro compounds by the addition of 50 mg. of thiosalicylic acid or glucose to the digest; 25 mg. were found to be insufficient. Results are given for a number of nitro-compounds. For compounds containing *N*–*N* linkages, glucose was slightly more efficient than thiosalicylic acid, but the results did not approach the theoretical values with either reagent. The temperature of 470° C. was found to be dangerously high and 45 minutes at 420° to 440° was sufficient. Nitro compounds with the structure $-C-C_6H_5-NO_2$, oximes, and *N*-oxides did not require reduction. R. E. S.

Sulphate Ion, Colorimetric Determination of. J. L. Lambert, S. K. Yasuda and M. P. Grotheer. (*Analyst. Chem.*, 1955, **27**, 800.) A colorimetric procedure for determining sulphate ion in the range of 0 to 400 p.p.m. is described, which uses an insoluble thorium borate-amaranth dye reagent; dye molecules are released from the reagent in direct proportion to the concentration of sulphate ion and are determined from their absorption at 521 mμ. Bicarbonate, phosphate, and fluoride ions interfere by reacting with the thorium-dye reagent to release dye into solution. The addition of lanthanum ion removed the fluoride ion with little effect on the sulphate ion while bicarbonate ion could be eliminated by passing the sample solution through Amberlite IRC-50(H) weak acid ion exchange resin. R. E. S.

Vitamin B_6, Assay of. N. A. Diding. (*Svensk farm. Tidskr.*, 1955, **13**, 321.) The paper describes the use of *Escherichia coli* (154–59 L, Dr. Davis' collection) in the microbiological assay of pyridoxine, pyridoxal and pyridoxamine. Details of the procedure and of the medium are given, the organism being incubated in tubes for 20 hours at 37° C.; growth is determined by measurement of the turbidity produced. Pyridoxal is a little more active than pyridoxine towards the organism, while for pyridoxamine a concentration about 10 to 20 times that for pyridoxine is necessary to obtain the same growth response; no growth is shown in blank tubes. Sterility is not absolutely necessary in performing assays, since the minimal medium used is too poor to permit growth from most contaminating organisms. The assay can be used for vitamin B_6 in multivitamin preparations as there is no growth response with aneurine, riboflavine, nicotinic acid or pantothenic acid although vitamin-free casamino acid caused a marked increase in response. R. E. S.

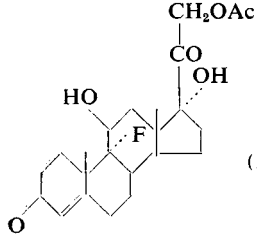
BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Catechol Amines, Inactivation of, by Liver Tissues. Chr. von Euler. (*Acta physiol. scand.*, 1955, **33**, Suppl. 118, 39.) When dopa is incubated with guinea-pig liver, dopamine, catechol acetaldehyde and catechol acetic acid may be demonstrated by chromatographic separation and formation of fluorescent condensation products with ethylenediamine. Noradrenaline, under the same conditions, forms catechol glycolic acid and catechol glycolaldehyde. Corbasil (3:4-dihydroxynorephedrine) forms no such similar products, indicating that it is not attacked by amine oxidase. The presence of large amounts of catechol acetic acid in normal urine suggests that this is formed by decarboxylation, deamination and subsequent oxidation of dopa. M. M.

Catechol Derivatives, Biologically Inactive in Urine. Chr. von Euler, U. S. von Euler and I. Floding. (*Acta physiol. scand.*, 1955, **33**, Suppl. 118, 32.) The normally occurring biologically active catechol amines (adrenaline, noradrenaline and dopamine) form only a small part of the total catechol compounds in urine. This is shown by a comparison of the biological activity with the strength of the fluorescence after condensation with ethylenediamine. It is suggested that it is catechol acetic acid, which is also present in urine, which gives an erroneously high value for the catechol content of urine when the ethylenediamine fluorescence reaction is used. This fluorescence method therefore is not suitable for the estimation of adrenaline and noradrenaline in urine. M. M.

1-Dehydro-9α-Fluorohydrocortisone Acetate: New Biologically Potent Steroid. R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler. (*J. Amer. chem. Soc.*, 1955, **77**, 3166.) A brief description of the preparation of 1-dehydro-9α-fluorohydrocortisone acetate (I) is given. It is the most potent glucocorticoid known; it possesses about 25 times the activity of hydrocortisone acetate in the mouse liver glycogen assay and in the rat systemic granuloma inhibition test.



(I)

A. H. B.

Noradrenaline and Adrenaline, Free and Conjugated, Preparation of Extracts of Urine and Organs for Estimation of. U. S. von Euler and I. Orwén (*Acta physiol. scand.*, 1955, **33**, Suppl. 118, 1.) This paper describes a modification of Euler's original procedure for the extraction of catechol amines from urine and tissue extracts. It is simpler and quicker and gives as great an accuracy. The method involves the adsorption of the free catechols on to aluminium oxide at a *p*H of 8·5 and subsequent elution with acid. Sulphuric acid is used when the solution is to be assayed biologically (80 per cent. recovery obtainable) and with oxalic acid when a fluorimetric determination is employed. Estimation of the conjugated catechol amine content is made as above, after an initial hydrolysis with boiling normal hydrochloric acid. M. M.

BIOCHEMICAL ANALYSIS

Blood in Urine, a Tablet Test for. E. J. Watson-Williams. (*Brit. med. J.*, 1955, **1**, 1511.) The tablets each contained citric acid 50 mg., barium peroxide 35 mg., *o*-tolidine 12·5 mg., and sodium carbonate 2·5 mg. If the tablets are kept in a closed screw-capped container they retain their sensitivity for at least 12 months. One drop of the urine to be tested is placed on an inch square of Whatman No. 1 filter paper and allowed to spread. A tablet is placed on the centre of the paper and 2 drops of cold tap-water are allowed to flow over the tablet. A definite blue colour appears round the tablet within 2 minutes if the urine contains at least 50 red cells/c.mm. or the equivalent concentration of hæmoglobin (150 μg./100 ml.). If a smaller quantity is present a blue colour develops after 2 minutes; and if none is present the tablet and the filter paper remain colourless for at least 15 minutes. The test is equally sensitive throughout the temperature range 4–37° C. If the urine is heated to 60° C. or boiled the test is much less sensitive. Variation of urinary *p*H 5–8 has no significant effect on the sensitivity, which is however slightly reduced if the urine is either very alkaline or very acid. False negatives may be encountered if the ascorbic acid content of the urine is high. False positives occur if the urinary concentration of iodide is greater than 20 mg./100 ml.; in these cases the urine should be boiled for 1 minute and immediately retested; if the colour is due to iodide it will then be deeper, whereas if due to blood a negative will be obtained. Pus, bromides and sweat give negative results, but any oxidising agent will give a false positive. In no case has hæmaturia been found by the pathological laboratory when the tablet has given a negative result. The tablet has been found particularly valuable as corroboratory evidence in a clinical diagnosis of cystitis or pyelitis, and as a daily test to discover when known hæmaturia ceases. It is also useful as an additional safeguard to prevent overdosage with anticoagulant drugs. S. L. W.

Chromium in Biological Media, Determination of. C. H. Grogan, H. J. Cahmann and E. Lethco. (*Analyt. Chem.*, 1955, **27**, 983.) A method is presented which consists of a wet or dry ashing of the sample, hypobromite oxidation of trivalent to hexavalent chromium, and spectrophotometric determination of the hexavalent chromium in the form of the red-violet complex formed on reaction with *sym*-diphenylcarbazide. The choice of wet or dry ashing depended on the type of material to be analysed; plasma or serum could be ashed equally well by either method; the wet ashing of filter paper was tedious, while the dry ashing proceeded smoothly; urine gave better results when wet ashed, as dry ashing yielded a difficultly soluble ash. Erratic results were obtained when egg albumin was dry ashed due to the transformation of the chromium present to refractory oxides or phosphates. The wet ashing process oxidation was performed with nitric acid and hydrogen peroxide; dry ashing was at 420° to 460° C. overnight. Recoveries of chromium, trivalent or hexavalent, added to human plasma ranged between 94 and 101 per cent. R. E. S.

Hydrogen Peroxide in Biological Materials, Estimation of. W. A. Andreae. (*Nature, Lond.*, 1955, **175**, 859.) A sensitive method is proposed for the estimation of hydrogen peroxide which employs the disappearance of the fluorescent peroxidase substrate scopoletin (6-methyl-7-hydroxy-1 : 2-benzopyrone). At concentrations up to $2{\cdot}5 \times 10^{-9}$ mole per ml., the intensity of fluorescence is proportional to the concentration of scopoletin. An aqueous solution of scopoletin is stable in diffused light and is not oxidised by either peroxidase or

hydrogen peroxide alone; with both present, however, oxidation with loss of fluorescence proceeds very rapidly. Results and graphs are given showing the quantitative relationship between the amount of hydrogen peroxide added and the disappearance of scopoletin using an aqueous extract of dehydrated horseradish; one mole of hydrogen peroxide was required for the oxidation of one mole of scopoletin, this simple relationship applying so long as 20 per cent. of scopoletin was present. Results are also given showing the rate of oxidation of scopoletin ($1{\cdot}2 \times 10^{-8}$ ml. per ml.) by pea juice (*p*H 6·8) with putrescine as source of endogenous hydrogen peroxide. Ascorbic acid, glutathione, and manganous ions interfered by competitively inhibiting the oxidation of scopoletin by peroxidase; esculetin and umbelliferone were also examined for fluorescence but scopoletin appeared to be the best fluorescent indicator for the peroxidative estimation of hydrogen peroxide, permitting the determination of amounts of endogenously produced hydrogen peroxide in the range of 10^{-10} mole.

R. E. S.

Noradrenaline and Adrenaline in Urine, Fluorimetric Estimation of. U. S. von Euler and I. Floding. (*Acta physiol. scand.*, 1955, **33**, Suppl. 118, 57.) A method for fluorimetric estimation of adrenaline and noradrenaline in urine is described. The urine extracts are prepared by adsorption on to aluminium oxide at *p*H 8·5 and elution with 0·3 N oxalic acid. The catechol amines in the extracts are oxidised to adrenochrome and noradrenochrome at *p*H 3·5 and 6·0 with potassium ferricyanide. The reaction is enhanced by zinc sulphate at *p*H 3·5. After treatment with strong alkali and stabilisation of the fluorescent product with ascorbic acid the fluorescence intensities are measured. At *p*H 6·0 the sum of the adrenaline and noradrenaline is determined and at *p*H 3·5 adrenaline plus about 4 per cent. of the noradrenaline. From these data and the relative fluorescence of adrenaline and noradrenaline the amounts of adrenaline and noradrenaline can be calculated. M. M.

CHEMOTHERAPY

Isoniazid in the presence of Hæmin, Destruction of. R. Knox, A. Albert and C. W. Rees. (*Nature, Lond.*, 1955, **175**, 1085.) When isoniazid (10^{-2}M) and hæmin (10^{-3}M) are shaken with air at 20° C. (*p*H 7·5) two substances are formed; di*iso*nicotinoylhydrazine (I) and *iso*nicotinic acid (II). Quantitative paper chromatography shows that after 24 hours half the isoniazid is unchanged and the other half is converted to equal parts of (I) and (II), (I) being an intermediate product in the formation of (II). Hæmin acts as a catalyst in the reaction; it also acts catalytically in very low initial concentrations of isoniazid; a concentration of isoniazid (10^{-4}M) falling to (10^{-7}M) in the presence of hæmin (10^{-4}M). Hæmin rapidly forms a hæmochromogen, with an excess of isoniazid or with less isoniazid plus a reducing agent—which is purple and distinct from other hæmochromogens. Solutions of this substance are stable only in the absence of air. Substance (I) slowly forms a hæmochromogen which may be the true catalyst as many hæmochromogens are more efficient oxidation catalysts than hæmin. The antagonism of hæmin to the action of isoniazid on *Myco. tuberculosis* was shown by adding hæmin to tubes containing isoniazid and *Myco. tuberculosis* in asparagine glycerol phosphate medium when the bacteria grow normally, but if its addition is delayed for a day growth is slow, and when addition is delayed for two or three days growth is entirely inhibited. Thus in three days the drug may reach a site in the bacillus inaccessible to hæmin or at too low an E_h to be oxidised, or isoniazid may irreversibly damage the cell in this period. G. P.

PHARMACY

NOTES AND FORMULÆ

Cetyltrimethylammonium Bromide, The Sterilisation of Blankets with. R. Blowers and K. R. Wallace. (*Lancet*, 1955, **268**, 1250.) Blankets were given a final rinse containing 0·036 per cent. cetyltrimethylammonium bromide (Cirrasol OD) after laundering with a non-ionic detergent (Lissapol N), which does not neutralise the bactericidal properties of the cationic surface-active agent. Before and after treatment the blankets were tested by pressing an inverted Petri dish firmly against each blanket and sweeping it across fairly rapidly and evenly so as to throw particles of dust and fluff on to the surface of the medium, and incubating the plate. The nutrient agar medium used contained 0·75 per cent. of Perminol COL to neutralise any cationic detergent in the sample. Before treatment large numbers of organisms were isolated from the blankets. After the treatment only a few organisms were detected, indicating that the process is an effective method of disinfection. Cetyltrimethylammonium bromide is active against *Staphylococcus aureus*, but is less effective against *Pseudomonas pyocyanea* than other organisms. The process is inexpensive to apply and does not damage the blankets. G. B.

Oil in Water Emulsions, Analysis of. T. Freen, R. P. Harker and F. O. Howitt. (*Analyst* 1955, **80**, 470.) A general method is given for the analysis, using ion exchange resins, of the constituents of emulsions stabilised by different types of detergents. Using columns of Zeo-Karb 225 in bead form mixed with powdered animal charcoal, percolation of soap solutions and soap stabilised emulsions gave clear liquors from which organic matter had been removed; percolation of the emulsion and subsequent elution with a series of solvents resulted in the isolation of the separate components. Emulsions stabilised by sodium cetyl sulphate were analysed successfully by this method; De-Acidite FF was used in the presence of cetyltrimethylammonium bromide. Using columns of Biodeminrolit (an intimate mixture of Zeo-Karb 225 and De-Acidite FF), percolation of lanolin—Lissapol N emulsions containing up to 1 per cent. of sodium chloride gave clear liquors, which on evaporation left no residue; columns containing powdered animal charcoal were equally effective but the Lissapol N was held too firmly for successful solvent elution. Lissapol N—soap-lanolin emulsions could be estimated accurately using a combination of the above methods. R. E. S.

PHARMACOLOGY AND THERAPEUTICS

Aldrin and Dieldrin, Autonomic Manifestations seen in Acute Poisoning with. C. W. Gowdey and G. W. Stavraky. (*Can. J. Biochem. Physiol.*, 1955, **33**, 272.) The parasympathomimetic actions of the insecticides aldrin (hexachloro-hexahydro-dimethano-naphthalene) and dieldrin (hexachloro-octahydro-epoxy-dimethano-naphthalene) were investigated in vagotomized and adrenalectomized cats under combined chloralose and urethane anæsthesia. Of the two, only aldrin had any peripheral effects, causing bradycardia and augmenting the effects of vagal stimulation on blood pressure and heart rate and of stimulation of the chorda tympani on blood pressure and salivary secretion from the decentralized sub-maxillary gland. Blood withdrawn five minutes after intravenous injection of aldrin showed a reduced rate of destruction of acetylcholine, assayed on the frog rectus abdominis muscle. These results are in accord with an anti-cholinesterase-like mode of action. Other effects included a potentiation of the excitability of spinal neurones to intra-arterial injections of acetylcholine, skeletal muscle twitches, potentiation of the crossed extensor reflex and

augmented transmission across the neuromuscular junction; large doses of the compound had a depressant action at these sites. More powerful actions common to both aldrin and dieldrin were stimulation of the vagal centres, hyperreflexia and a convulsant action. G. P.

Chlorpromazine in Psychiatric Disorders. I. M. Cohen. (*Amer. J. med. Sci.*, 1955, **229**, 355.) The experiences reported in this study cover a period of 9 months and were drawn from a series of about 1000 patients suffering from psychiatric illnesses of various types. Treatment with chlorpromazine was shown to be most effective where there is evidence of agitation, anxiety or aggression. In approximately 60 per cent. of the patients improvement occurred, varying in degree from reduction in intensity of symptoms to complete resolution of illness. Dosage requirements vary widely and it is believed that many failures with the drug are attributable to the use of inadequate dosage. In this series effective dosage for neurotics was in the range of 200–600 mg. daily and for psychotics from 400–800 mg. daily; as much as 2250 mg./day was administered without toxic effects. With rare exceptions psychogenic nausea and vomiting responded favourably to the drug; it was also effective in nausea and vomiting due to carcinomatosis, pregnancy, acute alcoholic gastritis and dumping syndrome, and the nausea and vomiting sometimes accompanying insulin shock therapy and electro-convulsive therapy. The most common early subjective complaints noted were dizziness, weakness, lethargy, dryness of the mouth and nasal congestion; less common were a burning sensation in the œsophagus, nausea and vomiting and constipation. Objectively, the most impressive finding was fall in blood pressure, but there was no case of circulatory collapse. Late effects included excessive appetite, blurring of vision, intense pruritus, photosensitisation, rest tremor and increased sexual urge. Swelling of the breasts and secretion of a colostrum-like fluid from the nipples were sometimes noted in female patients. The most frequent complication was dermatitis which occurred in about 10 per cent. of cases and usually appeared 2–3 weeks after starting treatment; it usually cleared in 3 or 4 days, and in most cases treatment could be resumed without a further recurrence. Jaundice occurred in 6 patients, and occasionally Parkinsonism developed, clearing in about 5–14 days after withdrawal of treatment. Rare instances of leucopenia and eosinophilia occurred but in no case of agranulocytosis. S. L. W.

Frenquel Corrects Certain Cerebral Electrographic Changes. F. Rinaldi and H. E. Himwich. (*Science*, 1955, **122**, 198.) Lysergic acid diethylamide (LSD–25) and mescaline induced changes in the electro-encephalograms of curarised unanæsthetized rabbits, consisting of disappearance or diminution of slower waves and increased frequency and decreased voltage of the fast low-voltage activity. Frenquel, (α-4-piperidyl benzhydrol hydrochloride), in suitable doses reversed these changes. It had been shown previously that this drug blocked the psychotic states induced in normal human subjects by LSD–25 (Fabing, *Science*, 1955, **121**, 208.) In the rabbit there was a direct relationship between the dose of hallucinogen administered and that of Frenquel necessary to reverse the subsequent EEG changes. Frenquel given alone had no effect on the EEG. Dyflos, amphetamine and Meratran (α-2-piperidyl benzhydrol hydrochloride), like the hallucinogenic substances, evoked fast low-voltage activity EEG patterns in rabbits, but Frenquel had no corrective action on the changes induced by these drugs, although one of them, Meratran, is a positional isomer of Frenquel. The blockade of LSD–25 and mescaline actions by Frenquel appeared to be limited to the central nervous system, since the mydriasis associated with these drugs was not affected by the blocking agent. G. P.

Hydergine, the Effect of, on Uterine Action. T. N. A. Jeffcoate and J. K. Wilson. (*Lancet*, 1955, **268**, 1187.) Hydergine, despite reports to the contrary, had slight oxytocic activity in patients in normal labour at term. Uterine activity was observed by clinical signs and by the use of a Lorand tocograph. Where uterine contractions had been induced by oxytocin, hydergine had no inhibitory activity; in some cases the two drugs acted synergistically. During and after the third stage of labour an apparent inhibitory action of hydergine was observed, but this may have been due to withdrawal of the drug at full cervical dilatation; similar inhibition has been reported where ergometrine or other ergot alkaloids were used during labour. G. P.

Hydrocortisone Ointment, A Valuation of. B. Russell, J. S. Pegum, N. A. Thorne and R. V. Grange. (*Lancet*, 1955, **268**, 1038.) The value of Hydro-Cortisyl ointment, a product containing 2·5 per cent. of hydrocortisone, in various skin conditions was assessed in comparison with concealed, alternating, self-contained controls, the patients themselves recording progress during 14 days. The controls used the vehicle alone, and the records were made on cards requiring an assessment of 4 grades of itching. Every patient was given the vehicle for a week and the medicated ointment for a week, the sequence being changed for each successive patient. In some cases, treatment was continued for several weeks. Some patients were given a 1 per cent. hydrocortisone ointment for comparison with the 2·5 per cent. preparation. The case notes and records were assessed by an independent observer. The vehicle itself, containing propylene glycol, polyethylene glycols and zinc stearate, was found to be remarkably effective as an emollient and antipruritic but its efficacy was far less than that of the medicated ointment in most conditions treated. Hydrocortisone ointment gave distinct or complete relief in 14 of 25 patients with anogenital pruritus, 10/21 with lichen simplex, 2/12 with infantile eczema, 3/22 with Besnier's prurigo, 9/23 with discoid eczema, 3/11 with idiopathic eczematous dermatitis of the hands, 7/11 with otitis externa, and 2/7 with itchy flexural and genital psoriasis. 1 patient complained of a burning sensation and in another infection increased during treatment. Only 1 patient was sensitive to the vehicle but relief was obtained with hydrocortisone in hydrous ointment. H. T. B.

2(β-Hydroxyethylaminomethyl)-1 : 4-benzodioxan Hydrochloride, Pharmacology of. R. F. Banziger, T. S. Miya and L. D. Edwards. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 302.) Of a series of derivatives of 2-aminomethyl-1 : 4-benzodioxan and 2-aminomethylcoumaran, the most effective antagonist of the pressor effect of adrenaline appeared to be 2(β-hydroxyethylaminomethyl)-1 : 4-benzodioxan. The compound was soluble in water, and non-irritating. It was active in dogs, cats and rats when given by mouth or by injection, the activity being of fairly short duration (1 to 2 hours). Larger doses were needed to produce adrenaline blockade of isolated organs such as ileum, uterus and heart. Intravenous injection into cats caused respiratory arrest, but this could be avoided by giving 2 mg./kg. intraperitoneally. After an interval of 30 minutes, 5 mg./kg. could be given intravenously without toxic effects. G. B.

5-Hydroxytryptamine, Action of, on Urine Flow and Chloride Excretion. V. Erspamer and P. Correale. (*Arch. int. Pharmacodyn.*, 1955, **101**, 99.) Further experiments are reported confirming that physiological doses of 5-hydroxytryptamine cause a significant reduction of diuresis in hydrated rats. Doses of 20 μg./kg. cause, over a period of 60 to 90 minutes, a 40 to 75 per cent. decrease in urine flow. A reduction in the absolute chloride content occurs but leaves unchanged the relative content. This is in contrast to the posterior pituitary antidiuretic principle which causes a conspicuous, absolute and relative increase in chloride excretion. G. F. S.

Miltown, a New Tranquilising Drug. L. S. Selling. (*J. Amer. med. Ass.*, 1955, **157**, 1594.) Miltown (2-methyl-2-*n*-propyl-1 : 3-propanediol dicarbamate) has been shown to possess a selective blocking action on interneurons; it produces relaxation of skeletal muscles without affecting respiration and other vital functions, and has important effects on the brain. The present study was made on 187 psychiatric patients. The drug was supplied in 400 mg. tablets, the usual dose being one tablet after each meal and one at bedtime. As soon as possible the dose was reduced, and the drug finally withdrawn. All patients had regular sessions of psychotherapy in addition to treatment with the drug. Patients were treated for periods ranging from less than a month to more than 8 months. In about half the patients withdrawal from Miltown could be effected within a week; in the other half gradual withdrawal was necessary and placebos were sometimes substituted towards the end. Only 3 of the patients were allergic to the drug, and 5 complained of gastric discomfort. One patient who hoarded a supply and ingested about 100 tablets within 24 hours suffered no serious adverse effects. Miltown was of considerable value in anxiety and tension states; of 86 patients complaining of these symptoms all but 7 showed marked improvement. The tension state was usually relieved in 3 to 4 months. Related psychoneurotic conditions, such as behaviour problems and conversion hysteria, were also favourably influenced. In alcoholism, Miltown helped to avoid serious withdrawal symptoms and assisted in keeping alcoholics sober after withdrawal was completed. In frank psychoses the results were not so favourable. The most dramatic reports of recovery or improvement came from those patients whose chief complaint was tension headache. Of 27 patients with this complaint 23 either recovered or were greatly improved. Miltown was very effective in producing sleep, and by adjusting the dosage it was found possible to produce sleep in every patient except in those suffering from a true psychotic depression. Patients who had previously been taking phenobarbitone and were put on to Miltown preferred the latter. By producing in the patient a feeling of ease and relaxation Miltown was found a useful adjunct to psychotherapy. S. L. W.

Miltown, Effect on Psychiatric States. J. C. Borrus. (*J. Amer. med. Ass.*, 1955, **157**, 1596.) This study involved 104 patients all of whom had failed to respond to barbiturate and mephenesin therapy. The largest group (67) had anxiety reactions. Favourable results were reported in 71 of the patients: 24 showed complete recovery, 17 obtained very favourable results, 30 reported some favourable effect, and the remaining 32 showed no appreciable benefit. Complete blood cell counts and urinalyses taken prior to and two months after continuous use of Miltown failed to reveal any evidence of toxic effect of the drug, and, within the limits of the dosage used, one to six 400 mg. tablets daily, no serious side-effects or toxic manifestations were noted. The chief side-effect was drowsiness which occurred in about half the patients during the first 2 weeks of medication but gradually subsided as therapy was continued. There were no complaints of dizziness, vertigo, nausea, vomiting, diarrhœa or dermatological manifestations. The drug seemed most effective in patients with both acute and chronic anxiety reactions. The ability to obtain more restful sleep was a prominent finding; the other chief effects of the treatment were lessening of tension, more complete relaxation and ability to feel at ease in groups. The drug appeared less effective in psychoses, though it may be of value in ambulatory schizophrenics. It also offers promise for further investigation in such diseases as epilepsy and paralysis agitans. The antagonistic action of Miltown to leptazol-produced convulsions suggests that in the event of an accidental or deliberate (suicidal) overdosage leptazol might be used as counteractant. S. L. W.

Proguanil and its Metabolite, Action on Neuromuscular and Synaptic Transmission. M. J. Dallemagne and E. Philippot. (*Brit. J. Pharmacol.*, 1955, **10**, 147.) Proguanil and its active metabolite, triazine, blocked neuromuscular transmission in dogs and rats. Transmission through the superior cervical ganglion of cats was also blocked. At the neuromuscular junction the action appeared to be competitive, since the drugs antagonised block by decamethonium and enhanced tubocurarine block. Also their blocking action was reduced by neostigmine and by adrenaline. There was, however, a transitory potentiation of the decamethonium block, before reversal, by both proguanil and triazine. The ganglionic blockade also seemed competitive as there was no stimulation before blockade. Triazine was more effective at both the neuromuscular junction and the ganglionic synapse than was proguanil, except with the frog rectus, where proguanil antagonized acetylcholine contracture more readily. *In vivo* proguanil was rapidly transformed into triazine. G. P.

Reserpine in the Treatment of Anxious and Depressed Patients. D. L. Davies and M. Shepherd. (*Lancet*, 1955, **269**, 117.) Of 67 outpatients, whose main symptoms were anxiety and depression, about half were treated with reserpine, 0·5 mg. twice daily, and the others with placebo. The trial covered a period of 6 weeks. Among the 54 patients completing the trial, those treated with reserpine showed more benefit than those receiving the placebo. No toxic effects were observed in any of the patients. In addition, 4 severely disturbed inpatients were treated with larger doses of the drug. They were given a 3-week course of reserpine by mouth, 3 of them receiving 10 mg. daily and 1 of them 15 mg. daily, for 3 weeks. Their condition remained unchanged by the treatment though all responded satisfactorily to subsequent electroconvulsion therapy. S. L. W.

Ethyl Pyrophosphate, Effect of Drugs in Antagonising the Toxicity of. J. R. Lewis, W. B. McKeon and A. M. Lands. (*Arch. int. Pharmacodyn.*, 1955, **102**, 371.) Tests are reported on a number of synthetic compounds and combination of drugs for the treatment of poisoning with organophosphorus compounds. The antidotal effects of the compounds were studied in mice and pigeons against ethyl pyrophosphate (TEPP). None of the compounds alone protected, even in large doses, but a combination of drugs gave more successful results. Atropine with Mytolon ($2:5\text{-}NH(CH_2)_3N(C_2H_5)_2\cdot OCH_2Cl$) gave excellent protection. Scopolamine with Mytolon was even more effective, while atropine methylnitrate and (+)-hyoscyamine were ineffective. The muscle relaxing compounds curare and gallamine were ineffective alone but were effective with atropine. Decamethonium and mephenesin were ineffective even with atropine. Mytolon has muscle relaxing properties, and compounds related to Mytolon were also studied and their curarimetic potencies compared with their anticholinesterase activities *in vitro*. The amine analogue was ineffective as an antidote with atropine. Compounds in which the quaternary group included benzyl chloride had the greatest protective action and these compounds also had high curarimetic and anticholinesterase activities, but there was no correlation of these activities with their protective action. None of the central nervous system depressants gave protection alone, but a combination of phenobarbitone and atropine gave protection. A combination of magnesium sulphate and atropine was not effective, nor were the anti-epileptic drugs diphenylhydantoin and trimethadione. The ganglionic blocking drugs penta- and hexamethonium gave protection in high doses with atropine, and of the anticholinesterase compounds, physostigmine with atropine gave protection

while neostigmine was not effective. In pigeons, atropine alone injected 15 minutes before TEPP gave slight protection. Mytolon with atropine and physostigmine with atropine gave protection. G. F. S.

Tropine 4-Chlorobenzhydryl Ether Hydrochloride (SL-6057), a Potent, Long-acting Antihistaminic Agent. J. Y. P. Chen. (*J. Pharmacol.*, 1955, **114**, 192.) Originally investigated for antispasmodic activity, SL-6057 was found also to have a high degree of antihistamine and local anæsthetic activity. Single oral or intraperitoneal doses of the drug afforded better and much longer protection to guinea-pigs against fatal histamine sprays than did promethazine, tripelennamine or prophenpyridamine. The compound was similarly effective in reducing the vasodepressor action of histamine in dogs. Local anæsthetic action, measured in rats by sciatic nerve block and in guinea-pigs by the intradermal weal method, was more prolonged than procaine, but local irritation was produced with the higher doses used. SL-6057 had about one-tenth of the antispasmodic activity of atropine on the isolated rabbit duodenum and on the intact ileum of the dog. The antisialogogue and mydriatic actions in the rabbit and inhibition of chromodacryorrhœa in rats were also moderate compared with atropine. Anti-emetic activity in dogs was one-fourth of that of chlorpromazine. SL-6058, the quaternary methyl bromide of SL-6057, had similar activity, but was generally less potent than SL-6057, except for anticholinergic actions. Toxicity studies, acute in mice, rats and dogs and chronic in rats and dogs, showed SL-6057 to be relatively non-toxic. G. P.

WIN 8077 in the Treatment of Myasthenia Gravis. R. S. Schwab, C. K. Marshall and W. Timberlake. (*J. Amer. med. Ass.*, 1955, **158**, 625.) The compound WIN 8077, *NN'*-bis(2-diethylaminoethyl) oxamide bis-2-chlorobenzylchloride, is a white crystalline powder with a molecular weight of 608·5 and a melting point of 184·3° C. It is very soluble in water and can be sterilised by heat. It has been found as active an anticholinesterase substance as neostigmine, and has an anticurare effect 2 or 3 times greater than neostigmine and of longer duration. Since February, 1954, the drug has been used in 50 patients with myasthenia gravis, whose ages ranged from 15 to 74 years. Of this number, 41 are still taking it and feel that their adjustment is superior to that with either neostigmine bromide or Mestinon (a dimethylcarbamate of 3-hydroxy-1-methyl pyridinium bromide). The compound is given in the form of a syrup containing 12·5 mg. in 4 ml. The dosage requirements of patients vary from 2 to 4 mg., to 57–75 mg., the doses being given at 2 or 3-hourly intervals. Several patients reacted unfavourably to the drug, developing typical symptoms of overdosage by an anticholinergic substance. In muscarinic effect the drug seems usually to stimulate the upper gastrointestinal tract, so that nausea and vomiting are more prominent than with neostigmine. On the other hand, 17 of the patients still taking the drug report a reduction in the side-reactions as compared to previous medication, and another 20, still taking it, report a very definite prolongation of the effect as compared to previous medication. It is of interest that, in patients with tracheotomies, when larger doses of the drug caused increased secretions these were almost entirely due to salivation, with little, if any, increase in tracheal and bronchial secretions; this is of great benefit in the management of patients in respirators. The parenteral use of the drug suggests a 1/30 to 1 ratio to the oral dose, with a prolonged effect of nearly 3 hours, but experience in this type of administration is insufficient to recommend its use at present. S. L. W.

(ABSTRACTS *continued on page* 1088.)