ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

Morphine, Codeine and Thebaine, Origin of the Methyl Groups in. A. R. Battersby and B. J. T. Harper. (*Chem. Ind.*, 1958, 365.) Methyl-^{14}C-L-methionine and ^{14}C-sodium formate have been fed separately to growing *Papaver somniferum* plants. Separation of the alkaloids found by counter-current distribution showed that in both experiments morphine, codeine and thebaine were radioactive. Cleavage of *O*- and *N*-methyl groups separately from each alkaloid (with hydriodic acid), fixation of the liberated methyl iodide as tetramethylammonium reineckate, and determination of the respective activities showed that the methyl groups of morphine, codeine and thebaine accounted for between 55 and 78 per cent of the total activity of the molecules in the methionine experiment. Results from the formate experiment were less conclusive on account of the low specific activities of the alkaloids. The results show, however, that both *O*- and *N*-methyl groups of the opium alkaloids can be derived from methionine, and less efficiently from formate, and are in accord with similar studies using them as precursors for the alkaloids hordenine, protopine, ricinine, hyoscyamine and nicotine. J. B. S.

ANALYTICAL

Adrenaline and Related Compounds, Determination of, on Paper Chromatograms. G. L. Ellman. (*Nature, Lond.*, 1958, **181**, 768.) The most sensitive chemical method for the estimation of adrenaline is the reaction with ethylenediamine. This reaction yields a number of products, some of which are fluorescent and which can be used for quantitative measurement. Noradrenaline produces a fluorescence of different colour so that mixtures of the two substances can be determined. The number of products formed in this reaction was determined by chromatographing the products formed by the interaction of the diamine and various catechols. This was done on paper using as solvent 5 per cent ammonium hydroxide and *n*-propanol (9:1). It was found that adrenaline yields some products different from those given by noradrenaline but under these conditions the products from catechol, noradrenaline, hydroxytyramine and epinine migrate similarly. The addition of ferricyanide or iodide to the ethylenediamine does not change the qualitative nature of the fluorescent pigments but does increase the amounts formed. Details of the method are then given. With such a method 0·03 μg. of adrenaline can be detected. M. M.

Solanaceous Alkaloids in Pharmaceutical Preparations, Colorimetric Estimation of. I. Nir-Grosfeld and E. Weissenberg. (*Drug. Standards*, 1957, **95**, 180.) Two colorimetric procedures are described, each of which is claimed to assay as little as 20 μg. of alkaloid. In both methods the alkaloids are first converted to the nitro derivatives. In the first method, (I) based on the Vitali reaction, after extraction with chloroform as described in the U.S.P. XV, an aliquot containing 0·25 to 1 mg. of alkaloid is evaporated to dryness on a water bath and nitric acid added. After heating until all the fumes have been driven off, the residue is dried at 105° for 15 minutes and cooled to room temperature. It is then dissolved in acetone and quantitatively transferred to a 25 ml. flask

and made up to the mark with acetone. To 5 ml. of this solution is added, with shaking, 2 ml. of *iso*propylamine and 0·1 ml. of 0·1 per cent methanolic potassium hydroxide. Exactly 1 minute after, readings are taken in a photometer at 540 mμ. Comparison is made with a standard curve prepared using pure atropine sulphate. In method (II), following extraction and nitration as for I, the residue is dissolved in 10 ml. of 50 per cent ethanol. To this is added 2·5 ml. of 10 per cent hydrochloric acid and 0·1 g. zinc dust, and the mixture heated on a water bath for 10 minutes. The mixture is then cooled to room temperature, filtered into a 25 ml. flask, washing the residue. One ml. of 1 per cent sodium nitrite is added, and after mixing, the contents are allowed to stand for 10 minutes. Excess nitrite is destroyed by the addition of 1 ml. of 2·5 per cent solution of ammonium sulphamate. Ten minutes later 1 ml. of 1 per cent aqueous solution of *N*-naphthylethylenediamine dihydrochloride is added, and the mixture made up to the mark with distilled water. After colour development for 30 minutes, readings are made at 550 mμ and compared with a standard curve as in I. A large number of different pharmaceutical preparations containing solanaceous alkaloids were assayed and checked by these methods, and results obtained were found to be both reproducible and satisfactory. J. R. F.

Strychnine, Colour Reactions for. M. Pećar. (*Acta pharm. Jug.*, 1957, **7**, 75.) When a small quantity of strychnine base is heated with sodium selenite and hydrochloric acid (37 per cent HCl) an intense red colour develops. On prolonged heating the colour changes to golden yellow. On cooling, a fine red precipitate forms, which is readily dispersed to give a liquid which appears light orange-red in reflected light, and light yellow by transmitted light. When 0·5 ml. of a solution containing strychnine is acidified with a drop of hydrochloric acid and mixed with a drop of a 10 per cent solution of potassium dichromate, the appearance depends upon the quantity of strychnine present, and with relatively low concentrations of the alkaloid an approximate assay may be carried out by measuring the intensity of the colour produced.

G. B.

PHARMACY

Alginate Mucilages, Investigations of their Preparation and Rheological Behaviour. R. Bolliger and K. Münzel. (*Pharm. Acta Helvet.*, 1958, **33**, 141.) The authors show that alginate solutions are pseudoplastic liquids, the viscosity of which decreases as the shearing stress increases. The pseudoplastic nature of the solutions is proved by the fact that the shearing stress is not proportional to shearing speed, as it would be in the case of an ideal liquid. It is also shown that the viscosity falls very rapidly with increase of temperature. For example, the viscosity in one case was only about 10 per cent at 90° of what it was at 10°. At temperatures of 70° or over there is evidence of some depolymerisation since the final viscosity is less. 70° is thus the maximum temperature recommended for the preparation of mucilages. Thus while it is possible to prepare mucilages by direct solution in water with vigorous stirring, it is best to rub down the alginate with sufficient ethanol or glycerol (2–4 per cent of the final volume), and then to add the water slowly with constant stirring. Such mucilages reach their maximum quasiviscosity within 1 hour, but the value soon begins to fall to a fairly constant value after 24 hours, although the viscosity must still be considered as very unstable. D. B. C.

PHARMACOGNOSY

Aloe Drugs, Paper Chromatographic Investigation of. W. Awe, H. Auterhoff and C. L. Wachsmuth-Melm. (*Arzneimitt.-Forsch.*, 1958, **8**, 243.) The paper chromatography of various species of *Aloes*, especially that of Cape aloes was reviewed and investigated. The process was carried out using paper 4 cm. × 50 cm. (Schleicher and Schüll 2043b Mgl.) and a butanol-glacial acetic acid-water (40 : 10 : 50) as solvent. One drop of a 1 per cent methanolic solution of the drug was used. The spots were viewed in ultra-violet light before and after development with 0·5N KOH solution. This alkali treatment revealed other spots. In Cape aloes the following spots were observed: R_F 0·5, an unidentified anthracene derivative possibly containing 1 : 8-dihydroxyanthraquinone structure; R_F 0·65, Cape aloin; R_F 0·81, *p*-cumaric acid and resin; R_F 0·88, aloe-emodin. D. B. C.

PHARMACOLOGY AND THERAPEUTICS

Antitussive Agents, Pharmacological Studies on New Synthetic. C. I. Chappel, M.-G. P. Stegen and G. A. Grant. (*Canada J. Biochem. Physiol.*, 1958, **36**, 475.) Three basic alkoxyalkyl esters of phenothiazine-10-carboxylic acid were synthesised and tested for antitussive activity, antispasmodic activity, local anaesthetic activity and acute toxicity. Antitussive activity was studied in lightly anaesthetised cats, "coughing" being induced by electrical stimulation of the superior laryngeal nerve and recorded on a revolving drum by means of a writing lever attached to the abdominal muscles just below the sternum. All three compounds possessed antitussive activity in the range of activity of codeine. The most potent antitussive agent was dimethylaminoethoxyethyl phenothiazine-10-carboxylate. It was shown to possess a moderate local anaesthetic action but only slight antispasmodic activity and low acute toxicity. Further studies on this compound showed it to be devoid of central depressant or analgesic properties and no evidence of chronic toxicity in the rat or dog was obtained. As a result of these findings the dimethyl derivative was chosen for clinical trial. W. C. B.

Cutaneous Absorption from Ointment Bases, Study of Pharmacological Methods for the Evaluation of. G. Valette and M. Huerre. (*Ann. pharm. franç.*, 1957, **15**, 601.) Physostigmine was incorporated into a series of ointment bases, and the speed of absorption by the skin of rats was determined by measurement of the increase in amplitude of contractions of the muscle on electrical stimulation of the sciatic nerve. Further experiments were carried out using leptazol, and assessing absorption by measuring the time interval before the occurrence of convulsions in mice. Absorption of testosterone was assessed by observations on the development of the comb in chicks. There were some discrepancies between the results by the three methods, but in all cases soft paraffin, lanolin-soft paraffin, and water-in-oil emulsion bases (emulsified with triethanolamine stearate) were ineffective in promoting absorption. Lard assisted the penetration of testosterone, but not of physostigmine or leptazol. Cold cream basis increased penetration to some extent, but an anhydrous basis of *p*-cymene with polyethylene favoured penetration more than any other type of base investigated. G. B.

5-Hydroxytryptamine, Histamine, Dextran, Eggwhite and Compound 48/80, Inhibition by Various Substances of Oedema Formation in the Rat Induced by. J. R. Parratt and G. B. West. (*Brit. J. Pharmacol.*, 1958, **13**, 65.) Dextran and eggwhite in the rat cause oedema by the release of 5-hydroxytryptamine. Drugs which deplete the tissues of 5-hydroxytryptamine (5-HT) or block its actions reduce or prevent the oedema. Oedema-producing substances were injected into the rat hind paw and the oedema assessed from the swelling and blueing of the paw, after an intravenous injection of Evan's blue. Of the 5-HT antagonists, 2-bromolysergic acid diethylamide prevented oedema formation by 5-HT, eggwhite and compound 48/80 but not histamine. Of the antihistamines, mepyramine and phenindamine were weak in inhibiting the oedema formation by most agents. Thenalidine was most efficient against dextran and eggwhite. The antimetabolites of 5-HT, 5-methoxy-2-methyltryptamine and 1-benzyl-5-methoxy-2-methyltryptamine did not markedly influence oedema production. Adrenaline was a potent inhibitor of dextran and eggwhite oedema and this was not due to vasoconstriction since noradrenaline was much less active. Of the phenothiazine derivatives the most active was the new compound methotrimeprazine which has potent antihistamine and anti-5-HT actions. This compound was the most active antagonist of the locally induced anaphylactoid reactions so far tested. The results of these experiments indicate that both histamine and 5-HT play rôles in increasing capillary permeability in the rat. G. F. S.

5-Hydroxytryptophan, Pharmacological Studies of. D. F. Bogdanski, H. Weissbach and S. Udenfriend. (*J. Pharmacol.*, 1958, **122**, 182.) In previous experiments it has been shown that 5-hydroxytryptophan (5-HTP), when given to animals, rapidly penetrates into most tissues and is converted to serotonin wherever the enzyme 5-HTP decarboxylase is present. In dogs it was found possible to raise the brain level of serotonin to 10 times normal by the administration of its precursor. The studies reported here consist of a general survey of the pharmacological actions of 5-HTP. It was found that the administration of 5-HTP to dogs, cats, rabbits, rats and mice produced somatic, autonomic and behavioural effects which resembled those of lysergic acid diethylamide. Those effects were associated with a rise in the serotonin levels in the blood, the central nervous system and the peripheral tissues. In dogs and cats low doses of 5-HTP decreased spontaneous activity. Larger doses caused excitement and disorientation accompanied by depressant effects on certain reflexes, motor control and sensory functions. Behavioural effects included disorientation and fear in dogs, and sham rage in cats. Rodents showed excitement and increased spontaneous activity. Large doses produced excitement followed by depression in all species. 5-HTP also produced mydriasis, piloerection, tachycardia, salivation, lacrimation, tachypnoea, retching, vomiting and increased intestinal motility. There was a marked increase in the serotonin concentration in the rat uterus. Much of this serotonin was found to be pharmacologically inactive. The possible functional significance of serotonin in the brain is discussed and it is suggested that 5-HTP may prove a useful tool in studying the function of serotonin. As a means of administering serotonin, 5-HTP offers a number of advantages over injection of the amine. Unlike serotonin, 5-HTP readily penetrates the blood-brain barrier and forms serotonin within the central nervous system. 5-HTP is converted to serotonin at sites where it is normally formed so that some of its effects may more nearly reflect the physiological functions of the amine. 5-HTP permits the maintenance of relatively high levels of tissue serotonin for long periods of time, while serotonin itself is rapidly destroyed when administered exogenously. M. M.

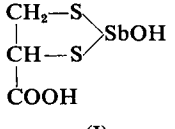
Mecamylamine, Gastrointestinal Secretion and Absorption of. E. J. Zawoiski, J. E. Baer, L. W. Braunschweig, S. F. Paulson, A. Shermer and K. H. Beyer. (*J. Pharmacol.*, 1958, **122**, 442.) Mecamylamine, after intravenous or oral administration, was secreted by the gastric mucosa of unanaesthetised Heidenhain pouch dogs with total antrum resections. A definite relationship existed between the amount of mecamylamine secreted and the acidity of the gastric secretions. In the presence of highly acidic gastric juice induced by stimulation with sodium acetate, histamine or acetyl-β-methylcholine, the secretion of mecamylamine was greatly enhanced. Simultaneous parotid secretion studies did not reveal the presence of mecamylamine in salivary collections and the suggestion is made that the alkalinity of the saliva might account for this. It was found that little, if any, mecamylamine was absorbed by the gastric mucosa in experiments in which mecamylamine was instilled directly into the gastric pouches. In a further series of experiments carried out on anaesthetised dogs, mecamylamine was injected into the lumen of the small intestine. At various time intervals after injection, intestinal loops were excised and the amount of mecamylamine remaining in them was determined. Plasma drug levels were determined simultaneously and were consistent with the interpretation that the decrease in recovery from the lumen was the result of absorption from the intestinal loops. At no time during these tests was any mecamylamine secreted into the small intestine of the dogs. The results demonstrate that there is a definite basis for a gastrointestinal cyclisation of mecamylamine which is favourable to its over-all physiological economy.

W. C. B.

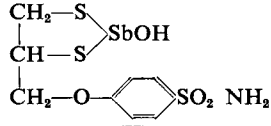
Rauwolfia A—An Alkaloid from *Rauwolfia verticillata* (Lour.) Baill, Pharmacological Studies on. L. Chi-chiang and C. Wei-chow. (*Acta Physiol. Sinica.*, 1957, **21**, 283.) Rauwolfia A, isolated recently by Chou from *R. verticillata* collected from Kwangtung province, was investigated for its effects on blood pressure, respiration, heart and acute toxicity. The alkaloid produced a hypotensive effect on anaesthetised rabbits and cats. In cats anaesthetised with pentobarbitone intravenous injections of 2 mg./kg. produced a prompt fall of arterial pressure and an average reduction of 27 per cent. After 1½–2 hours the blood pressure recovered gradually. Repeated administrations revealed no significant tachyphylaxis. There was bradycardia and, in most cases, slight depression of the respiratory amplitude during the early phase of pressure falling, but no influence on the respiratory rate. Rauwolfia A inhibited the pressor responses to electrical stimulation of the afferent vagi and sciatic nerves and also to the carotid occlusion pressor reflex. After its administration, acute carotid sinus neurotomy (after vagotomy) did not alter the blood pressure. The hypotensive effect was not eliminated by atropinisation or vagotomy. It caused inhibition and reversal of the pressor response to injected adrenaline. A larger dose of rauwolfia A inhibited the direct vasoconstriction caused by stimulation of splanchnic nerves, and reversed the subsequent adrenergic pressor effect. Thus, it may be regarded as having both a central site of action and adrenolytic effect. It produced a slowing of heart beat on the perfusion of isolated toads' hearts. In 1 : 5,000 dilution, A–V block occurred. It caused increase of the output in the concentration of 1 : 10,000 and 1 : 25,000. Although the minute output was reduced gradually at the lower dilutions, no significant change in stroke volume for each beat was recorded. In mice the acute LD50 after intraperitoneal injection of rauwolfia A was found to be 0·34 g./kg. It produced severe emesis but no respiratory failure or loss of equilibrium in pigeons at the dose of 20 to 40 mg./kg. given intravenously.

Serotonin, Displacement of, from Tissues by a Specific Antimetabolite. D. W. Woolley and P. M. Edelman. (*Science*, 1958, **127**, 281.) The aim of this work is to determine whether BAS (1-benzyl-2-methyl-5-methoxytryptamine), the benzyl analogue of serotonin, would displace serotonin in animal tissues. Rabbits were given 15 mg./kg. of BAS daily for 3 days. The serotonin content of the blood platelets was then assayed, both colorimetrically and pharmacologically on the isolated uterus of the rat. It was found that this treatment with BAS lowered the serotonin content of the platelets by about 50 per cent. Measurements were also made on the effect of BAS administration on the serotonin content of the stomach and the small intestine of mice. In these tissues there was only a slight reduction in the serotonin content. Measurements on the urine of mice treated with BAS showed that excretion of 5-hydroxyindoleacetic acid was not increased but that the urinary excretion of serotonin was markedly increased. Apparently the BAS inhibited the action of amine oxidase and consequently the displaced serotonin was excreted largely unchanged. The finding that there is a displacement of serotonin from tissues by a specific antimetabolite may have some bearing on the mode of action of reserpine. It may be that some of the pharmacological actions of reserpine arise from this antiserotonin property. The ability of reserpine to displace serotonin from tissues is a type of action possessed by specific antimetabolites, such as BAS. M. M.

Schistosomiasis japonica, Activity of Compounds with Dithiadihydrostibiol Structure against, in Mice. T. Yea-lin, C. Chiao-chen, C. Chih-chiang, L. Yu-i and T. Kuang-sheng. (*Acta physiol. Sinica*, 1956, **20**, 125.) A series of 8 new compounds with the dithia-dihydrostibiol structure has been compared for therapeutic activity against schistosomiasis japonica in white mice. Each drug, thoroughly mixed with the finely powdered food, was fed to healthy mice for 14 days, and the LD10 and LD50 were evaluated. At the dosages of LD10 and LD50 each drug was fed to treat diseased mice (beginning on the 36th day after percutaneous infection on the abdomen with 40 cercariae per mouse) for 14 days. After a holding period of another 14 days the mice were killed. Both portal system and liver were examined for worms. Basing on the average number of worms remained in each mouse, the therapeutic effects of compounds I and II out of the 8 compounds were better than that of tartar emetic administered orally.



(I)



(II)

Valyl-Oxytocin: Effect on Man. C. N. Smyth. (*Brit. med. J.*, 1958, **1**, 856.) A comparison was made of valyl-oxytocin, an analogue of synthetic oxytocin, with synthetic oxytocin itself in man. As an excitor of contractions valyl-oxytocin is four times as potent as synthetic oxytocin, even though the two substances are equiactive when assayed by the pharmacopoeial method. If, however, valyl-oxytocin is diluted four times so as to be equiactive with oxytocin then it is also practically equiactive in terms of the rise in milk ejection pressure in the rabbit mammary gland and in its action on the cat uterus *in situ*. Synthetic and natural oxytocin give roughly identical results when tested by any of the above methods and it appears that the milk-pressure assay, or that of the cat uterus *in situ*, might with advantage be used in addition to the pharmapoeial methods. Doses of valyl-oxytocin which are equiactive in the human

subject with oxytocin in exciting uterine contractions are not equiactive in effects on blood pressure. Blood pressure is affected only by extremely large doses of oxytocin, 2 units intravenously usually being required to produce a pressure fall lasting about a minute and occurring 2 to 3 minutes from the time of injection. Half a unit of valyl-oxytocin does not produce this effect but 2 units will do so. In this respect, the pharmacopoeial assay of the two substances on chicken blood pressure or isolated rat uterus is parallel to the comparison in man. Valyl-oxytocin was given to 8 parturient patients by intravenous infusion, using concentrations varying from 0·5 to 4 units per litre of 5 per cent dextrose. It produced a good contractile rhythm, no abnormal effects were noticed, and the babies showed no signs attributable to intrauterine anoxia or abnormal pressures. S. L. W.

Voacamine and Voacorine, Alkaloids of *Voacanga africana* Stapf., Comparative Pharmacological Study of. M. A. Quevauviller and O. Blanpin. (*Ann. pharm. franç.*, 1957, **15**, 617.) Experiments using various animals (mouse, guinea pig, rabbit, dog, cat) showed that voacorine and voacamine are 100 to 250 times less toxic than digitalis glycosides, and that voacorine resembles digitalis in its action on the heart. Voacamine differs in stimulating cardiac muscle without slowing the rhythm. Voacamine was shown to have a definite hypotensive effect, with some variation in sensitivity between the animal species used but voacorine appeared to have a hypertensive effect. Both alkaloids induced contraction of smooth muscle, voacorine by direct stimulation of the muscle, and voacamine by parasympathomimetic action. G. B.

APPLIED BACTERIOLOGY

8-Hydroxyquinoline Derivatives, Antimicrobial Effect of. N. Diding and S. Ström. (*Pharm. Weekbl.*, 1958, **93**, 201, also *Svensk. farm. Tidskr.*, 1957, **61**, 508.) The 8-hydroxyquinoline derivatives under examination were ground to fine powder, and sterile suspensions containing 200 μg./ml. in water were prepared. Serial dilutions were made in nutrient broth and Sabouraud broth and inoculated and incubated. In some of the tests a small proportion of tween 80 or benzalkonium chloride was added to indicate the effect of surface-active agents which are included in some tablet formulations. 5-Chloro-7-iodo-8-hydroxyquinoline and 2-methyl-5:7-dichloro-8-hydroxyquinoline were active against staphylococci, enterococci and *Candida albicans*. Some synergistic effect due to the surface-active agent was observed in the case of enterococci. 5:7-Diiodo-8-hydroxyquinoline was not effective against these organisms. The derivatives were less effective against *Escherichia coli*, and the addition of tween 80 increased the effect of the 5-chloro-7-iodo derivative only. The substances were not effective against *Pseudomonas aeruginosa*, *Salmonella typhi* and *Proteus vulgaris*, although in some experiments the addition of tween 80 again increased the effect of the 5-chloro-7-iodo compound. All three compounds seemed to have an inhibitory effect on the microflora in man. G. B.

Vitamin B_{12}, Microbiological Assay of, in Antibiotic Preparations. N. A. Diding. (*Pharm. Acta Helvet.*, 1958, **33**, 156.) A 30-fold increase in resistance to tetracycline of a mutant of *E. coli* was achieved by repeated subculturing of the organism in the presence of increasing concentrations of tetracycline. This could be used to assay a preparation containing B_{12} in the presence of 250,000 to 4,000,000 times the concentration of tetracycline. It is thought that this technique will be of value for the assay of other preparations containing antibiotics and vitamins. D. B. C.