ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ANALYTICAL

Barbiturates, Two-dimensional Paper Chromatographic Method for the Separation of. H. Möllerberg. (*Scand. J. clin. Lab. Invest.*, 1958, **10**, 59.) Paper chromatograms were first run with ammoniacal chloroform as solvent, by the descending technique. The second run, perpendicular to the first, was made using ammoniacal amyl acetate. The ammoniacal solvents were prepared by shaking 2 parts of solvent with one part of concentrated ammonia solution and separating. The chromatograms were dried at 100° and treated with ammonia vapour for 5 minutes, after which barbiturates were detected by examining the paper in ultra-violet radiation. On spraying the chromatogram with 0·02M potassium permanganate, barbiturates containing a reducing radical appeared as yellow spots on a red ground. Derivatives containing a *cyclo*hexenyl or *cyclo*heptenyl group showed delayed reduction and appeared as yellow spots about one minute after spraying. R_F values were determined for 18 derivatives, and it was shown that *N*-methylated derivatives have considerably higher R_F values than non-methylated ones. For the confirmation of the identity of unknown spots, solutions of authentic specimens should be chromatographed at the same time for comparison. G. B.

Cardiac Glycosides and Organic Nitrates, Chemical Determination of in Pharmaceutical Preparations. A. Kurkela. (*Pharm. Acta Helvet.*, 1958, **33**, 216.) The colorimetric reaction of cardiac glycosides with alkaline picrate (Baljet reaction) is suggested as a suitable basis for the assay of these in pharmaceuticals such as solutions, ampoules, tablets and suppositories containing more or less pure glycosides. The absorption maximum is at 492 mμ and this is non-specific. The standard curve must therefore be prepared from the same pure glycoside as that contained in the preparation. Most results fell within ± 5 per cent. The scillarins which do not give the Baljet reaction were assayed by the Lieberman reaction. Pharmaceutical organic nitrates such as glyceryl trinitrate and erythrityl tetranitrate were assayed either colorimetrically using phenoldisulphonic acid, or by reduction to ammonia and titration with sulphuric acid. Again, most results were within ± 5 per cent. D. B. C.

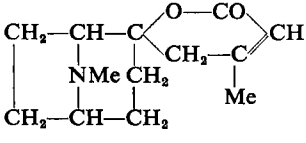
Colchicine, Chromatographic-Spectrophotometric Method for the Separation and Determination of. S. J. Smolenski, F. A. Crane and R. F. Voigt. (*J. Amer. pharm. Ass., Sci. Ed.*, 1958, **47**, 359.) Samples of about 10 g. of colchicum seed were defatted by continuous extraction with light petroleum, and the colchicine extracted with ethyl acetate containing 1 per cent of ethanol. This solvent was used in preference to pure ethanol because it was found to extract less resin with the alkaloid. The extract was freed from resinous impurities by chromatography on an alumina column, colchicine being eluted with 10 per cent methanol in chloroform. Other impurities were then removed by chromatography on a silica column. The purified colchicine was treated with nitric acid

followed by sodium hydroxide to produce a red colour, and determined quantitatively by measuring the light absorption at 350 mμ, calculating the amount of colchicine by reference to a standard curve prepared using known amounts of pure colchicine. The colour reaction with nitric acid, which gives rise to a succession of colours, followed by red on the addition of alkali, was used for checking the identity and purity of the product, and testing for completeness of extraction. G. B.

Lysergic Acid Diethylamide and Ergonovine, The Fluorimetric Determination of. E. S. Boyd. (*Arch. int. Pharmacodyn*, 1958, **115**, 43.) A fluorimeter in which the sample was irradiated with mono-chromatic light and the fluorescence analysed monochromatically, was constructed and tested. The instrument was basically similar to the Bowman fluorimeter. The fading of fluorescence of lysergic acid diethylamide and ergonovine in this instrument was investigated and found to be influenced to some extent by pH, the least amount of fading occurring between pH 5 and 7. The author concludes that instruments of this type are useful for quantitative analysis of various pure materials which fluoresce, providing fading of fluorescence is avoided and for obtaining excitation and fluorescence maxima which are not necessarily true values but which may be useful for comparison purposes as long as the same instrument is used for the comparisons. W. C. B.

ORGANIC CHEMISTRY

Dioscorine, Constitution of. J. B. Jones and A. R. Pinder. (*Chem. Ind.*, 1958, 1000.) 6-Oxotropane has been synthesised from 6β-hydroxytropinone by Wolff-Kishner reduction to 6α-hydroxytropane, and chromic acid oxidation of the latter. 6-Oxotropane showed carbonyl bands in the infra-red at 1750 cm.$^{-1}$ (liquid film) and its methiodide at 1778 cm.$^{-1}$ (Nujol) in contrast to that of the oxotropane obtained by degradation of dioscorine (Büchi and others, XVIth International Congress of Pure and Applied Chemistry, Paris, July 1957) which absorbed at 1730 cm.$^{-1}$ (present work, 1737 cm.$^{-1}$). Comparison of the two oxotropane picrates confirmed their non-identity, which was supported by marked differences in the stability of the corresponding methiodides to aqueous sodium hydrogen carbonate at 30°. It is concluded, therefore, that the dioscorine degradation product is 2-oxotropane and that the alkaloid is formulated as shown (I). J. B. S.



(I)

6α-Methyl-17α-Hydroxyprogesterone 17-acylates; a New Class of Potent Progestins. J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes and W. E. Dulin. (*J. Amer. chem. Soc.*, 1958, **80**, 2904.) The synthesis of 6α-methyl-17α-hydroxyprogesterone and its acetate from the bisethylene acetal of 17α-hydroxyprogesterone is reported. The latter with peracetic acid gave a mixture of 5α, 6α-epoxy- and 5β, 6β-epoxy-17α-hydroxy pregnane-3, 20-dione bisethylene acetals. The α-epoxide with methylmagnesium bromide gave the bisethyleneacetal of 5α, 17α-dihydroxy-6β-methylpregnane-3 : 20-dione, which was hydrolysed with acidic acetone to 5α, 17α-dihydroxy-6β-methylpregnane-3 : 20-dione. This on dehydration by very

dilute sodium hydroxide in pyridine afforded 6β-methyl-17α-hydroxyprogesterone, which was epimerised with hydrogen chloride in chloroform to 6α-methyl-17α-hydroxyprogesterone. Acylation with the appropriate reagent gave the 17α-acetate, the 17α-(β-*cyclo*pentylpropionate), propionate, caproate and phenylacetate. The McPhain modification of the Clauberg assay showed 6α-methyl-17α-hydroxyprogesterone17-acetate to be 50–60 times more active than progesterone on subcutaneous administration and 100–300 times more active than ethisterone on oral administration. As an ovulation inhibitor it was 10–20 times more active parenterally than progesterone. J. B. S.

PHARMACY

Alginate Mucilages, the Influence of Different Physico-chemical Factors on the Viscosity of. R. Bolliger and K. Münzel. (*Pharm. Acta Helvet.*, 1958, **33**, 225.) The following factors were studied:—the degree of polymerisation of the alginate, its concentration, the pH of the solution, the influence of hydrophilic liquids such as ethanol when added before and after gelation and the influence of electrolytes when added before and after gelation. For the same concentration the viscosity rose with degree of polymerisation. Viscosity rose approximately logarithmically with concentration up to a few per cent, i.e., doubling the concentration would cause a 10-fold increase in viscosity, three times the concentration would cause a 100-fold increase etc. The maximum viscosity for a given concentration was found to be at pH 7, falling slightly—to about 85 to 90 per cent of this—at pH 4·1 and 10. At a pH lower than 4·1 alginic acid is precipitated. Ethanol causes an increase in viscosity up to a certain concentration due to incomplete flocculation or partial dehydration; above this concentration coarse flocculation occurs. If the alcohol is added to the gelled alginate, this critical concentration is about 25 per cent. If however the alginate is first suspended in the alcohol, and gelled by the addition of water, the concentration required to produce flocculation is lower—about 15 per cent, the concentration of the alginate being 1 per cent in each case. With glycerol however, flocculation only occurs with a content of 70 per cent or more. This difference was explained by postulating the formation of hydrogen bonds between glycerol and alginate molecules, and was said to be related to the gelation of pectin and alginates on the addition of sugar. It was observed that 10 per cent ethanol or 20 per cent glycerol had a stabilizing effect on viscosity especially when added after hydration. Electrolytes raised the viscosity up to a critical conconcentration when flocculation occurred. For a 1 per cent mucilage, if sodium chloride or sodium benzoate was dissolved in the water used for preparation, only 1 and 2 per cent respectively brought about flocculation. If the electrolytes were added to the prepared mucilage, higher concentrations were tolerated e.g., 4 per cent sodium chloride. D. B. C.

Physostigmine Eye-drops, Stability of. J. Mørch. (*Dansk Tidsskr. Farm.*, 1958, **32**, 93.) Specimens of eye-drops of the Danish Pharmacopoeia 1948, containing 1 per cent of physostigmine salicylate and 0·75 per cent of sodium chloride were assayed by a method involving extraction with ether after making alkaline with sodium carbonate, evaporation of the solution and titration. This method is specific for physostigmine in the presence of its degradation products, and showed that the eye-drops lost 1 per cent of their physostigmine content on storage for 3 months at 20°. The corresponding loss at 30° was 3 per cent.

Heating at 100° for 15 minutes resulted in a loss of 1 to 4 per cent, and the development of a red colour. Discoloration was prevented by the addition of 0·1 per cent of sodium metabisulphite, but this resulted in the eye-drops becoming too acid on storage. The inclusion of 2 per cent of disodium hydrogen citrate (sesquihydrate) was sufficient to buffer the solution to pH 5·0, and such solutions showed a loss of 1 to 2 per cent with no discoloration or change in pH on heating at 100° for 15 minutes. The loss on storage at 20° for 6 months was 10 per cent. The addition of disodium ethylenediaminetetra-acetate did not prevent discoloration. G. B.

Vitamin B_{12}, Stability of, in the Presence of Aneurine and Nicotinamide in Aqueous Combinations. A. S. Gambier and E. P. G. Rahn. *J. Amer. pharm. Ass., Sci. Ed.*, 1958, **47**, 356). In a continuation of a previous investigation (abstract *J. Pharm. Pharmacol.*, 1957, **9**, 637) it was shown that rapid inactivation of vitamin B_{12} occurs in the presence of 5000 times the quantity of aneurine, even when special precautions are observed in making the solutions. It was found possible to produce stable aqueous solutions containing aneurine, nicotinamide and vitamin B_{12} at pH 3·3, provided that the quantity of aneurine was not more than 120 times that of vitamin B_{12}. The tendency of the mixed vitamin solutions to darken was increased with rise in pH and temperature, and it was shown that the proportion of air in the ampoules is of importance. With a liquid to air volume ratio of 1·73, neither darkening nor precipitation occurred, but decreasing the ratio gave rise to darkening, and increasing it caused precipitation. Pyridoxine did not affect the stability of the mixed vitamin solutions. Stability tests at 37°, 40°, and 45° appeared to be more informative than those carried out at higher temperatures. G. B.

PHARMACOLOGY AND THERAPEUTICS

Anileridine and Pethidine in Man, Narcotic Potency and Side Effects of. F. F. C. Chang, P. Safar and L. Lasagna. (*J. Pharmacol.*, 1958, **122**, 370.) Anileridine is a new synthetic narcotic drug which is chemically related to pethidine. In animals this compound has been found to approach the analgesic potency of morphine, to be ten to twelve times the potency of pethidine, and to be relatively free of side effects such as respiratory depression, vomiting and sedation. Early clinical studies however suggested that it was only slightly more potent than pethidine. This work is therefore an attempt to evaluate the narcotic potency of anileridine and pethidine in surgical cases, and the side effects in both patients and healthy volunteers. The ability of the drugs to reinforce nitrous oxide analgesia under controlled experimental conditions was studied. It was found that while anileridine was a potent analgesic it was no more potent than pethidine. It produces respiratory depression and subjective side effects to as great an extent as pethidine, when given in equipotent doses. Thus the analgesic activity of anileridine in man compares unfavourably with its effect in animals. M. M.

Barbiturate, *N*-Methylated, and Acetylsalicylic Acid, Absorption of, from Different Suppository Bases. U. Samelius and A. Åström. (*Acta pharm. tox. Kbh.*, 1958, **14**, 240.) Suppositories were prepared with theobroma oil, Carbowax (polyethylene glycols), and Imhausen bases (glycerides of fatty acids) with and without the addition of Tweens. A preliminary series of experiments was carried out in rabbits, using hexobarbitone sodium as the medicament, absorption being assessed by depth of anaesthesia and death rates. In this

series the drug appeared to be rather better absorbed from theobroma oil than from the other bases. No absorption took place when hexobarbitone was used instead of the sodium derivative. A more extensive series of experiments was carried out using acetylsalicylic acid suppositories in human subjects, and determining the concentration of salicylic acid in the plasma. Maximum plasma concentrations of about 35 to 45 μg./ml. were observed 1–1½ hours after administration of 0·75 g. of acetylsalicylic acid in suppositories. In this series Imhausen bases permitted somewhat greater absorption than theobroma oil or Carbowax bases. The plasma levels obtained were comparable with those following the oral administration of acetylsalicylic acid following a light meal. Rectal administration of acetylsalicylic acid may therefore be of value in certain clinical cases, but attention is drawn to the occurrence of individual variations in absorption. Decreased absorption was observed in a person with an anal fissure.

G. B.

Bemegride, Analeptic Activity of, to Structurally Unrelated Hypnotics. A. Shulman and G. M. Laycock. (*Austral. J. exp. Biol. med. Sci.*, 1957, **35**, 559.) Previous work has shown that bemegride (β-methyl-β-ethylglutarimide, Megimide) can antagonise the hypnosis induced in mice by diverse but structurally related hypnotics such as monoureides, barbiturates, thiobarbiturates, glutarimides, diketo-piperidines, diketo-tetrahydropyridines, diketo-thiazanes and diketo-thiazolidines. It can also reverse the hypnotic activity of a wide range of structurally unrelated hypnotics such as saturated and unsaturated alcohols, aldehydes, carbamates, cyclic ethers and sterols. It was found that ether prevented or terminated convulsions induced by bemegride in mice, but the reverse form of antagonism could not be demonstrated. Bemegride antagonised morphine-induced respiratory depression in dogs but did not reverse the analgesia or hypnosis due to morphine in these animals. No obvious signs of antagonism or potentiation between these two substances were observed in mice. Thus bemegride is of possible value in the clinical management of respiratory depression caused by opiates as well as by barbiturates. Reference is made to the widespread safety associated with the administration of bemegride as an analeptic and to preliminary quantitative data which support the suggestion of a selective antagonism by bemegride to hypnotics structurally related to it.

M. M.

Carboxy Vinyl Polymer: a Bulk Laxative, Pharmacological Effects of. R. L. Cahen, E. Groskinsky and G. Leeson. (*Arch. int. Pharmacodyn*, 1958, **114**, 258.) A carboxy vinyl polymer (CP) the physical data of which is given has been found not to form a gel in the acid medium of the stomach but in an alkaline medium gel formation gradually occurs. This fact and other physical data warranted the pharmacological investigation of this compound as a possible laxative. Data obtained shows 1) the low toxicity of CP following oral administration to rats, mice, guinea pigs, and dogs and its high safety margin; 2) the hydrophilic laxative activity of CP in rats and dogs; 3) the absence of toxic effects by accumulation or sensitization following 14 months' repeated administration of a high dose of CP to parent generation rats and after 32 months' administration to dogs; 4) the absence of toxic effects on first filial and second filial generations of rats exposed to CP for 17 and 24 months respectively and 5) the absence of toxic effects on the first filial generation of dogs following 27 months' repeated oral administration. Comparison of the hydrophilic laxative potency with other bulk laxatives in the rat shows that CP is ten times more active than methylcellulose. In dogs CP produces a significant increase in the moisture of the faeces in contrast with the effects of bran and mineral oil. M. M.

Insulin Zinc Suspension: Clinical Experiences. W. M. Lancaster and I. Murray. (*Brit. med. J.*, 1958, **1**, 1331.) A review of 335 diabetic patients treated for at least 6 months with I.Z.S. showed that satisfactory control was obtained in 82·5 per cent of 134 new patients, and in 64·7 per cent of 201 patients previously receiving some other form of insulin. In 94 of the latter group, I.Z.S. produced a better degree of control. It proved unsatisfactory in 15 patients. For the 189 old patients shown as retaining equally good, or obtaining better, control the dose of I.Z.S. was greater than that of the former insulin in 86 cases, but in 40 a smaller dose sufficed. Where the dose had to be raised the increase was usually about 50 per cent, though some required as much as double the former dose. Neither the age of the patient nor the duration of the diabetes appeared to affect the nature of the response to transfer to I.Z.S. In the presence of intercurrent infection lapse from diabetic control with I.Z.S. appears to occur more readily than with some other insulins. It is suggested that in such conditions it is I.Z.S. crystalline which becomes relatively ineffective, since transfer temporarily to two injections a day of I.Z.S. amorphous has been shown to re-establish control. S. L. W.

Levonor (1-Phenyl-2-aminopropane Alginate) in Obesity. R. J. Gadek, H. S. Feldman and R. J. Lucariello (*J. Amer. med. Ass.*, 1958, **167**, 433.) Levonor was administered with diet in a dose of 5 mg. three times daily, half an hour before meals, to 80 overweight patients. Many of the patients received an additional dose at 8 or 9 p.m. The average weight loss was 2 lb. per week. There was a remarkable absence of side-effects. There were no adverse changes that affected either the blood pressure or the heart rate, and the drug can be used in the evening without causing insomnia. It has no effect on blood sugar levels nor on central vasomotor reflexes and can therefore be used in patients with diabetes and hypertension and in pregnant women. The drug is of no value for depressed obese patients or where psychic stimulation is indicated.

S. L. W.

Lysergic Acid Diethylamide, Comparison of Effect of, with Potassium Cyanide and other Respiratory Inhibitors on the Siamese Fighting Fish. H. A. Abramson B. Weiss and M. O. Baron. (*Nature, Lond.*, 1958, **181**, 1136.) Although it is known that lysergic acid diethylamine enters the brain, the mechanism by which it acts to produce the psychotic patterns in man is unknown. Experiments which are designed to investigate the brain process in the intact animal might lead to a concept that could be developed to study the chemical processes originating or connected with schizophrenia. This paper deals with the effect of potassium cyanide, sodium azide, hydrazine and lack of oxygen on the Siamese fighting fish. It has previously been shown that the behaviour of these fish changes markedly in the presence of small doses of lysergic acid diethylamide in the surrounding water. It is now found that potassium cyanide and sodium azide act similarly. Hydrazine sulphate was without effect. However anoxia and asphyxia also produced reactions similar to lysergic acid diethylamide. It has often been observed that human subjects under the influence of lysergic acid diethylamide suffer from confusion and other symptoms that are associated with anoxia. It may be therefore that lysergic acid diethylamide acts by poisoning some parts of the enzymatic processes connected with oxidation. It may also be that the schizophrenic process may be connected with a similar process where special respiratory enzymes of the brain are not functioning adequately.

M. M.

Meprobamate, Phenobarbitone and Dexamphetamine, effects of, on Reaction Time and Learning in Man. C. Kornetsky. (*J. Pharmacol.*, 1958, **123**, 216.) The effects of meprobamate (800 and 1600 mg.), dexamphetamine (5 and 15 mg.) and phenobarbitone (60 and 120 mg.) on simple motor behaviour, choice reaction time and learning rate were studied in a series of controlled experiments on normal human subjects. A multiple stimulus-response apparatus was employed which allows the measurement of a variety of types of behaviour while always evoking the same motor response on the part of the subject. Neither phenobarbitone nor dexamphetamine significantly affected motor co-ordination time, reaction time or learning. Meprobamate, at both dose levels, significantly affected the learning rate and at the higher dose level impaired motor co-ordination and reaction time. W. C. B.

Methocarbamol in Neuromuscular and Neurological Diseases. D. S. O'Doherty and C. D. Shields. (*J. Amer. med. Ass.*, 1958, **167**, 160.) Methocarbamol (3-o-methoxyphenoxy-2-hydroxypropyl-1-carbamate), a skeletal muscle relaxant, was evaluated in 75 trials in 70 patients with skeletal muscle hyperactivity secondary to neurological disorders. The drug was given in a dose of 1 to 4 g. daily by mouth in divided doses for a minimum period of 2 months in chronic conditions and for 2 weeks in acute conditions (unless recovery occurred earlier); the majority of patients with severe spasticity and contractures were treated for 6 months to a year. An excellent result was obtained in all patients with acute skeletal muscle spasm. A good result was obtained in 72 per cent of patients with both acute and chronic spasm. In the doses administered failures were noted in all patients with contractures, rigidity, spasticity and chronic myofibrositis. In six cases of herniated lumbosacral disc and eight cases of acute fibromyositis there was prompt alleviation of symptoms and the results were lasting with an average total dose of 4 g. An improvement in all patients (8) with incoordination was observed.

S. L. W.

Methocarbamol in Orthopaedic Conditions. H. F. Forsyth. (*J. Amer. med. Ass.*, 1958, **167**, 163.) Methocarbamol in an average daily dose of 6 g. in divided doses was given to 58 patients with acute orthopaedic conditions (especially herniated lumbar and cervical discs) causing painful muscular spasms, 7 patients with chronic conditions, and 18 patients recovering from orthopaedic surgery. A significant response was obtained in 94 per cent of the patients. Relief from pain was often prompt and striking, with resultant facilitation of treatment and hastening of recovery. No serious reactions to the drug were observed and very few unpleasant side-effects, apart from drowsiness, headache, slight lightheadedness, and nausea in a few patients. Methocarbamol was also used intravenously in some cases in a dose of 500–625 mg. three to four times daily, injected over 1 to 2 minutes in the form of a 2·5 per cent solution in saline.

S. L. W.

Morphine and Papaverine, Antipruritic effect of, in Experimental and Pathological Itch in Man. S. G. Macris, G. M. Smith and H. K. Beecher. (*J. Pharmacol.*, 1958, **123**, 220.) The effects of papaverine, morphine, pentobarbitone, aminophylline, tripelennamine and placebo were studied on experimental pruritis induced with cowhage. Only papaverine reduced experimental prutitis to a significant degree. In the case of pathological itch, however, morphine appeared to be effective while papaverine did not.

W. C. B.