ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

Neogermitrine, a New Ester Alkaloid from *Veratrum viride*. J. Fried, P. Numerof and N. H. Coy. (*J. Amer. chem. Soc.*, 1952, **74**, 3041.) A new alkaloid, neogermitrine, was isolated from an amorphous fraction from *Veratrum viride* from which all the previously known crystalline alkaloids had been removed. The infra-red spectra of this alkaloid, along with those of the ester alkaloids present in *Veratrum viride*, as well as those of germine, *iso*germine and protoveratrine are recorded. Neogermitrine, $C_{36}H_{55}O_{11}N$ was shown to be a diacetate-mono-(*laevo*)-α-methylbutyrate of the alkamine germine, and degradation with dilute methanol yielded first the known diester alkaloid germidine and finally, germine. It possesses hypotensive activity of the order of germitrine. Although the new alkaloid was found as the main active constituent in two batches of root collected during 1948 and 1949, it had not been encountered in a previous batch collected during 1947. It was concluded that the observed differences in the composition of the ester alkaloid function were referable either to the year-to-year variability of climate, to local conditions of growth at the sites chosen for collection, or possibly to the occurrence of different strains within the general area mentioned, or to a combination of these factors. A. H. B.

ANALYTICAL

***p*-Aminosalicylic Acid, Determination of *m*-Aminophenol in.** P. Jacobs. (*Pharm. Weekbl.*, 1952, **87**, 385.) In the method of Pesez the compound is diazotised, when the diazo compound of *p*-aminosalicylic acid rapidly decomposes to β-resorcylic acid, while that of *m*-aminophenol couples to give a colour, which is a measure of the amount of *m*-aminophenol present. In practice it is not possible to obtain a sample of *p*-aminosalicylic acid which does not give a colour, as the decomposition of its diazo compound is not complete under the conditions chosen. It is therefore necessary to prepare a standardisation curve using *p*-aminosalicylic acid free from *p*-aminophenol, which may be obtained by repeated precipitation with ether from a methanol solution until the colour produced in the reaction is constant. Actually the colour produced by 1 mg. of pure sodium *p*-aminosalicylate is equivalent to that from 2 μg. of *m*-aminophenol, that is, a content of 0·2 per cent. The colour developed with *m*-aminophenol is not due to coupling with the β-resorcylic acid, as assumed by Pesez, but to coupling with some other compound probably derived from decomposition of the diazonoium salt of *p*-aminosalicylic acid.

G. M.

Bismuth Mercaptoimidazole as Specific Colour Reagent for Iodides. R. A. McAllister. (*Nature, Lond.*, 1952, **169**, 708.) The reagent is prepared by adding 50 mg. of bismuth sulphate (acid) and 1 ml. of N sulphuric acid to 10 ml. of a 0·1 per cent. aqueous solution of 1-methyl-2-mercaptoimidazole. After mixing, the undissolved bismuth sulphate is allowed to settle and the yellow-coloured supernatant fluid used for the test. The addition of one or two drops of the reagent to a small crystal of an iodide gives a red coloration

which, on standing or agitation, forms a red microcrystalline precipitate. The sensitivity of the reaction is in the region of 100 μg. Free iodine reacts similarly but the colour disappears on standing. Iodates and periodides do not react, nor do other metals and radicals. Metals which form insoluble sulphates give a white precipitate. The complex iodide formed in the reaction is practically insoluble in water and dilute mineral acids; oxidising agents liberate iodine from it. When prepared in bulk the red complex exhibits some degree of fluorescence, which is lost on shaking the reaction mixture with ethyl acetate, the resulting solution having a yellow colour. S. L. W.

Novocaine and its Products of Hydrolysis, Estimation of. F. Cotta-Ramusino and R. Monacelli. (*Ann. Chim. appl., Roma*, 1952, **42**, 331.) The authors recommend titration with excess of solution of bromate. A 0·01N solution of novocaine hydrochloride contains 0·682 g./l. and 5 to 20 ml., corresponding to 3·41 to 13·04 mg., is a suitable quantity to use for the test. 0·02N bromate contains 0·5567 g./l. of potassium bromate and about 7 g. of potassium bromide. The novocaine solution is placed in a stoppered 100 ml. flask, with excess of 0·02N bromate, acidified with 5 ml. of 4N hydrochloric acid and diluted with water to about 50 ml. After standing for 15 minutes, 5 ml. of 10 per cent. potassium iodide solution is added and after 2 minutes the liberated iodine is titrated with 0·01N thiosulphate. A blank should be carried out and the result deducted from the figure obtained. With quantities above 15 mg. and using 0·1N bromate a precipitate is produced which makes the end-point uncertain. To estimate the products of hydrolysis, 10 to 20 ml. of solution of novocaine hydrochloride is made alkaline (*p*H about 11) with 10 ml. of 10 per cent. solution of sodium carbonate, transferred to a separator and extracted 4 times with an equal volume of carbon tetrachloride. The alkaline solution contains the *p*-aminobenzoic acid. The mixed carbon tetrachloride solutions are shaken out 3 times with half the volume of 0·5N hydrochloric acid. The novocaine and the *p*-aminobenzoic acid can be determined by bromate as described above. A blank with solution of sodium carbonate shaken out with carbon tetrachloride is necessary. H. D.

Phenols, Improved Ferric Chloride Test for. S. Soloway and S. H. Wilen. (*Analyt. Chem.*, 1952, **24**, 979.) It was found that the addition of relatively small amounts of pyridine to solutions of anhydrous ferric chloride and phenol in such solvents as benzene, toluene, *o*-xylene, chloroform, chlorobenzene, butyl bromide, and ethylene dibromide, gave deep purple colours. With the exception of 2:6-di-*tert.*-butyl-*p*-cresol and many phenolic carboxylic acids, every phenol derivative tried gave a colour test with one of the revised procedures using an organic solvent and pyridine. In each test approximately 30 mg. of solid or 1 drop of liquid of the substance to be tested was added to 1 ml. of each of the solvents water, methanol, chloroform, and diethylene glycol diethyl ether, together with 2 or more drops of ferric chloride in the same solvent. To the solutions or suspensions in water and methanol one or more drops of sodium bicarbonate solution were added; pyridine was also used as an alkalising agent and was generally found to be more convenient. The effects caused by a variation of solvent on a large number of phenols are reported and the results are discussed. R. E. S.

Quaternary Ammonium Compounds, Determination of as Reineckates. J. B. Wilson. (*J. Assoc. off. agric. Chem., Wash.*, 1952, **35**, 455.) The use of ammonium reineckate for the quantitative analysis of dilute solutions containing

quaternary ammonium compounds was investigated. Approximately 10 to 100 mg. of quaternary ammonium compound in 100 ml. of water was mixed with sufficient ammonium reineckate solution (1·5 per cent.) until the liquid was bright pink in colour. The precipitate was dissolved in acetone, which was allowed to evaporate in a warm place, and the residue was dissolved by warming in ethanol; this solvent was also allowed to evaporate spontaneously and the residue was dried in a desiccator and weighed. Several of the reineckates crystallised with one molecule of water of crystallisation. When 100 mg. quantities were determined, recoveries were from 91·4 to 101·9 mg. on the anhydrous basis or from 96·2 to 106·9 on the hydrated basis; with 50 mg., 44·7 to 51·2 mg. on the anhydrous basis and 47·0 to 53·5 on the hydrated; with 20 mg., 14·5 to 20·9 mg. on the anhydrous basis and 15·3 to 21·8 mg. on the hydrated. When 10 mg. was present, from 7·1 to 10·7 mg. was recovered on the anhydrous basis and 7·5 to 11·2 on the hydrated basis. R. E. S.

Quaternary Ammonium Compounds, Reineckates of. A. H. Tillson, W. V. Eisenberg and J. B. Wilson. (*J. Assoc. off. agric. Chem. Wash.*, 1952, **35**, 459.) Ammonium reineckate was chosen as a possible reagent for the identification of quaternary ammonium compounds. In preparing the crystals an aqueous solution of the quaternary ammonium compound was treated with an excess of ammonium reineckate and stirred; if 20 or more mg. of the quaternary compound was present, a precipitate formed at once, but with smaller quantities the mixture had to stand at room temperature for 30 minutes or more. After separation of the precipitate, dissolving in acetone, evaporating and recrystallising from ethanol (95 per cent.), the crystallographic properties were studied. Refractive indices and optical crystallographic data are recorded for trimethylammonium, lauryldimethylbenzylammonium, alkyldimethylbenzylammonium, cetyldimethylbenzylammonium, cetyltrimethylammonium, cetyldimethylethylammonium, di-*iso*butylphenoxyethoxymethyldimethylbenzylammonium, di-*iso*butylphenoxyethoxyethyldimethylbenzylammonium, di-*iso*butylcresoxyethoxyethyldimethylbenzylammonium, dodecylacetamidyldimethylbenzylammonium, lauryldimethyldichlorobenzylammonium, laurylpyridinium, and cetylpyridinium reineckates. R. E. S.

Sodium Nitrite and Sulphamic Acid, Reaction of. R. C. Brasted. (*Analyt. Chem.*, 1952, **24**, 1111.) It was found experimentally that the reaction between sulphamic acid and sodium nitrite is not stoicheiometric with regard to nitrogen since nitrogen and oxides of nitrogen were evolved in substantial and equal amounts. The amount of sodium nitrite decomposed by hydrogen ions present varied from about 2 per cent. for 0·1 to 0·3M to nearly 10 per cent. for concentrations greater than 0·5M sodium nitrite. A method was developed in which a pre-weighed system containing an aliquot portion of nitrite solution was treated with excess of sulphamic acid at constant temperature; the system was reweighed at the completion of the reaction, the difference in weight serving as a basis for the calculation of the amount of nitrite consumed in the reaction. The loss in weight, multiplied by the factor 0·9746 to compensate for the composition of the gases evolved, was then taken as pure nitrogen and the amount of nitrite calculated. Solutions of nitrite may be analysed as described with an error of about $\pm$ 2 mg., the method offering the advantages of simplicity and of lack of interference due to ions and coloured solutions. Satisfactory determinations are possible in the presence of copper and nitrate ions, and in freshly mixed, nearly neutral solutions containing nitrate, cobalt, copper, and chromium ions. R. F. S.

ORGANIC CHEMISTRY

Racemic Substances, New Procedures for Resolution of. H. M. Powell. (*Nature, Lond.*, 1952, **170**, 155). Recent extensions of the hand-sorting process, in particular in relation to trithymotide, are described. In one method a racemic substance forms a crystalline molecular compound with an optically inactive substance. Instead of *dl*-, there crystallise from the solution M*l* and M*d*, where M is the optically inactive substance. This has been found with trithymotide, which forms a series of molecular compounds $2C_{33}H_{36}O_6.M$, where M may be benzene, chloroform or a large variety of other substances; most of these molecular compounds are spontaneously resolved. In a second method trithymotide is crystallised from a solvent which is itself a *dl*-mixture and forms with it a molecular compound, and the cavities of any one crystal will enclose preferentially the *d'*- or *l'*- form of solvent molecule; any process for separating the *d'*- and *l'*-trithymotide should separate *d'*- and *l'*- simultaneously. The process has been applied to resolve secondary butyl bromide; a single crystal was grown and in other experiments homogeneous crops were developed from a single seed crystal by repeated division and growth. The crop when dissolved in chloroform showed a large rotation due to trithymotide. This decayed rapidly through racemisation and left a much smaller permanent rotation due to the secondary butyl bromide. With trithymotide the method is applicable to a range of substances although it may be expected to fail with molecules which are too large for the cavities; it could be extended by the discovery of substitutes for trithymotide. The method of resolution has the advantage that no chemical reaction is evolved and it could, for example be applied to paraffins. The methods are discussed fully and the advantages and potentialities are considered. R. E. S.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Ketosteroids in Alkali, Absorption Characteristics of. J. M. Cross, H. Eisen and R. G. Kedersha. (*Analyt. Chem.*, 1952, **24**, 1049.) A modified Zimmermann reaction which consisted essentially of treating a 3-, 17-, or 20-ketosteroid with 3:5-dinitrobenzoic acid and an organic alkali such as benzyltrimethylammonium hydroxide was applied to cortisone acetate, but a satisfactory absorption maximum was not obtained. When cortisone acetate was heated with either inorganic or organic alkali, an absorption maximum was observed at 373 mμ; details of the method are given. Full development of this maximum occurred in 30 minutes and the colour was stable for 12 hours. A concentration-optical density curve at 373 mμ showed adherence to Beer's law over a range of 10 to 80 μg. of cortisone acetate. Results for a number of steroids showed that Δ^4-unsaturated 3-ketosteroids when heated with akali show a characteristic absorption maximum in the area 373 to 375 mμ. R. E. S.

Pancreas, Glycogenolytic Factor in. G. Audy and M. Kerly. (*Biochem. J.*, 1952, **52**, 77.) In an attempt to find a richer source of the glycogenolytic factor, extracts of pacreas from cats, rats, ferrets and guinea-pigs were assayed for their glycogenolytic factor content; rabbit pancreas was also examined for comparison with the results of Sutherland and Duve (*J. biol. Chem.*, 1948, **175**, 663). Assays were also carried out on extracts of tissue from the teleost fish *Lophius piscatorius*, a species in which islet tissue occurs

separately from the pancreas proper, mostly in easily recognisable encapsulated structures. Activity was expressed as the weight of pancreas required to produce 50 per cent. of maximum activity, as determined by testing extracts at several concentrations and plotting the activity against the weight of pancreas equivalent to the amount of extract used. Similar values were obtained for the glycogenolytic factor content of pancreatic extracts from rabbit, rat, cat, guinea-pig and ferret; extracts of islet tissue from *Lophius piscatorius* were active whilst those of acinar tissue were almost inactive. R. E. S.

BIOCHEMICAL ANALYSIS

Aneurine, Fluorimetric Determination of. A. E. Teeri. (*J. biol. Chem.*, 1952, **196**, 547.) The determination depends on the production of a fluorescent compound in the reaction between aneurine and cyanogen bromide. The sample to be assayed is adjusted to contain between 0 and 0·5 μg. of aneurine per ml.; to 10 ml. of this solution are added 5 ml. of *p*H 6·6 buffer solution (aqueous ethanolic sodium phosphate) and 5 ml. of cyanogen bromide reagent (4 per cent. aqueous solution). After allowing the mixture to remain at room temperature for 30 minutes, fluorescent readings are made in a suitable instrument. The fluorescence depends upon the length of time the solution is allowed to stand after addition of cyanogen bromide and the time factor must be carefully controlled. Nicotinic acid, nicotinamide, pyridoxine, and pyridoxamine do not interfere; pyridoxal when present in large amount shows a fluorescence.

R. E. S.

Dihydrostreptomycin and Mannosidostreptomycin, Determination of. W. A. Vail and C. E. Bricker. (*Analyt. Chem.*, 1952, **24**, 975.) An investigation into the periodate oxidation of dihydrostreptomycin showed that the excess of periodic acid and iodic acid formed could be quantitatively precipitated with lead acetate. The resulting precipitate was quickly centrifuged and the formaldehyde determined by chromotropic acid, with no interference on the clear centrifugate liquid. This procedure was extended to the assay of dihydrostreptomycin and to the determination of this compound in the presence of streptomycin. When lead acetate was used to remove the periodate and iodate ions in the dihydrostreptomycin determination, the supernatant liquid, on standing, developed a yellow colour. Under similar conditions, streptomycin gave nearly the same yellow colour, whereas mannosidostreptomycin produced a rose or pink colour. The determination of mannosidostreptomycin in the presence of streptomycin by this process was investigated, but it was found that the colours were very time-sensitive and optimum conditions for maximum sensitivity and differentiation must be carefully followed. The method was of low sensitivity but was not affected by the presence of carbohydrates. R. E. S.

Vitamin A in Low Potency Fish Oils, Chromatography of. M. W. Dowler and D. H. Laughland. (*Analyt. Chem.*, 1952, **24**, 1047.) Chromatographic methods were applied to the estimation of vitamin A in low potency fish oils in view of the magnitude of the correction obtained in the application of the Morton-Stubbs procedure to the unsaponifiable fraction. The procedure employed was a modification of that described by Eden (*Biochem. J.*, 1950, **46**, 259). Skellysolve solutions of vitamin A were run through a 6 × 50 mm. layer of bone meal, vitamin A acetate being eluted with Skellysolve B and vitamin A alcohol with 20 per cent. acetone in Skellysolve B. It is concluded that the extracts

obtained in chromatography contain less irrelevant absorption than do the unsaponifiable extracts of the same oil, and the precision of the estimation is thus improved. R. E. S.

Vitamin B_6, Determination of. J. P. Sweeney and W. L. Hall. (*J. Ass. off. agric. Chem. Wash.*, 1952, **35**, 479.) Methods available for the determination of pyridoxine are discussed and a method is presented in particular for the determination of the vitamin in pharmaceutical preparations. After solution the pyridoxine is separated from nicotinic acid and other materials by adsorption on decalso at *p*H 7 and elution with ammonium hydroxide. The eluate is evaporated to dryness and oxidised with sulphuric acid and selenium, the final colour being developed by reaction with cyanogen bromide and sulphanilic acid. Details of the method are not given. Pyridoxine and pyridoxal gave the test after oxidation with sulphuric acid and selenium; with pyridoxamine a very faint colour was produced. When pyridoxamine was treated with sodium nitrite and hydrochloric acid and oxidised with sulphuric acid and selenium, it was found to give the colour reaction, thus making it possible to differentiate pyridoxamine from pyridoxine and pyridoxal. R. E. S.

Vitamin B_{12}, Chemical Method for Determination of. G. O. Rudkin and R. J. Taylor. (*Analyt. Chem.*, 1952, **24**, 1155.) The method described is based on the difference between the visible spectrum of vitamin B_{12} and the spectrum of the dicyanide complex formed in solutions containing excess of cyanide ions, the difference $\Delta E^{1\%}_{1\,cm.}$ 582 mμ being 54. The method automatically allowed for irrelevant absorption but was not applicable directly to crude fermentation broths owing to the low concentrations of vitamin B_{12}. To apply the process to crude concentrations a preliminary extraction was necessary, the cyanide-treated sample being first extracted with benzyl alcohol, the vitamin B_{12} being re-extracted with water after the addition of chloroform. Experiments with known amounts of vitamin B_{12} gave recoveries ranging from 97 to 103 per cent. R. E. S.

CHEMOTHERAPY

2-Aminoalkoxyalkanes as Vasoconstrictors. B. M. Sutton and J. B. Data. (*J. Amer. pharm. Ass., Sci. Ed.*, 1952, **41**, 328.) The following were prepared:—2-amino-3-methoxypropane, 2-amino-3-ethoxypropane, 2-amino-3-propoxypropane, 2-amino-3-butoxypropane, 2-amino-3-(2-methylpropoxy)propane, 2-amino-3-pentoxypropane, 2-amino-4-methoxybutane, 2-amino-4-ethoxybutane, 2-amino-4-propoxybutane, 2-amino-5-ethoxypentane and 2-amino-5-propoxypentane. The following methods of preparation were used. (1) Reaction of a chloride or bromide with diethyl methylmalonate, followed by hydrolysis and decarboxylation to the monocarboxylic acid and treatment with hydrazoic acid to form the amine. (2) Condensation of ethyl acetoacetate with an alkoxyalkyl bromide, hydrolysis and decarboxylation to the ketone and treatment with formamide to yield the amine. All the 2-amino-alkoxyalkanes prepared showed pressor activity in the pithed rat. The most active compound was 2-amino-3-(2-methylpropoxy)propane. G. B.

Benzazoles, Relation Between Structure and Paralysing Action of. E. F. Domino, K. R. Unna and J. Kerwin. (*J. Pharmacol.*, 1952, **105**, 486). The pharmacological actions of some 50 derivatives of benzimidazole and other benzazoles are reported. Many of the compounds produced paralysis, similar

to that produced by mephenesin. The effects produced were a mixture of stimulation and depression, the stimulating effects usually occurring first. Of the unsubstituted benzazoles, benzotriazole was most potent in mice; while benzimidazole had about the same potency as mephenesin. Of the substituted benzazoles, 2-amino-benzothiazole was the most potent paralysing compound of the series, but methylation of the amino group decreased activity. The presence of the azole ring was essential for paralysing activity, but it mattered little whether the heterocyclic ring was 5- or 6-membered. Tautomerism in the azole ring was necessary for high paralysing activity. Substitution of a pyridine ring for a benzene ring in benzimidazole produced a convulsant; a napthalene ring replacing the benzene ring of 2-aminobenzothiazole caused a flaccid paralysis. None of the benzazoles acted like curare. Some produced hæmolysis of erythrocytes when injected intravenously and some had a weak local anæsthetic action. G. F. S.

Mephenesin, Central Depressant and Anticonvulsant Properties of Glycerol Ethers Isomeric With. F. M. Berger. (*J. Pharmacol.*, 1952, **105**, 450.) The pharmacological properties of mephenesin (3-*o*-toloxy-1:2-propanediol) and other 3-toloxy-1:2-propanediols were compared with 1:3-propanediols substituted in the 2 position with toloxy or benzyloxy groups. The compounds were tested in mice for their ability to produce paralysis, and to modify electroshock seizures and the convulsions produced by strychnine, picrotoxin and tetanus toxin. None of the compounds was as effective as mephenesin in its paralysing action and in its ability to relax spasm and rigidity produced by tetanus toxin; but 2-*o*-toloxy-1:3-propanediol had the greatest activity in preventing electroshock seizures and in antagonising strychnine. Paralysing action appeared to be most closely related to clinical effectiveness. G. F. S.

PHARMACY

GALENICAL PHARMACY

Vitamin B_{12} (Cyanocobalamin) in Pharmaceutical Preparations. T. J. Macek and B. A. Feller. (*J. Amer. pharm. Ass. Sci. Ed.*, 1952, **41**, 285.) The anhydrous substance is hygroscopic, but the hydrated material containing about 12 per cent. of water is stable in air. It should be protected from strong light. Triturations with mannitol, sodium chloride, glucose, lactose or maize starch are stable. They may be prepared by adding an ethanolic solution of crystalline vitamin B_{12} to the anhydrous diluent and drying *in vacuo*. Talc is not a suitable basis because the vitamin B_{12} is adsorbed and cannot be eluted from it with water. Solutions of crystalline vitamin B_{12} in water, 0·5 per cent. redistilled phenol, 0·9 per cent. sodium chloride and 1·5 per cent. benzyl alcohol are stable for at least 2 years at room temperature or 5 months at 40° C. Solutions in saline solution are stable at elevated temperatures and show only a small loss on autoclaving, although solutions of less pure samples should not be autoclaved. Some samples of liquefied phenol contain trace impurities and reducing substances which decompose vitamin B_{12} giving discoloured solutions or precipitates. Chlorbutol is not suitable as a preservative because hydrolysis leads to a decrease of *p*H on autoclaving and storage. Crystalline vitamin B_{12} is compatible with other vitamins of the B group, and with ethanol, glycerol, propylene glycol and tween 80. In the experiments on stability, assays by the microbiological and ultra-violet methods were carried out. G. B.

NOTES AND FORMULÆ

Sodium Carboxymethylcellulose (Thylose Sodium). (*New and Nonofficial Remedies, J. Amer. med. Ass.*, 1952, **149**, 663.) Sodium carboxymethylcellulose is prepared by the interaction of alkali cellulose and sodium monochloroacetate, under conditions giving about 0·8 of a sodium carboxymethyl group for each anhydroglucose unit in the cellulose molecule. It is a white to light buff, odourless, hygroscopic powder, which turns brown at 226° to 228° C. and chars at 252° to 253° C. A 1 per cent. solution is heavy, mucilaginous and opalescent. It has a viscosity of 1300 to 2200 centipoises and a *p*H of 6·5 to 8·0, and yields the following reactions: 5 ml. becomes hazy when treated with 8 ml. of ethanol (presence of carboxymethylcellulose); a fine, white, cloudy precipitate forms when the *p*H is adjusted to 0·5 with hydrochloric acid (presence of carboxymethylcellulose and distinction from methylcellulose); no precipitate forms on boiling (distinction from methylcellulose); when heated with hydrochloric acid, and neutralised with sodium hydroxide, a yellow to bright red precipitate forms on the addition of Fehling's solution. Sodium carboxymethylcellulose yields sulphated ash equivalent to about 7 per cent. of sodium. The degree of substitution, which is about 0·8, is determined as follows. A solution of the dried, powdered substance in sodium hydroxide solution is heated with sulphuric acid under a reflux condenser for 3·5 hours, cooled, and diluted to volume with sulphuric acid. The resulting solution is heated with a 0·01 per cent. solution of 2:7-dihydroxynaphthalene in sulphuric acid, cooled, and diluted with water. The colour of the final solution is read at 5400 Å with a Beckmann spectrophotometer against a blank prepared from water. From a standard curve prepared by treating glycollic acid in a similar manner, the concentration of glycollic acid corresponding to the absorption of the test solution is obtained, and the degree of substitution is calculated from the expression $162A/(76-80A)$, where 76 is the molecular weight of the anhydroglucose unit of cellulose, 80 is the net increase in the weight of the anhydroglucose unit of cellulose for each sodium carboxymethyl group substituted, and A = (100 × weight of glycolic acid)/weight of sample.

G. R. K.

PHARMACOLOGY AND THERAPEUTICS

Analgesic Drugs: Effect on Sensation of Thermal Pain in Man. H. Jackson. (*Brit. J. Pharmacol.*, 1952, **7**, 204.) Temperature measurement is claimed to be the most satisfactory method of determining the intensity of a thermal stimulus applied to the skin, and on this basis the threshold to thermal pain in man and the tail response in the rat are similar. The thermal threshold in man is very resistant to elevation; in most subjects tested therapeutic drugs had no significant effect. Relatively large doses of morphine and diamorphine raised the threshold by as much as 4° C. (to 48° or 49° C.) in a minority of subjects. This appears to be the maximum increase attainable in man and corresponds with the maximum temperature of response observed in the rat. The magnitude of the dose required to elevate the threshold, the small change which may occur, and the uncertainty of response in different subjects imply that in man thermal stimulation of the skin is an unsuitable method for assessing the analgesic potency of drugs.

S. L. W.

Analgesic Potency of Drugs: Evaluation by Thermal Stimulation in the Rat. H. Jackson. (*Brit. J. Pharmacol.*, 1952, **7**, 196.) A technique and apparatus for evaluating the potency of analgesic drugs by application of a thermal

stimulus to the tail of the rat and measuring the temperature of reaction are described. Under the influence of an analgesic drug the normal temperature of reaction, which is about 40° C., may rise to a maximum of about 48° C. Should no reaction have occurred at 48° C. it is unlikely to be elicited at higher temperatures, and the attainment of this temperature is therefore regarded as a maximum "analgesic" effect. The intravenous potencies of various analgesic drugs (morphine, diamorphine, phenadoxone, pethidine, ketobemidone and amidone) are compared in terms of intensity and duration of effect. After intravenous injection of any of these drugs the maximum effect is reached almost invariably within 1 minute. Whereas administration of morphine, pethidine and amidone intravenously, compared with subcutaneously, appears to have little effect on analgesic potency, diamorphine and phenadoxone show greatly enhanced activity when injected intravenously, as regards both intensity and duration of effect. S. L. W.

Barbituric Anæsthesia: Effect of Various Solutions on. R. K. Richards, E. L. Bertcher and J. D. Taylor. (*Arch. int. Pharmacodyn.*, 1952, **89**, 463.) Guinea-pigs recovering from barbiturate anæsthesia (thiopentone, hexobarbitone, pentobarbitone) can be returned to sleep by intraperitoneal injection of various organic and inorganic solutions. Thus, the intraperitoneal injection of 2 to 3 ml. of 25 per cent. dextrose solution in awakening animals caused return of sleep lasting from 3 to 7 minutes in 3 out of 4 animals injected with 18 mg./kg. of thiopentone. Similar results were obtained with 2 to 4 ml. of 25 per cent. sodium acetate solution, 10 per cent. sodium malonate solution, and 50 per cent. sucrose solution (but not in animals injected with either hexobarbitone or pentobarbitone). The following substances were similarly effective in doses of 2 to 4 ml. of 20 to 50 per cent. concentrations injected intraperitoneally in guinea-pigs recovering from thiopentone, hexobarbitone or pentobarbitone anæsthesia: sodium thiocyanate, sodium chloride, exsiccated sodium sulphate, urea, sodium *N-cyclo*hexylsulphamate. By intracardial injection smaller volumes (0·1 to 1 ml.) of these solutions are effective: by this route, water, blood and polyvinylpyrrolidone are also effective. There is no obvious connection between the chemical nature of the solutions and their ability to produce this effect and no complete explanation of the phenomenon can be given at present. S. L. W.

Benzoylcholine: Pharmacology of. A. Akcasu, Y. K. Sinha and G. B. West. (*Brit. J. Pharmacol.*, 1952, **7**, 331.) Benzoylcholine possesses strong nicotine-like and weak muscarine-like properties. It has a direct stimulant action on gut and heart, which action is unaffected by atropine. It restarts the frog heart and rabbit auricles after they have been stopped by excess of acetylcholine. It blocks the acetylcholine response on gut, heart and trachea. Although benzoylcholine in structural formula resembles many local anæsthetics, such as procaine, it is not a local anæsthetic. S. L. W.

Hexamethonium: Effect on Insulin Responses. D. R. Laurence and R. S. Stacey. (*Brit. J. Pharmacol.*, 1952, **7**, 255.) The effect of hexamethonium on insulin hypoglycæmia in man and in rabbits has been examined. Hexamethonium potentiates the convulsant action of insulin by increasing the degree of hypoglycæmia. It also abolishes or markedly alters the symptoms of insulin hypoglycæmia in man. Thus, there was absence of sweating, of increased tachycardia and of palpitations when hexamethonium was given, and restlessness

and anxiety were markedly diminished; the E.E.G. changes were also modified. The blood sugar level at which insulin convulsions develop is not affected by hexamethonium. The authors draw attention to the possibility of symptomless hypoglycæmia occurring when insulin and hexamethonium are used together. Thus, a diabetic receiving a ganglionic blocking agent in the course of treatment for hypertension or any other condition would be unlikely to have any of the warning symptoms of a hypoglycæmic reaction and might slip quietly into coma, as did two of their subjects. S. L. W.

6-Methyladrenaline: Pharmacological Actions of. R. S. Grewal. (*Brit. J. Pharmacol.*, 1952, **7**, 338.) The pharmacological properties of 6-methyladrenaline (*N*-methyl-3:4-dihydroxy-6-methylphenylethanolamine) have been examined. It is a substance of considerable pharmacological interest since, owing to the methyl group, it is incapable of forming an adrenochrome-like compound, and the blocking of this pathway of degradation may modify its properties. It possesses the stimulant actions of adrenaline, with the exception of that on the heart, and possesses also the inhibitory action on the intestine. It lacks the characteristic inhibitory action of adrenaline on the uterus of the cat, and is much weaker as a bronchodilator. S. L. W.

Morphine Antagonism. F. H. Shaw and G. Bentley. (*Nature, Lond.*, 1952, **169**, 712.) Dogs narcotised to the point of unconsciousness with morphine or morphine and hyoscine can be brought to a state of complete and intelligent wakefulness within 2 minutes of the intravenous injection of certain analeptic drugs. The drugs employed and the doses used are as follows: aminacrine (1-methyl-5-aminoacridine) (5 to 10 mg./kg.); rivanol (2:5-diamino-6-ethoxyacridine lactate) (40 mg./kg.); 5 (ethylamino)-acridine (2·8 mg./kg.); 1:2:3:4-tetrahydro-5-aminoacridine (5 mg./kg.); 4-aminoquinoline (5 mg./kg.); 2-aminopyridine (5 to 12 mg./kg.); 4-aminopyridine (3 mg./kg.); 2:3-diamino-5-phenylthiazole (20 mg./kg.); and the alkaloids eserine (0·25 to 1 mg./kg.) and nicotine (1 to 2 mg./kg.). Eserine, the 2- and 4-aminopyridines and 2:4-diamino-5-phenylthiazole are active when given intramuscularly; the others in the series are not. Another important fact is the marked respiratory stimulation which occurs with most of these drugs, commencing about half to one minute after the injection. The acridines (except rivanol) usually cause a varying degree of excitement. The results with these drugs are so clear-cut that a clinical trial is justified in cases of acute morphine poisoning. The analeptics of choice would be, in order of activity, 1:2:3:4-tetrahydro-5-aminoacridine, 4-aminoquinoline, aminacrine, 2:4-diamino-5-phenylthiazole and eserine, or a mixture of eserine and aminacrine (for suggested human dosages, see Shaw and Bentley, *Med. J. Aust.*, 1949, 868). Preliminary tests suggest that the action of these analeptics is specific towards morphine (and hyoscine); they do not arouse rats, cats and guinea-pigs treated with pentobarbitone. The analgesic action of morphine is also (on rats) unaffected by these analeptics. S. L. W.

Penicillin Treatment, Intrathecal, Anaphylactic Reactions after. E. Hoen. (*Dtsch. med. Wschr.*, 1952, **77**, 204.) A 7-month old baby, suffering from purulent meningitis, was treated with sulphacetamide and later with intramuscular and intralumbar penicillin. After the fever had subsided and there had been considerable clinical improvement, on the fourteenth day and following the fifth intralumbar dose of penicillin, the child died with disturbance of the central respiratory system, severe tonic-clonic spasms and failure of the circulation. The post-mortem examination, together with the clinical picture, gave

the impression of an anaphylactic reaction caused by the penicillin. It would appear desirable, in meningococcal meningitis, to avoid the use of penicillin, since sulphonamides are often superior in their action in such cases. If other penicillin-sensitive organisms are found, the penicillin treatment should be restricted to the first few days, using a maximum dose, for children, of 10,000 units intrathecally. Special care should be taken when there is a family history suggestive of allergic reactions. G. M.

Podophyllin, Ineffectiveness and Toxicity of, in Tinea Capitis. S. Schwebel, W. Snyder and W. N. Slinger. (*J. Amer. med. Ass.*, 1952, **149**, 261.) Preliminary clinical trials of podophyllin, 0·2 per cent. in carbowax, in scalp infections due to *Microsporon audouini* yielded encouraging results, although in 3 of the patients a form of alopecia developed which was assumed to be a toxic effect of podophyllin. In none of the children studied was there any systemic toxic reaction. In a subsequent series of 19 children with scalp infections due to *M. audouini*, treated similarly, the condition remained unchanged in 13 of the children; in 4, it showed some decrease in extent or severity of infection; and in 2, clinical and cultural cure resulted after 2 and 3 months treatment respectively. 8 patients showed a temporary irritation at the sites of application, characterised by erythema, œdema, crusting and kerion-like lesions with pain and tenderness. Of these 8 patients, 5 showed no change in the ringworm infection, 2 showed a decrease of fluorescence by Wood's light examination, and only 1 was cured, in contrast with the claim that podophyllin-induced inflammation is beneficial. G. R. K.

Polyethylene Glycols as Vehicles for Injections. C. P. Carpenter and C. B. Shaffer. (*J. Amer. pharm. Ass. Sci. Ed.*, 1952, **41**, 27.) Polyethylene glycol 300, propylene glycol and arachis oil were injected into rats in doses up to 10 ml./kg. subcutaneously and 2 ml./kg. intramuscularly. Subcutaneous injection of polyethylene glycol 300 and of propylene glycol was followed by scab formation within 2 days. After 4 days, increased vascularisation and fibroblastic repair tissue were present but after 14 days only slightly increased vascularisation was observed. Arachis oil caused no visible reaction. Intramuscular injection of polyethylene glycol 300 produced a mild chemical inflammation of the tissue and ischæmic necrosis of the muscle fibres when the substance entered a muscle bundle. No evidence of injury was observed 14 days after the injection. Arachis oil produced no reaction but accumulated in nearby fat depots. For polyethylene glycol 300, the LD50 in rats was 7·1 ml./kg. In experiments with anæsthetised dogs, an indwelling catheter was placed in the bladder and saline solution infused intravenously to maintain the flow of urine. Polyethylene glycol 300 was injected subcutaneously in the thoracic region and subcutaneously in the hind legs, in doses of 2 ml./kg. Most of it was excreted within 24 hours. Polyethylene glycols appear to be no more harmful than propylene glycol and it is suggested that they should be tried clinically as vehicles for subcutaneous and intramuscular injections. G. B.

***iso*Propyl Vinyl Ether, Anæsthetic Action of.** J. C. Krantz, C. J. Carr, G. Lu and M. J. Fassel. (*J. Pharmacol.*, 1952, **105**, 1.) *iso*Propyl vinyl ether is a volatile, colourless, mobile liquid, with an odour resembling that of divinyl oxide. It has b.pt. 56° C. and sp.gr. 0·75 at 26° C. Its vapours are readily respirable in several species of laboratory animals and in man, and it has an anæsthetic potency approximately twice that of ethyl ether and about equal to that of ethyl vinyl ether. It produced no functional hepatic damage, as

shown by the bromsulphalein test, in the dog, and no histopathological changes in the liver or kidneys of the dog or rat. Neither the monkey's nor the dog's heart showed any significant cardiographic changes under anæsthesia with *iso*propyl vinyl ether; the blood pressure of the dog was observed to be 10 to 15 per cent. lower than under ethyl ether anæsthesia. These pharmacological findings appear to be confirmed in man. 30 surgical procedures have been carried out under this anæsthetic. The induction period was smooth, and recovery rapid and uneventful. Blood pressure and pulse were not significantly altered. The vapour did not irritate the upper respiratory tract. S. L. W.

6-Sulfanilamido-2:4-dimethylpyrimidine (Elkosin), Activity of. P. C. Eisman, S. G. Geftic, F. Ligenzowski and R. L. Mayer. (*Proc. Soc. Exp. Biol., N.Y.*, 1952, **80**, 493.) This compound is appreciably more soluble in urine over a wide *p*H range than sulphamethazine and sulphadiazine and has in addition a very low order of acetylation. It was shown to possess a high degree of effectiveness on experimental mouse infections induced by *Streptococcus pyogenes*, *Diplococcus pneumoniæ* and representative species of the Gram-negative bacteria. No evidence of protection was observed against *Clostridium tetani* and only slight activity was shown in *Salmonella typhi* infection. Favourable results were obtained in infections with *Noc. asteroides* and *Candida albicans*, it was highly effective in the latter infection. 10 uninfected mice were given the drug orally, 1 and 5 g./kg. daily in 2 divided doses for 5 consecutive days; the mice showed no indication of toxic effects. S. L. W.

Succinylcholine Chloride: an Ultra-short-acting Relaxant. A. P. Balthasar and C. A. Sara. (*Med. J. Aust.*, 1952, **1**, 540.) When injected intravenously the drug first produces muscular fibrillation of the face, usually evident within 15 seconds. Non-coordinated muscular contractions are pronounced, and when observed in the upper extremities some movements of the limbs may occur. The whole excitation process takes about 15 seconds. The contractions appear last in the lower extremities; by this time the muscles of the head and neck are usually completely relaxed, and the relaxation occurs in the same order as the contractions. The paralysing effect of the drug has completely disappeared within 5 minutes. Apnœa invariably occurs with ordinary clinical dosage intravenously, the duration of the apnœa varying, but spontaneous respiration always returning within 2½ minutes, respiratory amplitude returning to normal in another 1 or 2 minutes. Because of the very unpleasant subjective symptoms it is advised that thiopentone be given either with the agent or immediately preceding it. If precautions are taken, the drug (issued in ampoules containing 100 mg. in 2 ml. of solution) is miscible with 5 per cent. thiopentone solution, but the amount added must never exceed half the volume of the thiopentone solution, and the mixture should be used within 10 minutes after preparation. It may be administered either (1) by direct mixing with excess of thiopentone, (2) by administration of each drug from a separate syringe, each syringe being attached to a common two-way tap, leading into a capillary rubber vein seeker and needle, or (3) by the use of a separate syringe for each drug, the thiopentone being first injected, the syringe disconnected and the succinylcholine injected. Because of the ultra-short action of the drug it will not displace decamethonium iodide, but it is of value (1) as an aid to intubation, (2) for production of profound relaxation for orthopædic manipulations, (3) for prevention of severe muscle spasm in electro-convulsive therapy. S. L. W.