# ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

## CHEMISTRY

### ALKALOIDS

**Cuscohygrine, a Normal Constituent Alkaloid of *Atropa belladonna*.** P. Reinouts van Haga. (*Nature, Lond.*, 1954, **174**, 833.) Cuscohygrine has been identified chemically as a constituent of the dried roots of *Atropa belladonna*, and confirmed by a chromatographic comparison with synthetic cuscohygrine. Chromatography has been used to show its presence in the roots of *Atropa belladonna*, *Hyoscyamus niger*, *Datura stramonium*, *D. innoxia*, *D. ferox*, *D. metal*, *Scopolia lurida*, *S. sinensis*, *Physochlaine orientalis*, *P. physaloides* and *Mandragora officinalis*. J. B. S.

**Raumitorine and Seredine, New Alkaloids from *Rauwolfia vomitoria* Afz.** J. Poisson, A. Le Hir, R. Goutarel and M-M. Janot. (*C.R. Acad. Sci., Paris*, 1954, **239**, 302.) The alkaloids are separated by chromatography on alumina of the weakly basic fraction contained in the benzene extract of the roots of the drug. Raumitorine is eluted before reserpine in the benzene fraction and seredine is obtained by elution with acetone after washing the column with benzene-acetone 9:1. Raumitorine m.pt. 138° C. $[\alpha]_D^{20} + 60°$ (*c*, 0·54 in chloroform) crystallises from methanol in white crystals slightly soluble in methanol and ethanol, very soluble in acetone, ether and chloroform. Formula $C_{22}H_{28}O_4N_2$. The ultra-violet spectrum shows an absorption in the 250 m$\mu$ region suggesting R–OOC–C=C–OR′ and in the 280 m$\mu$ region, a band suggesting an indole derivative. The infra-red spectrum shows the presence of OH or NH vibrations in the region of 3 $\mu$ and 2 strong bands in the 6 $\mu$ region. The ester band at 5·89 $\mu$ and the C = C band at 6·17 $\mu$ confirms R–OOC–C=C–OR′. Seredine, m.pt. 291° C. $[\alpha]_D^{20} - 1° \pm 1°$ (*c*, 0·43 in chloroform) crystallises from methanol in small white prisms, which are slightly soluble in methanol, ethanol, acetone and chloroform. Formula $C_{23}H_{30}O_5N_2$. The ultra-violet spectrum is very similar to that of methyl reserpate, showing absorption characteristic of derivatives of 6-methoxyindole. The infra-red spectrum shows an OH or NH band and a single band at 5·87 $\mu$ corresponding to an ester grouping. The preliminary indications of the constitution of these alkaloids suggest that they are derived biogenetically from the condensation of tryptophane and dihydroxyphenylalanine. J. R. F.

### ANALYTICAL

**Atropine Sulphate in the Presence of Butacaine Sulphate, Detection of.** W. E. O'Malley, J. W. Forrest and J. C. Krantz, Jr. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 769.) On warming atropine with concentrated sulphuric acid a pleasant odour resembling oil of rose is produced by the conversion of tropic acid into phenylethanol. On the addition of potassium dichromate, oxidation to benzaldehyde occurs, and an odour of bitter almond may be observed. Butacaine, which does not contain the tropic acid grouping, does not give this reaction, nor interfere in the detection of atropine by this test. G. B.

**Barbiturates, Isolation and Identification of.** F. J. Sabatino. (*J. Ass. off. agric. Chem., Wash.*, 1954, **37**, 1001.) Procedures are described for the paper chromatographic separation of 5 common barbiturates and for the quantitative isolation of phenobarbitone from other barbiturates by column partition chromatography. In the paper chromatographic separation, ethylene chloride was used as the mobile phase, the stationary solvent being 0·5 M sodium carbonate solution. $R_F$ values are given for phenobarbitone, butobarbitone, amylobarbitone, pentobarbitone and quinalbarbitone although the quantity of sodium carbonate solution on the paper affected the time of development and $R_F$ values so that, for comparison, standards must be developed on the same sheet as the unknowns. In the column chromatography, Celite was used for the medium and a solution of the sample was adsorbed on Celite before adding to the column. Pentobarbitone, quinalbarbitone, amylobarbitone and butobarbitone were eluted with a mixture of *iso*octane-chloroform, the phenobarbitone being removed last with chloroform. Good recovery results for known mixtures are given. R. E. S.

**Codeine Phosphate in Combinations with Aspirin, Phenacetin and Caffeine, The Determination of.** M. Pernarowski, L. G. Chatten and L. Levi. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 746.) The determination depends upon the titration of codeine phosphate in solution in phenol, chloroform and acetonitrile. Under the specified conditions, codeine can be titrated as a strong base, whereas caffeine shows only feebly basic properties and does not interfere in the titration. For the assay of tablets and other materials, a quantity equivalent to about 32 mg. of codeine phosphate is dissolved in 5 g. of phenol and 10 ml. of chloroform. The solution is filtered and the filter washed with a further 5 g. of phenol and 10 ml. of chloroform. To the filtrate and washings, 50 ml. of acetonitrile is added and the solution titrated electrometrically with 0·05N perchloric acid in dioxan. The presence of aspirin, phenacetin and caffeine does not affect the accuracy of the determination, but certain commercial tablets cannot be assayed satisfactorily by this method owing to the presence of gelatin. In such cases a sample equivalent to about 32 mg. of codeine phosphate is mixed with 25 ml. of water and 4 ml. of a 20 per cent. solution of sodium hydroxide, and the alkaloid shaken out with chloroform. The solution is washed with water, concentrated on a water bath, mixed with acetonitrile and the determination completed by electrometric titration as above. When magnesium stearate is present as a tablet excipient, the second method should be used as the first gives results about 1 per cent. high. G. B.

**Opium Alkaloids, Differentiation of.** S-S. Cheng. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 767.) A double-colouration test is applied to several minute crystals or solid fragments of alkaloid or alkaloidal salt, by adding 1 drop of Marquis reagent (2–3 drops of formalin in 3 ml. of sulphuric acid) followed immediately by 1 drop of Mandelin's reagent (ammonium vanadate 0·5 per cent. w/w in sulphuric acid). Characteristic colours are produced by opium alkaloids. For example, morphine gives a peach-red colour, followed by blue-violet turning to purple, whereas papaverine yields a brilliant greenish-blue followed by beautiful sky-blue, fading to yellow. The colours produced by codeine, morphine, narcotine, papaverine, thebaine, and certain alkaloidal mixtures, are tabulated. Chloride, oxalates, carbonates and strong reducing agents vitiate the test by causing the evolution of gases, etc. They should be eliminated by extracting the base with organic solvent, and applying the test to the isolated alkaloid. G. B.

**Organic Phosphate Insecticides, New Spot Test in Paper Chromatography of.** J. W. Cook. (*J. Ass. off. agric. Chem., Wash.*, 1954, **37**, 984.) A method is given for the detection on paper chromatograms of small quantities of organic phosphate insecticides containing sulphur. The paper is sprayed with a solution of *N*-bromosuccinimide (0·002 M in washed methyl chloroform) as a brominating agent and then, after drying, overspraying with a solution of fluorescein (slightly alkaline, approximately 0·0003 M in ethanol); the insecticides appear as highly fluorescent yellow-green spots on a pink background of brominated fluorescein. Technical samples of systox, parathion, methyl parathion, chlorthion, malathion, EPN and diazinon all gave positive results with the technique, using amounts ranging from 1 to 10 $\mu$g.; tetraethyl pyrophosphate (TEPP) and octamethyl pyrophosphoramide (OMPA) failed to show positive tests when 40 $\mu$g. were spotted. The chromatograms retained their colour for appreciable periods when protected from light. R. E. S.

**Organic Phosphate Insecticides, Separation and Identification of.** J. W. Cook. (*J. Ass. off. agric. Chem., Wash.*, 1954, **37**, 987.) Details are given of a paper chromatographic method for the separation and identification of a number of thiophosphate pesticides by means of reverse phase chromatography, in combination with the spot test of Cook (*vide supra*). The separation was accomplished by reverse phase paper chromatography with mineral oil as the stationary phase and ethanol, acetone, and water (1 + 1 + 2, v/v) as the mobile phase. $R_F$ values are recorded for systox, parathion, methyl parathion, chlorthion, malathion, EPN and diazinon. R. E. S.

**Reserpine, Ultra-violet Spectrophotometric Determination of.** E. H. Sakal and E. J. Merrill. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 709.) Relatively pure samples of reserpine containing no interfering substances may be assayed by determination of the ultra-violet absorption at the 267 m$\mu$ absorption peak. Samples containing contaminants whose absorption is linear in the region of the absorption peak may be assayed in the same way, by applying a correction for the irrelevant absorption, based on measurements at 259·25 and 275 m$\mu$. In the presence of a contaminant exhibiting non-linear absorption, whose absorption spectrum is accurately known, it may be possible to choose a wavelength at which the absorption of the contaminant is negligible compared with that of reserpine, or to calculate the quantity of reserpine from absorption measurements by the use of simultaneous equations. In the presence of unknown contaminants such as occur in crude extracts of rauwolfia root, reserpine may first be separated by ionophoresis on strips of filter paper moistened with 5N acetic acid. The reserpine zone (the slowest migrating zone showing a yellowish-green fluoresence in ultra-violet radiation) is cut from the paper, the alkaloid extracted with 5N acetic acid and the absorption measured at 259·25, 267 and 275 m$\mu$. The content of reserpine is calculated, correcting for irrelevant absorption, in comparison with a known quantity of pure reserpine applied to a similar area cut from a control ionophoresis paper and extracted with 5N acetic acid as above. For the analysis of reserpine tablets, a sample is shaken with methanol in an atmosphere of nitrogen, allowed to stand and the supernatant liquid assayed for reserpine, correcting for the absorption due to tablet excipients by the use of equations or an excipient blank. Tablets containing mixed alkaloids of rauwolfia may be assayed by the ionophoresis method. G. B.

# BIOCHEMISTRY

## GENERAL BIOCHEMISTRY

**Anticholinesterase Oxamide, A New.** A. Arnold, A. E. Soria and F. K. Kirchner. (*Proc. Soc. exp. Biol., N.Y.*, 1954, **87**, 393.) In the bis-(benzyl-dialkyl-ammonium-alkylamino)-benzoquinone series of neuromuscular blocking agents it was found that substitution on the benzene ring of the benzyl quaternising group increased anticholinesterase activity. Applying this finding to quaternised amino-alkyl amides of dicarboxylic acids, a series of oxamides was synthesised. One compound of this series, *NN'*-bis-(2-diethyl-aminoethyl)-oxamide bis-2-chlorobenzyl chloride, was about six times more effective in inhibiting hæmolysed red cell cholinesterase than was neostigmine methyl sulphate. Activity was measured by an electrometric titration method. G. P.

**Cytotoxic Substances, Anticholinesterase Activity of.** K. Bullock. (*Chem. Ind.*, 1955, 36.) A number of epoxides, methanesulphonyloxy-derivatives and nitrogen-mustards, all cytotoxic agents, have been examined for inhibitory power against acetylcholinesterase and pseudocholinesterase. The results show that the epoxides do not have any marked anticholinesterase activity, inhibition only being shown in isolated cases and then when the epoxide was at a concentration of 0·1 M or greater. Methanesulphonyloxy-derivatives are more active but still of low anticholinesterase activity. A number of ethyleneimines showed moderate levels of activity, but none were more active than nitrogen-mustard in the inhibition of brain esterase. It is concluded that there is no close relationship between cytotoxic and anticholinesterase activity. J. B. S.

**Histamine, Chromatography of.** G. B. West and J. F. Riley. (*Nature, Lond.*, 1954, **174**, 882.) Tissue histamine which has been extracted with 10 per cent. aqueous trichloroacetic acid or trifluoroacetic acid shows anomalous spots when chromatographed on paper using *n*-butanol-acetic acid-water. The normal spot ($R_F = 0{\cdot}11$) is accompanied by a fast-running spot ($R_F = 0{\cdot}65$), though an eluate of the fast-running spot when re-chromatographed gave the normal spot only. Three factors are known to influence the migration of the fast-running spot, the concentration of histamine, the concentration of trichloroacetic acid, and the presence of a basic amino-acid such as arginine, lysine or ornithine. It is concluded that the ability of trichloroacetic acid to extract histamine from tissues is related not only to its coagulative effect on protein, but also to its participation in a loose complex containing histamine. J. B. S.

## BIOCHEMICAL ANALYSIS

**Compound 48/80, Quantitative Determination of Mast Cell Fragmentation by.** S. Norton. (*Brit. J. Pharmacol.*, 1954, **9**, 494.) Mast cell disruption in pieces of rat mesentery, by exposure to graded concentrations of the histamine liberator 48/80 in Ringer-Locke, yielded reliable estimates of the relative potencies of different batches of the drug. There was a sigmoid relationship between percentage disruption and concentration of 48/80. Decreasing the concentration of extracellular ions by diluting the Ringer-Locke greatly decreased the disrupting activity of the 48/80. This supports the hypothesis that the disruption was due to the mast cells being rendered more permeable to ions by the 48/80. The time for maximum effect of the 48/80 depended on concentration and varied between 30 and 60 minutes. G. P.

**Pyruvic and α-Ketoglutaric Acids, Blood Concentrations of.** M. J. H. Smith and K. W. Taylor. (*Lancet*, 1955, **268**, 27.) This is a report on an investigation of the claim that blood concentrations of α-keto acids are increased in diabetes. The blood pyruvate, α-ketoglutarate and glucose concentrations were estimated in 7 normal people and 8 ambulant diabetic out-patients. All the patients were receiving insulin and were healthy apart from their diabetes. The authors devised a method for the separation and estimation of pyruvic and α-ketoglutaric acids in blood using 1 : 2-diamino-4-nitrobenzene, which acts as a specific reagent for α-keto acids with which it forms stable derivatives separable by paper chromatography. The reagent is allowed to react with the deproteinised blood filtrate for 12 to 16 hours, and the derivatives are extracted with ethyl acetate and removed from the organic solvent with 5 per cent. w/v sodium carbonate solution. After the acidification of the sodium carbonate solution the derivatives are re-extracted with ethyl acetate, which is then evaporated to dryness. The residue is dissolved in acetone and the derivatives separated by paper chromatography. The separated derivatives are eluted with 30 per cent. ethanol and the optical densities of the resulting solutions measured at 280 mμ. The results showed that there was no significant difference between the two groups in the blood levels of α-keto acids. In the diabetic patients there was no correlation between the blood concentrations of glucose and of the two α-keto acids. S. L. W.

## CHEMOTHERAPY

**Albomycin, its Preparation and Chemical Nature.** M. G. Brazhnikova, N. I. Lomakina and L. I. Murav'eva. (*Doklad. Akad. Nauk S.S.S.R.*, 1954, **99**, 827.) The properties of albomycin, an antibiotic separated from cultures of *Actinomyces subtropicus*, are described. The active material forms an amorphous brick-red sulphate, readily soluble in water, slightly soluble in methanol and insoluble in other organic solvents. Tests on a standard strain of *Staphylococcus aureus* showed the antibacterial activity to be 700,000 units/mg. It contains 4 per cent. of iron, which can be removed by treating an acetone solution with hydrochloric acid, hydrobromic acid, hydriodic acid or hydroxyquinoline; removal of the iron is accompanied by loss of colour and reduction of the antibacterial activity to about one-fifteenth of the original. Addition of ferric chloride solution to an aqueous solution of the iron-free compound restores both the colour and the activity. The active material appears to be an iron–chelate complex, stable within the *p*H range 4 to 10; the molecular weight is not less than 1300 and the absorption spectrum shows maxima at about 290 and 420 mμ. Free amino groups are not present. Chromatography on paper of the acid hydrolysate indicates the presence of ornithine, serine, glutamic acid, alanine, glycine, proline and an unidentified seventh component. The results suggest that albomycin is a complex of iron with a cyclic polypeptide, the basic properties being due to the presence of a free δ-amino group derived from ornithine. E. H.

**Gramicidin-S: Relationship of Cyclic Structure to Antibiotic Activity.** B. F. Erlanger and L. Goode. (*Nature, Lond.*, 1954, **174**, 840.) The antibacterial activity of the open-chain dipeptide L-valyl-L-ornithyl-L-leucyl-D-phenylalanyl-L-prolyl-L-valyl-L-ornithyl-L-leucyl-D-phenylalanyl-L-proline trihydrochloride has been compared with that of the cyclic Gramicidin-S which contains the same amino-acid sequence. In a synthetic medium with an inoculum

of 600,000 organism/ml. the peptide is bactericidal against *E. coli* at a concentration of 60 μg./ml., whereas Gramicidin-S gave a similar effect at 5 μg./ml. The surviving organisms showed evidence of possessing enzymes which are capable of destroying or neutralising the compound, but this power was lost after a single transfer to fresh medium. Bactericidal concentrations against *Staph. aureus* were 120 μg./ml. and 3 μg./ml. respectively. It is concluded that the cyclic structure is not directly or intimately related to activity. The inactivity of the pentapeptide, L-valyl-L-ornithyl-L-leucyl-D-phenylalanyl-L-proline dihydrochloride rules out the specific influence of D-phenylalanine or L-ornithine, although these may in some other way be an essential part of a structure possessing activity. It is suggested that the greater activity of Gramicidin-S may be due to a lesser susceptibility to destruction by bacterial enzymes, since a cyclic structure could only be attacked by endopeptidases. J. B. S.

# PHARMACY

## NOTES AND FORMULÆ

***iso*Propyl Myristate as a Vehicle for Parenteral Injections.** E. L. Platcow and E. Voss. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 690.) Acute toxicity tests were performed by intraperitoneal injection of *iso*propyl myristate into mice and subacute toxicity tests by intraperitoneal injection into rats. Sensitising properties were assessed by measuring the extent of the local inflammatory reaction produced by a final injection of the substance, 2 weeks after a course of 10 sensitising intracutaneous injections. Irritation tests were done in rabbits, in the eye, and parenterally. *iso*Propyl myristate was non-toxic to mice, of low irritability and did not give rise to sensitivity. Its freedom from toxicity for rats was doubtful. A suspension of procaine penicillin in *iso*propyl myristate containing 2 per cent. of aluminium stearate was capable of maintaining effective therapeutic penicillin blood levels up to 48 hours after it was injected intramuscularly into rabbits. In experiments with ovariectomised rats *iso*propyl myristate was as effective as sesame oil when used as a repository vehicle for α-œstradiol. G. B.

**Tablet Implants, Formulation of.** K. S. Patel and E. P. Guth. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 754.) In a preliminary series of experiments, the time for the complete absorption of tablets implanted into rats varied from 36–48 hours for polyethylene glycol 6000 to 17–19 days for methylcellulose (methocel 4000). No absorption of cholesterol or sterotex (hydrogenated fat) tablets was observed even after 8 weeks. To evaluate bases giving favourable results in the preliminary tests, tablets were prepared containing about 0·1 per cent. of phenol red, a substance which is completely excreted by rats. Tablets were made by the moist granulation process, using a 7/32 inch die and keeping the pressure employed constant as far as possible. The weight of the tablets was varied according to the base employed, in order to keep the thickness constant. The tablets were assayed for content of phenol red and implanted into rats. The urine of the rats was collected every 6 hours, made alkaline and the content of phenol red determined colorimetrically. Cholesterol tablets released the dye within 30 hours, whereas sterotex did not release it at all. Pharmagel B (gelatin) was satisfactory for implants intended to last not more than 72 hours, but was difficult to compress. Polyethylene glycol (carbowax) 6000 implants released the dye in 6 hours and methocel 4000 in 30 hours. The rate of release could be controlled by using varying proportions of these bases. G. B.

**Vitamin $B_{12}$, Instability of, in the Presence of Aneurine and Nicotinamide.** M. Blitz, E. Eigen and E. Gunsberg. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 651.) Following the observation that commercial solutions of the vitamin B complex lose vitamin $B_{12}$ (cyanocobalamin) on storage at room temperature, solutions were prepared at *p*H 4·5 (optimum for the preservation of vitamin $B_{12}$). One ingredient of the vitamin B complex was omitted from each solution. The loss of vitamin $B_{12}$ on heating at 100° C. for 4 hours was considerably less when (aneurine) thiamine or nicotinamide were absent. Further experiments indicated that vitamin $B_{12}$ was stable in the presence of nicotinamide alone. Although some destruction of vitamin $B_{12}$ occurred in the presence of high concentrations of aneurine, the vitamin was much more rapidly destroyed when nicotinamide and aneurine were present together. The results at 100° C. were confirmed in experiments at 45° C. In the presence of 1 mg./ml. each of aneurine and nicotinamide, 27·3 per cent. of vitamin $B_{12}$ was destroyed in 3 weeks at 45° C. Oxidation did not seem to be involved in the destruction, as the same results were obtained when the vials were nitrogen-filled. G. B.

## PHARMACOGNOSY

**Capsicum, Determination of Capsaicin in.** M. Fujita, T. Furuya and A. Kawana. (*J. pharm. Soc. Japan*, 1954, **74**, 766.) About 1 to 5 g. of powdered capsicum is extracted with acetone and the capsaicin in the extract is isolated by paper partition chromatography using benzene saturated with methanol as the developing agent. The capsaicin is treated with 3 per cent. phosphomolybdic acid and 0·1 N sodium hydroxide to produce a blue colour, whose extinction at 730 m$\mu$ after one hour is measured. A calibration curve is made using either pure capsaicin or vanillin; if the latter is used a correction must be made according to the following equation:—

$$\text{Capsaicin content} = \frac{\text{Vanillin content}}{23}$$

The method has been applied to samples of the crude drug and of the tincture. J. W. F.

***Digitalis purpurea*, The Uptake of $^{14}C$ by.** L. E. H. Djao and H. W. Youngken Jr. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 425.) Digitalis plants were grown in hydroponic culture solution containing 10 mg. of sodium acetate, labelled with $^{14}C$ at the carboxyl group. This concentration was found to be non-toxic to the plants. At the end of 12 hours, about 59 per cent. of the radioactive carbon remained in the solution, 3·2 per cent. was collected from the air in the form of carbon dioxide, and 0·27 per cent. was respired from the plant in the form of carbon dioxide. 9·9 per cent. was present in the root and 0·17 per cent. in the leaf material of the plants. In the following period, the proportion of $^{14}C$ stored in the leaves increased, reaching a maximum of 1·81 per cent. in 10 days. G. B.

**Opium Alkaloids, Labelled with $^{14}C$, Biosynthesis of.** M. Kuzin and V. I. Merenova. (*Biokhimiya*, 1954, **19**, 616.) In a study of the biosynthesis of labelled morphine, codeine and narcotine, three methods of introducing $^{14}C$ into the ripening capsules of *Papaver somniferum* were compared: (i) The stems of 3 freshly cut capsules were immersed for 3 days in a solution containing radioactive glycine or acetate (50 $\mu$C.). (ii) A total activity of 200$\mu$C. was introduced into 10 ripening capsules under field conditions, 0·1 ml. of an 0·1M

solution being injected into the centre of each capsule by means of a syringe; growth was then allowed to proceed for 10 days before collection. (iii) Twenty plants were kept from the moment of flowering to collection (25 days) in a special chamber fed with radioactive carbon dioxide. At the end of each experiment, the alkaloids were extracted and the amount of radioactive carbon present was measured. The best results were obtained by the third method; the experiment yielded 260 mg. of morphine having an activity of 7·1 $\mu$C. (0·36 per cent. of the total activity fed to the chamber). Paper chromatography of the morphine obtained showed it to be free of radioactive impurities. E. H.

## PHARMACOLOGY AND THERAPEUTICS

**p-Aminosalicylic Acid Salt of Isoniazid, Resistance of *Myco. tuberculosis* to.** H. Brodhage. (*Science*, 1954, **120**, 998.) The *p*-aminosalicylic acid salt of isoniazid showed high tuberculostatic activity *in vitro* even against strains of *Myco. tuberculosis* resistant to both isoniazid and *p*-aminosalicylic acid. Primary cultures of the resistant strains were inoculated into liquid Dubos-Tween medium and after growth standardisation were re-inoculated into liquid Dubos medium containing graded concentrations of the tuberculostatic agents to be tested. Strains resistant to streptomycin, isoniazid or *p*-aminosalicylic acid were sensitive to the new salt. On the other hand strains resistant to both *p*-aminosalicylic acid and isoniazid showed a slight degree of cross-resistance to the salt. Patients refractory to isoniazid, *p*-aminosalicylic acid or streptomycin therapy responded to treatment with the salt (Hueck, *Tuberk, Arzt. Jahrg.*, 1954, **8**, 423), confirming *in vitro* results. G. P.

**Antihistamines, Pharmacological Properties of Two New.** S. Y. Pan, J. F. Gardocki and J. C. Reilly. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 653.) Meclozine (*p*-chlorobenzhydryl-*m*-methylbenzylpiperazine) and buclizine (*p*-chlorobenzhydryl-*p-tert.*-butylbenzylpiperazine) protect guinea-pigs against nebulised histamine or lethal doses of histamine injected intravenously. The onset of the protective action is slow, especially for buclizine, but it persists for a long period. 100 per cent. protection of guinea-pigs against intravenous histamine continues over 24 hours for meclozine and 5 days for buclizine, compared with 3 hours for tripelennamine and 17 hours for chlorcyclizine. Buclizine has no action, and meclozine a very weak one, against histamine-induced spasm of the guinea-pig ileum. The substances are relatively non-toxic when given orally or intraperitoneally to mice, by mouth to rats or by stomach tube to dogs. Possibly the prolonged action of these antihistamines is due to their being converted into active substances after absorption. G. B.

**Chlorpromazine and Tissue Metabolism.** M. Finkelstein, W. A. Spencer and E. R. Ridgeway. (*Proc. Soc. exp. Biol., N.Y.*, 1954, **87**, 343.) Chlorpromazine depressed oxygen consumption of cat left ventricle heart slices, and cerebral cortex slices and homogenates, but only in concentrations much greater than plasma levels of the drug achieved in eliciting a pharmacological response *in vivo*. It is suggested that depression of brain and heart oxygen consumption do not occur *in vivo* with therapeutic doses of the drug. G. P.

**Chlorpromazine, Inhibition of Hypothalamic, Medullary and Reflex Vasomotor Responses by.** S. R. Dasgupta and G. Werner. (*Brit. J. Pharmacol.*, 1954, **9**, 389.) Intracisternal injection of 0·25 to 0·5 mg. of chlorpromazine into rhesus monkeys under allobarbitone anæsthesia caused a fall in blood pressure and abolition of the carotid sinus pressor reflex. The pressor response to

intravenous adrenaline was not affected by this dose. A similar fall in blood pressure was seen in decorticate cats with an intravenous dose of 50 to 100 $\mu$g./kg. of chlorpromazine. In these animals the pressor responses to stimulation of the sciatic nerve and of the hypothalamic and medullary pressor areas (located with a Horsley-Clark stereotaxic instrument and verified histologically) were also suppressed. With cats under chloralose anæsthesia blockade of hypothalamic, medullary and sciatic nerve pressor responses was less regular; in some animals these were relatively unaffected by 1 mg./kg. of chlorpromazine. Also, in the anæsthetised cat the drug had little or no hypotensive action. This could be explained by the fact that in the decorticate cat there is high central sympathetic activity, which would appear to be easily suppressed by the drug. G. P.

**Chlorpromazine, Promethazine and Pethidine, Comparison of Pharmacology of.** J. Kopera and A. K. Armitage. (*Brit. J. Pharmacol.*, 1954, **9**, 392.) The following properties of the three drugs were compared: (1) The fall in rectal temperature of mice. (2) Paralysis of the cat sciatic-gastrocnemius and rat phrenic nerve-diaphragm preparations; this action was exerted directly on the muscle and not through neuromuscular blockade. (3) Chronic toxicity in young rats; a temporary retardation of growth was observed. (4) Extension of the duration of sleep induced in mice with pentobarbitone. (5) Potentiation of morphine analgesia in mice; contrary to previous reports, no potentiation was found with chlorpromazine and pethidine, and promethazine had only a slight action. (6) Anti-adrenaline action on the vessels of the rabbit ear, the blood pressure of the spinal cat and the isolated rabbit uterus. (7) Anti-acetylcholine action on the isolated guinea-pig ileum and on the mouse pupil. Chlorpromazine alone was tested on the salivary secretion of the cat and found to have a definite inhibitory action. (8) Antihistamine activity on the guinea-pig ileum and bronchial resistance. (9) Local anæsthetic activity by the guinea-pig weal method and by ability to induce plexus anæsthesia in frogs. The comparison showed chlorpromazine to be more active than promethazine except in its anti-acetylcholine, antihistamine and morphine-potentiating actions. Pethidine was the least active on all preparations. Chlorpromazine more effectively antagonised the vasopressor effects of adrenaline than of noradrenaline in the spinal cat. No adrenaline reversal was noted, even when the pressor effect was abolished. The actions of chlorpromazine, promethazine and pethidine were discussed in the light of clinical findings. G. P.

**Chlorpromazine, Action of, on Diencephalic Sympathetic Activity and on the Release of Adrenocorticotrophic Hormone.** M. Holzbauer and M. Vogt. (*Brit. J. Pharmacol.*, 1954, **9**, 402.) Inhibition of the diencephalic sympathetic activity and prevention of the release of adrenocorticotrophic hormone (ACTH) have been suggested as an explanation for the sedative action and protection from shock in animals treated with chlorpromazine. Hypothalamic activity was measured in cats by the depletion by morphine of hypothalamic noradrenaline and total sympathomimetic amines in the adrenal medulla. Chlorpromazine (25 mg./kg.) injected subcutaneously had no effect on this action of morphine, but decreased other actions such as salivation, vomiting, tremors and excitement. Nalorphine, on the other hand, inhibited all the observed actions of morphine, including the central sympathetic stimulation. The release of medullary amines by morphine was sufficient to overcome the anti-adrenaline action of the chlorpromazine and in all cats mydriasis occurred, particularly where the pupil had been chronically denervated. Chlorpromazine (1·5 mg./kg.) injected intravenously into the chloralosed dog gave rise to an anti-adrenaline action

lasting 30 minutes, during which time the pressor action of adrenaline was reversed; 3·0 mg./kg. acted similarly for 2 hours 20 minutes. With these doses, there was no evidence of block in the superior cervical ganglion. Chlorpromazine (10 mg./kg. s.c.) did not prevent the release of ACTH (measured by the depletion of adrenal ascorbic acid) in rats under stress consisting of laparatomy and handling of the intestine under urethane anæsthesia; nor was the release of ACTH by adrenaline (200 $\mu$g./kg. s.c.) prevented. Since chlorpromazine in larger doses (15 mg./kg.) released ACTH to the same degree as operational stress, it was not possible to investigate fully any inhibitory effect the drug might have had. G. P.

**Cortisone and Salicylates in Rheumatic Fever.** K. S. Holt, R. S. Illingworth, J. Lorber, J. Rendle-Short, and W. M. Gibson. (*Lancet*, 1954, **267**, 1144.) The object of this investigation was partly to determine whether salicylates are more effective in large doses than in small ones, and partly to compare the effect of (*a*) salicylates given alone, and (*b*) salicylates in large doses, given with cortisone. Three groups, each of 10 patients, were treated as follows. Group 1. (Cortisone with salicylates.) Sodium salicylate 1½ grains/lb. bodyweight daily, the dose being adjusted to give a serum-salicylate level of 30 to 40 mg./100 ml. Cortisone by mouth, 200 mg./day for 4 days; 100 mg./day for the remainder of the first 3 weeks; 75 mg./day for the 4th and 5th weeks; and 50 mg./day thereafter. Sodium was restricted to less than 2 g./day if there was rapid gain in weight. Potassium chloride by mouth, 2 g./day to children of 60 lb. or less, and 3 g./day to those weighing more. Group 2. (Salicylates in high dosage.) Sodium salicylate in same dosage as Group 1. Group 3. (Salicylates in low dosage.) Sodium salicylate 5 grains 4 times daily to children under 50 lb. and 10 grains 3 times daily to children of 50 lb. or more. The E.S.R. fell significantly more quickly in Group 1 than in the other two groups. With the combined treatment the average number of days before the E.S.R. first reached normal was 17·0, compared with 39·2 days in children receiving salicylates in high dosage and 50·3 days in those receiving salicylates in low dosage. The average duration of treatment in Groups 1, 2 and 3, was 34·0, 79·6, and 67·4 days respectively. There was a correspondingly rapid improvement in the clinical condition of the patients in Group 1. Further study is required to determine whether the addition of salicylates to cortisone treatment is of benefit or not. In the meantime it seems likely that salicylates, given alone, are not the best drug treatment of rheumatic fever. S. L. W.

**Cyclizine Hydrochloride (Marezine), Pharmacological Properties of.** S. Norton, K. I. Colville, A. E. Light, A. L. Wnuck, R. V. Fanelli and E. J. deBeer. (*J. Pharmacol.*, 1954, **112**, 297.) In small doses (0·5 mg./kg.) cyclizine (1-benzhydryl-4-methylpiperazine hydrochloride) blocked the vasodepressor response to stimulation of the peripheral end of the divided vagus, decreased the tone and spontaneous rhythm of the ileum and blocked injected histamine in anæsthetised cats. The blood pressure response to acetylcholine was not affected even by doses up to 8 mg./kg. At this dose level the pressor responses to adrenaline and noradrenaline were likewise unaffected, but the vasodepressor response to serotonin was blocked. The drug had no neuromuscular or ganglion-blocking action and did not alter the blood pressure response to tracheal occlusion or to stimulation of the central end of the divided vagus. In protecting guinea-pigs against a histamine aerosol, cyclizine was equal in potency to diphenhydramine. The drug was also highly active against histamine on the isolated ileum and tracheal muscle of the guinea-pig. By the guinea-pig weal method, cyclizine had about equal potency to procaine as a local anæsthetic. G. P.

**Lysergic Acid Diethylamide, Pyretogenic Effect of.** A. Horita and J. M. Dille. (*Science*, 1954, **120**, 1100.) Lysergic acid diethylamide (LSD) when administered to normal rabbits produced a marked hyperpnœa and an increase in body temperature. After subcutaneous or intravenous administration of 0·1 mg./ml., without dilution, no significant difference was observed in the amount of fever, but the time of onset and duration of action was shortened with the intravenous route. A rise in rectal temperature was produced in rabbits, dogs and cats, but the rabbit was most affected, a subcutaneous injection of 50 $\mu$g./kg. producing a rise within 10 to 20 minutes, which reached a peak after 2 to 4 hours, and had a duration of 7 to 9 hours. Attempts to lower the induced fever by the administration of antipyrine, dihydroergotamine, Hydergine and dibenamine were ineffective, but pentobarbitone sodium (30 mg./kg. i.v.) showed marked antagonism. Previous administration of the barbiturate prevented the pyretogenic response for as long as the animal was anæsthetised, and when given at the height of the temperature rise, the LSD produced fever was reduced and the temperature restored to normal. Further studies to determine the mechanism of this effect are being made. J. R. F.

**Mephentermine, Pharmacological Properties of.** D. K. Eckfield, L. L. Abell and J. Seifter. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 705.) Mephentermine, *N*-methyl-$\omega$-phenyl*tert.*-butylamine, an optically inactive sympathomimetic amine was found to be about two thirds as toxic as amphetamine or (+)-desoxyephedrine and 3 times as toxic as (−)-ephedrine, when administered intra-abdominally to mice. In anæsthetised dogs with the vagi intact or severed, the pressor response, effect on the heart rate and ability to shrink the nasal mucosa were similar to that of (−)-ephedrine. Absorption from the frontal sinuses of dogs, assessed by the effect on the blood pressure after the instillation of mephentermine was not greater than for (−)-ephedrine. The cerebral stimulant effect in chicks, cats and dogs was one third to a half that of amphetamine or (+)-desoxyephedrine. The substance had no effect on the normal ciliary activity of the trachea, no spasmolytic action on intestinal smooth muscle and it produced no anæsthetic effect when applied to the rabbit's eye. G. B.

**Methylpentynol, Effects of.** P. Trotter. (*Lancet*, 1954, **267**, 1302.) In 3000 unselected ambulant dental patients premedicated with methylpentynol no deleterious effects were observed. The object of this investigation was to determine the effect of methylpentynol on the speed of reaction of ambulant persons. The tests were made on a number of healthy students, using a car-type reaction tester and a McDougall-Schuster dotter. Similar tests were made using alcohol. In the tests made with the McDougall-Schuster dotter, blank capsules were used as controls. In all, 768 tests were conducted. Almost all the students tested noted subjective effects following administration of 500 mg. of methylpentynol. The onset was fairly constant at 10 to 15 minutes, when there was a feeling of elation lasting 15 to 30 minutes, and from then until the effect wore off there was a period of contentment, calm, and confidence. The total effect of 500 mg. lasts about an hour, but varies with individuals. In the majority of cases the speed of reaction was improved within 15 minutes after administration; in this its action differed from that of alcohol, which either has little effect on the speed of reaction or causes a deterioration. A dose of 500 mg. of methylpentynol does not seem to produce any of the undesirable signs of intoxication by alcohol, though possibly larger doses than this might give rise to similar symptoms. S. L. W.

**Myleran in Chronic Myelocytic Leukæmia.** W. C. Levin, A. P. Thaddeus, J. R. L. Vaughan and S. Y. Tsai. (*J. Lab. clin. Med.*, 1955, **44**, 890.) Six patients with chronic myelocytic leukæmia were treated with Myleran (1:4-dimethanesulphonoxybutane) in a dosage of 4 to 6 mg. per day, with variable rest periods depending on each patient's individual response. In every instance there was initial clinical and subjective improvement, which usually became apparent within 1 to 7 days after commencement of therapy. There was also constant hæmatological improvement, though 1 to 4 weeks elapsed before hæmatological alterations became maximal. In all cases improvement was characterised by a fall in the total leucocyte count, restoration of absolute numbers of mature neutrophils, reduction in severity of anæmia, and maintenance of platelet values at or above normal (except in one case). Clinical improvement was very striking and there was dramatic subjective improvement. This was followed by reduction of the degree of hepatosplenomegaly and subsidence of symptoms of hypermetabolism. In one case, characterised by severe symptoms due to infiltration of the kidneys, there was prompt regression following the institution of treatment. There were no troublesome gastro-intestinal symptoms. One patient developed moderate marrow hypoplasia but there is now evidence of spontaneous marrow regeneration. The most alarming occurrence in this series is that 2 of the patients developed acute myeloblastic transformations and promptly succumbed. There is some evidence that this compound may in some instances potentiate the virulence of chronic myelocytic leukæmia.

S. L. W.

**Nalorphine, Effect of, in the Presence of Quinalbarbitone.** C. M. Gruber, Jr. (*J. Pharmacol.*, 1954, **111**, 409.) Nalorphine given subcutaneously to mice, after an intraperitoneal injection of quinalbarbitone sodium, increased the sleeping time. With low doses of nalorphine the effects of the two drugs appeared to be slightly synergistic. When the dose of nalorphine was increased there was a sudden increase in deaths due to toxicity to nalorphine developing. Nalorphine gave no protection against quinalbarbitone sodium. G. F. S.

**Œstrogenic Activity of *iso*Flavone Derivatives.** E. Cheng, L. Yoder, C. D. Story and W. Burroughs. (*Science*, 1954, **120**, 575.) The presence of œstrogenic substances in subterranean clover led to the isolation of an *iso*flavone derivative, genistein. Both genistein and its glucoside genistin are œstrogenic in mice. Four *iso*flavone derivatives, genistein, biochanin A, diadzein and formononetin have been synthesised. They were fed to mice with an average daily intake of 2·5 mg. and the effects on the uterus compared with stilbœstrol. Each of these *iso*flavones had œstrogenic activity; diadzein was the most active ($\simeq$ 0·042 $\mu$g. stilbœstrol), genistein and biochanin A both 0·033 and formononetin only 0·009. The latter compound alone had only one free OH group. Biochanin A has recently been isolated from red clover and the glucoside of diadzein from soya bean meal. It is concluded that œstrogenic activity in livestock feeds is due to *iso*flavone derivatives. While their activity is low, sufficient may be ingested in the feed to have physiological effects. G. F. S.

**Piperazine Citrate in the Treatment of Roundworm.** L. G. Goodwin and O. D. Standen. (*Brit. med. J.*, 1954, **2**, 1332.) Field trials of piperazine citrate were carried out in a highly endemic area of Tanganyika on about 100 children and adults. Patients were selected on the basis of direct microscopical examination of the stools in diluted Lugol's iodine, and only those showing numerous ascaris eggs of normal appearance were treated. Piperazine citrate was given in the form of tablets, each equivalent to 0·5 g. of the hydrate, and were swallowed with a draught of water. No restrictions were imposed on the intake

of food or alcohol and no purge was given before treatment, but most patients were given magnesium sulphate 24 hours after the dose of piperazine, whether they had passed worms or not. The results indicated that a single dose of 3 g. of piperazine citrate should be given to all except children weighing less than 20 kg.; small children should be given 2 g. This dose was effective in removing roundworms from the gut without causing any toxic side-effects. The worms were narcotised by the drug and not killed; they recovered in a few hours when placed in Ringer's solution at 37° C. For the eradication of a focus of infection it would be advisable to treat the whole population at monthly intervals for at least 4 months. No effect was observed against hookworm or *Strongyloides*. S. L. W.

**Piperazines as Adrenergic Blocking Agents.** A. P. Swain and S. K. Naegele. (*J. Amer. chem. Soc.*, 1954, **76**, 5091.) The synthesis of symmetrical 1:4-substituted piperazines in which the substituents are 1:4-benzodioxan-2-ylmethyl, 2-phenoxyethyl, 3-phenoxypropyl, tetrahydropyran-2-ylmethyl, tetrahydrofurfuryl or 2-ethoxyethyl groups is reported. Several unsymmetrical 1:4-disubstituted piperazines were also prepared. Long-acting sympatholytic and adrenolytic activity by both oral and parenteral routes of administration was exhibited by some of the compounds. A. H. B.

**Stilbene and Diphenylethane Derivatives, Chemical Constitution and Pharmacology of.** G. Cavallini, E. Costa, W. Ferrari and E. Massarini. (*Arch. int. Pharmacodyn.*, 1954, **99**, 283.) The relation of structure to curarizing activity was examined in two series of bis-trialkylammonium derivatives of stilbene and diphenylethane. All of the compounds studied (including the bis-trimethyl derivatives) resembled tubocurarine in mode of action in the rabbit and pigeon and on the frog rectus abdominis muscle. Progressive substitution of *N*-methyl by *N*-ethyl groups decreased the paralysing action of the compounds in the rabbit and pigeon. The logarithms of curariform potency and duration of action were inversely related to the total number of carbon atoms on each quaternary nitrogen. The bis-diethylbenzylammonium compounds were exceptions to the rule in that the duration of action was very prolonged. High anticholinesterase activity both against horse brain and serum cholinesterases was exhibited by both series, the benzyl-dialkylammonium compounds being particularly active. There was no correlation with curare-like activity. The diphenylethane derivatives were the more active as anticholinesterases, while the stilbene derivatives showed greater paralysing and anti-acetylcholine effects. G. P.

**Tetracycline in the Treatment of Sonne Dysentery.** J. D. Abbott and H. E. Parry. (*Lancet*, 1955, **268**, 16.) The values of tetracycline, phthalylsulphathiazole, and oral streptomycin were compared in the treatment of 84 bacteriologically proved cases of Sonne dysentery; 27 of the patients were treated with tetracycline, 32 with phthalylsulphathiazole, and 25 with oral streptomycin. The dosages of tetracycline and phthalylsulphathiazole were as follows.

| | Tetracycline | | Phthalylsulphathiazole | |
|---|---|---|---|---|
| Age (yr.) | Regimen | Total dosage (g.) | Regimen | Total dosage (g.) |
| Less than 5 | 125 mg. 6-hourly for 7 days | 3·5 | 0·5 g. 6-hourly for 7 days | 14 |
| 5-15 | 250 mg. 6-hourly for 7 days | 7·0 | 1·0 g. 6-hourly for 7 days | 28 |
| More than 15 | 500 mg. 6-hourly for 7 days | 14·0 | 2·0 g. 6-hourly for 7 days | 56 |

(ABSTRACTS *continued on page* 359)