ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

Couch Grass Ergot, Study on. L. C. Schramm and J. L. Beal. (*J. Amer. pharm. Ass., Sci. Ed.*, 1958, **47**, 326.) Ergots found growing on couch grass in central Ohio were assayed for total and water-soluble alkaloids by a modification of the method of Silber and Schulze (*Pharmazie*, 1953, **8**, 675) in which the defatted material was first extracted with ammoniated ether in a Soxhlet apparatus. The ergotoxine content was above, and the ergometrine content below the U.S.N.F.X. minimum requirements. Parts of the sample infested with a small beetle-like insect had a lower content of alkaloid and fat. By means of partition chromatography it was shown that the ergots contained ergometrine, and probably ergotamine, ergotaminine, ergosine, ergosinine, ergocornine, ergocorninine, ergocristine, ergocristinine, ergocryptine and ergocryptinine, together with lysergic acid. G. B.

***Sedum acre*, Alkaloid Mixtures Isolated under Different Conditions from.** L. K. Bergane and A. Nordal. (*Medd. Norsk. Farm. Sels.*, 1958, **20**, 70.) Extracts of *Sedum acre* were submitted to paper chromatography, using butanol saturated with water, or butanol 4, acetic acid 1, water 5, as solvent, and examining the spots after treatment with a modified Dragendorff's reagent. This procedure was satisfactory for the separation of sedamine and sedridine. Canadian, Dutch, German and Norwegian specimens, collected at different times of year, were all found to yield sedamine and sedridine. Sedamine was the main alkaloid of the plant, from which it could be extracted by a simple process. A special technique was required for the extraction of sedridine.

G. B.

ANALYTICAL

Adrenaline and Noradrenaline, Fluorimetric Determination of, in Aqueous Solution. S. Roston. (*Analyt. Chem.*, 1958, **30**, 1363.) This method depends upon the differential transformation of adrenochrome and noradrenochrome into the corresponding fluorescent products adrenolutine and noradrenolutine. Two identical samples of mixture were taken and oxidised under the same conditions with ferricyanide to form mixtures of adrenochrome and noradrenochrome. One sample was then treated so as to form preferentially noradrenolutine and the other to form preferentially adrenolutine and the fluorescence measured in each case. From two simultaneous equations based on these readings and standard curves of the pure substances, the concentration of each in the mixture was calculated. The conditions for these preferential reactions depended upon interaction with varying amounts of alkali and ascorbic acid and have been carefully worked out. For 0·03–1 μg. of adrenaline and 0·05–1 μg. of noradrenaline the recovery of the amines was within 10 per cent of the amount added. As little as 0·01 μg. of adrenaline and 0·02 μg. of noradrenaline could be determined to within an error of $\pm$20 per cent.

D. B. C.

Chloramphenicol and Chloramphenicol Palmitate, Assay of, by Non-aqueous Titration. B. Salvesen. (*Medd. Norsk. Farm. Sels.*, 1958, **20**, 65.) Chloramphenicol and its palmitate may be assayed by hydrolysis at the amide linkage, followed by non-aqueous titration of the resulting aminopropanediol against perchloric acid. Chloramphenicol is readily hydrolysed with 25 per cent hydrochloric acid, but the ester must be dissolved in alcohol and boiled with hydrochloric acid. In either case the dichloroacetic acid and excess hydrochloric acid are removed by evaporating to dryness, after which the aminopropanediol hydrochloride is titrated with perchloric acid in the presence of mercuric acetate, using crystal violet as indicator. Direct titration of chloramphenicol or its palmitate with perchloric-acetic acid provides a basis of a rapid purity test to determine small quantities of aminopropanediol which may be produced during storage. A suitable technique is described, and 0·05 ml. of 0·01N perchloric acid is suggested as a suitable limit when using 0·1 g. of chloramphenicol or 0·2 g. of palmitate. G. B.

Prednisone in Tablets, Polarographic Determination of. H. P. Deys and J. A. C. van Pinxteren. (*Pharm. Weekbl.*, 1958, **93**, 760.) Preliminary experiments with prednisone showed that 10 mg., dissolved in 4 ml. of ethanol and 4 ml. of an acetate buffer, pH 5, and the mixture deoxygenated, gave a distinct wave between −1 V. and −1·5 V. When applied to tablets, it was found that the tablet excipients had a small but constant influence. Provided the temperature was controlled, a 5 mg. tablet could be assayed with an accuracy to within ±1 per cent of the mean, and the method required only half an hour since no extraction process was necessary. Prednisolone could be similarly assayed and could be distinguished from prednisone in that its half-wave potential was 0·05 V. more negative than the latter. In the case of prednisolone, the method was not applied to tablets, although the authors feel confident that it could be. D. B. C.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

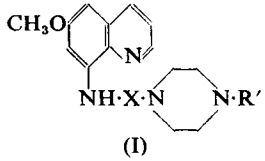
5-Hydroxytryptamine and Hyperglycaemia. G. B. West. (*Nature, Lond.*, 1958, **182**, 182.) It has been suggested that the hyperglycaemic substance present in the blood of the pancreatico-duodenal vein of animals treated with growth hormone is 5-hydroxytryptamine (5-HT). However, injections of 5-HT into normal dogs fail to produce a significant rise in blood sugar, although similar injections into depancreatised animals result in hyperglycaemia. Studying the distribution of 5-hydroxytryptophan decarboxylase, it was found that the pancreas possesses a considerable degree of enzyme activity. This was true for the rat, guinea pig, rabbit, cat and dog. In some instances the values compared favourably with those of the kidney, the richest known source of the enzyme. The method used was that of Gaddum and Giarman, substituting iproniazid for choline *p*-tolyl ether, as the inhibitor of monoamine oxidase. When 5-HT was used as the substrate and iproniazid omitted it was possible to estimate the monoamine oxidase activity of the homogenates. Again the pancreas was found to have a high value. This observation probably explains why the 5-HT content of the pancreas is low. It should now be possible to identify the hyperglycaemic substance in the pancreatico-duodenal blood after injections of growth hormone, and to test its action on the blood sugar of animals treated with monoamine oxidase inhibitors. M. B.

5-Hydroxytryptamine in Blood Platelets, Increase of, by Iproniazid. A. Pletscher and A. Bernstein. (*Nature, Lond.*, 1958, **181**, 1133.) It has been found that iproniazid causes an increase in the 5-hydroxytryptamine (serotonin, 5-HT) and noradrenaline content of the brain in various species. A significant rise in the catechol amine content of the myocardium of guinea pigs has been observed after the administration of iproniazid. These effects are probably due to the inhibition of monoamine oxidase, an enzyme present in brain and heart and which is markedly inhibited by iproniazid. Isoniazid, a compound which inhibits monoamine oxidase much less than iproniazid, causes little or no rise in the noradrenaline or 5-HT content of brain or heart. This paper deals with the effect of iproniazid on the 5-HT content of blood platelets. The amount of 5-HT was measured by a spectrophotofluorimetric method. In rabbits the daily administration of 30 mg./kg. of iproniazid for 4 days caused a marked rise in the blood 5-HT. In man the daily oral administration of 5–8 mg./kg. of iproniazid caused the platelet 5-HT to rise gradually. Isoniazid caused a much smaller rise. Thus it seems probable that this effect is connected with monoamine oxidase inhibition. It is possible that certain pharmacological actions of iproniazid are mediated by the increase of 5-HT in platelets. This might be true for certain effects of iproniazid on the heart, since the cardiovascular system is relatively sensitive to 5-HT. M. B.

Noradrenaline, Demonstration of 3-Methoxy Analogue of, in Man. A. Sjoerdsma, W. M. King, L. C. Leeper and S. Udenfriend. (*Science*, 1958, **127**, 876.) Recent studies have shown that a major metabolite of noradrenaline and adrenaline found in human urine is 3-methoxy-4-hydroxymandelic acid. Subsequently it was shown that the 3-hydroxy position of both noradrenaline and adrenaline can be methylated by animal tissues to yield the corresponding 3-methyoxy analogues. Since the conversion of catechol amines to their methoxy analogues may play some part in the physiology of these agents it seemed important to determine whether these substances exist in man. It was not possible to demonstrate the methoxy amines in human urine but on subjecting a human phaeochromocytoma to various extraction procedures followed by paper chromatography and spectrophotofluorimetry, 25 μg./g. of the 3-methoxy analogue of noradrenaline was detected. Preliminary studies suggest that these tumours contain the enzyme which transfers the methyl group from *S*-adenosylmethionine to the 3-hydroxy group of the catechol amines. M. B.

CHEMOTHERAPY

Leishmanicides, New Series of. E. Beveridge, L. G. Goodwin and L. P. Walls. (*Nature, Lond.*, 1958, **182**, 316.) A series of compounds of structure (I), in which X is a straight or branched alkylene chain and R is H, alkyl or hydroxyalkyl, have been shown to possess activity against *Leishmania donovani* in hamsters. The active members were more effective than pentavalent antimonials and aromatic diamidines when given subcutaneously, and moreover are also effective orally. The introduction of a third basic group in the alkylene chain as in I [X = $\cdot(CH_2)_2NH(CH_2)_2\cdot$] leads to inactivity, as does replacement of the terminal piperazine group by morpholino, piperidino or pyrrolidino rings. The 6-hydroxy-, 6-ethoxy- and 5:6-dimethoxy-compounds are also active, but the 6-chloro- and 6-unsubstituted compounds



(I)

are inactive. High activity is shown by compounds where X is $—(CH_2)_2—$. Some compounds of the series possess high activity against *Plasmodium gallinaceum* in chicks. J. B. S.

PHARMACOGNOSY

Cinchona Alkaloids, Biosynthesis of. J. Relijk. (*Pharm. Weekbl.*, 1958, **93**, 625.) Evidence is presented in support of the view that the crystalline alkaloids of cinchona bark are derived from amorphous alkaloidal precursors with an indole structure which are first formed in the leaves and later transported to the bark. This is in accord with a biosynthesis propounded by Woodward which starts from tryptamine and *m*-hydroxyphenylacetaldehyde. Evidence of an indole structure in a mixture of amorphous leaf alkaloids (which could not be further purified) is based on the similarity of the ultra-violet absorption spectrum to compounds such as cinchonamine, tryptophane and yohimbine which contain an indole structure. Many colour reactions of the above substances and the R_F value of cinchonamine are also similar to those of the leaf alkaloids. D. B. C.

PHARMACOLOGY AND THERAPEUTICS

Amiphenazole and Morphine in the Production of Analgesia. S. Gershon, D. W. Bruce, N. Orchard and F. H. Shaw. (*Brit. med. J.*, 1958, **2**, 366.) The combination of amiphenazole and morphine has been used for the treatment of intractable pain in terminal carcinoma in more than 500 patients over a period of 4 years. In the presence of amiphenazole (*a*) morphine may be given in large doses (200 mg. four times daily at 6-hourly intervals) without any risk to the patient, provided small doses are given initially; (*b*) drowsiness does not develop unless there is gross liver damage; (*c*) addiction to morphine does not develop (there is no euphoria, no craving, and no withdrawal symptoms on abrupt cessation of morphine administration). Complete analgesia for 24 hours in the day can be obtained. The dose of amiphenazole must be reduced at night to avoid insomnia. In some cases, where the patient becomes aware of his hopeless condition, and there is rapid deterioration, it is necessary to omit the amiphenazole. The mechanism of the combined action is still unknown, but it is suggested that the drugs combine, probably in the liver, to form a non-narcotic analgesic substance. The doses of amiphenazole used at present are much greater than those previously recommended; as much as 200 mg. three or four times daily may be given either orally or intramuscularly. Ten case histories are given. S. L. W.

Digitalis Glycosides, Effect of, on the Oxygen Consumption of Heart Muscle *In Vitro*. E. Peschel and C. Schlayer. (*J. Lab. clin. Med.*, 1958, **52**, 417.) The problem here was to see whether an increase of oxygen consumption is associated with the action of digitalis glycosides on heart muscle *in vitro*, and whether a difference could be demonstrated for the action of these substances on heart muscle as compared with other muscle. All experiments were done using the direct method of Warburg, employing rat heart slices. In any one experiment all slices were from the same animal. Homogenised or minced heart tissue was unsatisfactory. It was found that the digitalis glycosides stimulate the oxygen consumption of the rat heart slices by 12–19 per cent.

The effective concentration is about 10^{-5} M. The oxygen consumption of other tissues, such as kidney and liver, is slightly depressed by corresponding concentrations of the glycoside. The oxygen consumption of the diaphragm is depressed by even very small concentrations of the glycoside. This depression, increasing with dosage, is probably an indication of temporary cell damage. This might explain the liberation, by therapeutic doses of digitalis in man, of intracellular potassium without any effect on the sodium and potassium balance of the heart. M. B.

Fibrinolysin in the Treatment of Thromboembolic Disease. K. M. Moser. (*J. Amer. med. Ass.*, 1958, **167**, 1695.) A study of the effects of intravenously administered fibrinolysin (plasmin) was carried out in 52 patients with various forms of thromboembolic disease, the object being to achieve a level of plasma fibrinolytic activity which would be capable of dissolving an intravascular thrombus without undue toxic effects. The conditions treated included deep venous thrombophlebitis, pulmonary embolism, peripheral arterial occlusion, and superficial thrombophlebitis. The profibrinolysin used was a highly purified derivative of human plasma protein fraction 3. It was activated to fibrinolysin (Actase) with small amounts of purified streptokinase, after which the residual streptokinase was removed and the activated material lyophilised. One fibrinolytic unit of fibrinolysin has been defined as that amount of a standard preparation which will change the turbidity of a standard fibrinogen-thrombin clot by 50 per cent in 10 minutes. The fibrinolysin was dissolved immediately before use in 500–1000 ml. of 5 per cent dextrose in water, the infusion being carried out over 2–4 hours. Thirteen patients received infusions of 30,000 fibrinolytic units (FU), 19 patients 40,000–50,000 FU, and 20 patients 69,000–90,000 FU. In the doses used toxicity appeared to be limited to pyrogenicity, which occurred in 49·2 per cent of the patients. There were 2 cases of delayed allergic skin reaction. No embolic events followed the infusions, and no haemorrhagic phenomena occurred in any patient, including 29 who were simultaneously receiving anticoagulant drugs. Fibrinolytic activity of the plasma was consistently enhanced by the infusions, the intensity and duration of this activity running parallel with the total fibrinolysin dosage. Anticoagulant drugs should be used in all patients to prevent rethrombosis, unless it is clear that the factors which led to thrombosis have subsided. The therapeutic results were encouraging and justify the view that fibrinolysin may prove a safe and effective agent for achieving acute lysis of intravascular clot, but firm conclusions must await completion of large-scale controlled studies.

S. L. W.

Framycetin Sulphate in the Treatment of Skin Infections. D. Burrows. (*Brit. med. J.*, 1958, **2**, 428.) Fifty patients with skin infection were treated with framycetin sulphate 1·5 per cent in a water-soluble ointment base. The cases were made up of impetigo 32, infective dermatitis 9, secondarily infected eczema 4, infected papular urticaria 2, folliculitis and sycosis barbae 1. Twenty-two of the cases of impetigo were cured within one week, and only 2 failed to respond —one of impetigo and one of infective dermatitis. The ointment was applied three or four times daily, removing crusts with a 1 per cent solution of cetrimide. In 38 patients all of whom responded, *Staphylococcus aureus haemolyticus* was isolated; in 19 cases *Streptococcus haemolyticus* was isolated and only 5 were sensitive to the antibiotic; this may reduce its effectiveness in general use. No case of contact sensitivity or irritation was observed. S. L. W.

Methylpentynol Carbamate, Susceptibility to. E. Marley. (*Brit. med. J.*, 1958, **2**, 493.) Methylpentynol carbamate was administered in a dose of 0·2 g. four times daily to 10 patients who had previously developed toxic symptoms while receiving a 5-day therapeutic trial of methylpentynol, 0·5 g. four times daily. Except in one patient who showed a maximal toxic response, it was shown during a similar 5-day period that the carbamate was much superior in its freedom from incidental toxicity. However, in a population known to be especially sensitive to methylpentynol, the use of the carbamate as an alternative in doses of 1 g. a day or greater is likely to be followed by the early manifestation of toxic symptoms. S. L. W.

Morphine, Inhibitory Action on Guinea Pig Ileum. H. W. Kosterlitz and J. A. Robinson. (*Brit. J. Pharmacol.*, 1958, **13**, 296.) Small concentrations of morphine inhibit the peristaltic reflex of the guinea pig isolated intestine. A study of its effects on the longitudinal muscle has shown that it markedly inhibits the contractions produced by nicotine, barium and 5-HT; while the actions of acetylcholine, carbachol and histamine were hardly affected. After morphine the addition of atropine reduced the residual contractions of nicotine and 5-HT, but had scarcely any effect on barium. The additional effect of atropine on nicotine was always greater than on 5-HT. While hexamethonium depressed the action of barium alone, after morphine the residual contraction was unaffected. With nicotine the residual contraction after morphine was further depressed by hexamethonium. The morphine antagonists nalorphine and levallorphan had both a morphine-like action and at the same time a morphine-inhibiting action, which varied with the antagonist used. The morphine-like actions were most pronounced on the effect of 5-HT, which was antagonised; while the morphine protecting action was most strongly present on the effect of nicotine. G. F. S.

Pentacynium Methylsulphate; Effect on Renal Circulation in Hypertension. J. R. Cox and J. J. Daly. (*Brit. med. J.*, 1958, **2**, 78.) The effect of pentacynium methylsulphate on the renal circulation was studied in 9 patients with hypertension. The drug was given subcutaneously in a dose of 25 mg. in seven patients and 12·5 mg. in two. A fall of blood pressure to normal levels occurred in all subjects and persisted for at least 16 hours. Reduction in effective renal blood flow (E.R.B.F.) and glomerular filtration rate (G.F.R.) occurred initially in all patients in 30 minutes. In 4 patients the mean E.R.B.F. and G.F.R. had risen to 50 per cent of the mean control value by 60 to 110 minutes; in 2 patients with severe renal damage these values had risen to greater than their control values after 110 minutes. Similar changes in renal haemodynamics occur with other ganglion-blocking drugs, but pentacynium has the advantage that it is effective with a single daily administration and therefore causes less frequent changes in these values than other drugs requiring more frequent administration. S. L. W.

Sodium Diethyldithiocarbamate (Dithiocarb) in Nickel Carbonyl Poisoning. F. W. Sunderman and F. W. Sunderman, Jr. (*Amer. J. med. Sci.*, 1958, **236**, 26.) Eleven workers suffering from accidental exposure to the vapours of nickel carbonyl were successfully treated with sodium diethyldithiocarbamate (dithiocarb), the drug being given by mouth in doses of 0·5 g. three or four times

daily, together with 0·5 g. of sodium bicarbonate and a glass of water. Nickel carbonyl is one of the most toxic chemicals encountered industrially and owing to its high volatility it is difficult to avoid exposure to inhalations during handling. Measurement of nickel concentration in the initial 8-hour collection of urine is a valuable aid in determining the severity of poisoning. The upper normal limit for the concentration of nickel in urine is 3·0 μg./100 ml. If the initial 8-hour specimen has a concentration of less than 10 μg./100 ml. the exposure is classified as mild, and serious delayed symptoms will probably not develop; if the concentration is above 10 μg. but less than 50 μg./100 ml. the exposure is moderately severe, and delayed symptoms are likely to develop; and if the concentration is above 50 μg./100 ml. the exposure is severe and serious illness is likely. In the moderate or severe cases dithiocarb therapy is instituted and continued until the patients are free from symptoms and the concentration of nickel in the urine is less than 10 μg./100 ml. In critical cases it is suggested that dithiocarb may be administered parenterally, in an initial dose of 25 mg./kg. bodyweight, the total amount during 24 hours being limited to 100 mg./kg. bodyweight: so far, no patients have been treated parenterally. In the 11 patients in this series (in one of whom the initial nickel concentration was 200 μg./100 ml.) the symptoms of poisoning were relieved within a few hours after administration of dithiocarb. Delayed reactions were minimal and convalescence uneventful, normal levels of nickel concentration in the urine being reached within 16 days of exposure. This was in marked contrast to the treatment previously of 31 cases of severe nickel poisoning with dimercaprol, in which 2 patients died and the majority required several months convalescence. Patients treated with dithiocarb should abstain from alcohol, or symptoms similar to those following the use of disulfiram may occur. S. L. W.

Substance P—Effect on Peristaltic Reflex. D. Beleslin and V. Varagić. (*Brit. J. Pharmacol.*, 1958, **13**, 321.) Substance P potentiated the peristaltic reflex of the guinea pig isolated ileum when introduced into the lumen. In fatigued preparations substance P produced vigorous peristalsis, it also abolished the depressant action of 5-HT on the reflex. The effect of substance P on peristalsis was abolished by hexamethonium. Injection of substance P into the lumen of the intestine, from which the mucous membrane had been removed, did not restore the peristaltic reflex. The experiments show that substance P may produce peristalsis when the tryptamine receptors have been saturated, and therefore the receptors for this substance may differ from those for tryptamine. G. F. S.

Trifluoperazine in the Treatment of Chronic Psychotics. M. E. Forrester. (*Brit. med. J.*, 1958, **2**, 90.) A short trial of trifluoperazine (Stelazine) was undertaken with 25 chronic psychotic patients. The dosage was built up over a period of two weeks to 30 mg. daily (in 2 patients to 40 and 45 mg. daily respectively). Treatment lasted for 4 weeks and the dosage was then gradually reduced until discontinuance. Benzhexol, 6–8 mg. daily, was used to counteract side-effects. The changes in behaviour were: very slightly improved, 6; no change, 10; worse, 6; much worse, 3. With the dosage used, the side-effects, chiefly of the Parkinson type, were so marked and unpleasant that it is doubtful whether the drug would be acceptable for routine use, and in view of the lag of time between stopping the drug and the subsidence of side-effects it would appear that the drug is cumulative in the body. The amount of improvement in a few cases was not sufficient to encourage further use. S. L. W.