ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

Dehydrolaudanosoline, Alkaloids Related to. J. Ewing, G. K. Hughes, E. Ritchie and W. C. Taylor. (*Nature, Lond.*, 1952, **169**, 618.) A simple derivative of "dehydrolaudanosoline" of Robinson and Sugasawa (*J. Chem. Soc.*, 1932, 789), was obtained from the bark of *Cryptocarya bowiei* (Hook) Druce, collected in northern Queensland. A water-soluble alkaloid, $C_{20}H_{24}NI$, m.pt. 214° C. (decomp.) $[\alpha]_D^{21°\,C.}$–151° (water) was isolated in about 0·7 per cent. yield; it contained three methoxy groups, and on methylation gave an *o*-methyl ether, $C_{21}H_{26}O_4NI$, m.pt. 153° to 155° C., $[\alpha]_D^{21°\,C.}$–175° (water), which alkali converted to methine-A, $C_{21}H_{25}O_4N$, m.pt. 102° C., $[\alpha]_D^{20°\,C.}$–221° (chloroform). Furthur methylation and alkaline degradation eventually gave optical inactive methine-B, $C_{22}H_{27}O_4N$, m.pt. 111° C., identical with an authentic specimen prepared in the same way from dehydrolaudanosoline iodide. Reactions of the products obtained are given. Bark collected in southern Queensland did not contain this alkaloid, but yielded (1·5 per cent.) a different alkaloid, $C_{19}H_{20}O_4NI$, m.pt. 246° C., $[\alpha]_D^{21°\,C.}$–186° (water), which had one methoxy, one methylenedioxy and one hydroxyl group, *o*-methyl ether, $C_{20}H_{22}O_4NI$, m.pt. 227° C., $[\alpha]_D^{21°\,C.}$–179° (water); this second alkaloid is probably a derivative of dehydrolaudanosoline. R. E. S.

ANALYTICAL

Acid-base Titrations in Non-aqueous Solvents. J. A. Riddick. (*Anal. Chem.*, 1952, **24**, 41.) A review of the subject is given, including historical and theoretical aspects, details of solvents and indicators, and the various standards and methods employed. The solvents used can be divided into two classes; aprotic solvents which are inert, and amphiprotic solvents which take part in the reactions. Aprotic solvents are not believed to take part in neutralisation reactions, having a zero or very small dipole and not readily forming complexes; most of the saturated and benzene-type hydrocarbons and some of the halogenated hydrocarbons, such as carbon tetrachloride and chloroform, belong to this group. Amphiprotic solvents have an appreciable dipole moment, or have groups with dipoles such as *p*-dioxan; lower fatty acids, alcohols and amines belong to this class. The relative acidity of two acids will vary from solvent to solvent, and the variation of the ratio of their activity will be greater the more different are the acids. The choice of a solvent depends almost entirely on the nature of the substance to be determined; there is considerable evidence that mixed solvents may be superior to a single solvent in general solvent power and in sharpness of the indicator colour change or potentiometric break. Most analytical methods have been developed using acetic acid (anhydrous) as the solvent. There is no absolute criterion of acidity or basicity in non-aqueous solutions; acids and bases of unlike nature may undergo a change in the relative position of their respective strengths in different solvents and, generally, a satisfactory method has not been found to determine absolute acid or base strengths in a variety of solvents. As indicators, *p*-aminophenyl benzenesulphonamide, 1-naphthyl-6-sulphonamide, and 1-naphthyl-7-sulphonamide in acetic acid solution fluoresced strongly in ultra-violet light

and could be titrated visually with perchloric acid, using the fluorescent colour change as indicator. Methods for acid-base titrations have been reported which employ the following indicators: modified methyl orange (xylene cyanol), methyl red, thymol blue, methyl violet, 1-naphtholbenzein, bromocresol yellow, crystal violet, phenolphthalein, benzyl auramine, methyl orange, and cresol red. Most of the early potentiometric measurements were made using a lithium chloride bridge; references to many electrode systems are quoted. Perchloric acid is the strongest acid in organic solvents; it is the most suitable acid titrant in acid type amphiprotic solvents and has been used for the determination of a wide variety of substances; the most widely used bases for amphiprotic solvents, particularly the alcohols, are alkali metal alkoxides and alkali metal hydroxides; potassium hydroxide appears to be more suitable than sodium hydroxide. There is no satisfactory acid for use in aprotic solvents; *p*-toluene sulphonic acid in chloroform has been used and trichloracetic, *d*-camphor-sulphonic, and picric acids have been used as titrants to demonstrate the applicability of bromophthalein magenta as an indicator in aprotic solvents. Derivatives of guanidine appear to be the most satisfactory base titrants in aprotic solvents; 1:3-diphenyl-, di-*o*-tolyl-, and di*cyclo*hexylguanidine appear to be the strongest bases in benzene. With reference to the methods used for titrations in acetic acid the titrant must be kept and used at a constant temperature or a temperature correction must be applied; details and references relating to the procedure are given. Among the substances which can be titrated are listed: salts of carboxylic acids, amines, amino-alcohols, oxazolines, amino-acids, amides of carboxylic acids, chlorides, bromides, nitrates, sulphates, quinine, alkylene oxides, nicorinic acid, nicotinamide and related compounds, sulphonamides, and basic nitrogen in oils. For the estimation of weak acids Polit proposed a 1:1 mixture of ethylene glycol or propylene glycol and *iso*propanol with perchloric acid as the titrant and methyl red as the preferred indicator; the mixture was regarded as an almost universal solvent for alkali metal salts of monobasic organic acids; alkali metal salts of monocarboxylic acids, amines, mixed acids, salts of inorganic acids, boric acid and alkali in soap were titrated using this solvent. Other solvents which have been used are methanol-benzene, monobutylamine, pyridine, alcohols, and chloroform. Other aspects discussed are: the effect of water, the standards to be used and the accuracy and precision of the method. R. E. S.

Amidone (Methadone), Analytical Studies of. J. Demonceau. (*J. Pharm. Belg.*, 1952, **7**, 36.) The addition of powdered sodium perchlorate to a solution of an amidone salt gives an oily precipitate which becomes crystalline on shaking for a few seconds. The sensitivity of the reaction is about 1 in 4000, and the microcrystalline clusters of needles derived from amidone may be distinguished from the polyhedrons produced by phenadoxone or the other microcrystalline forms from morphine, pethidine, codeine, etc. A more sensitive reagent is a mixture of equal volumes of 5 per cent. mercuric chloride solution and 40 per cent. potassium bromide solution. Characteristic crystals are obtained with amidone in concentrations from 1 to 500 to 1 in 30,000. At higher concentrations the precipitates are amorphous. The addition of 2 drops of nitric acid (20 per cent. HNO_3) and 3 to 4 ml. of sulphuric acid to 1 ml. of amidone hydrochloride solution gives a pink to purple-red colour according to the concentration and this reaction will detect 25 μg. of amidone hydrochloride. Potassium nitrate may be used in place of nitric acid. The presence of chloride is necessary for formation of the red colour (amidone base gives an orange colour) but an excess of chloride ions decreases the sensitivity of the test.

Phenadoxone gives the same colour as amidone, morphine and brucine give the colour on the addition of a few drops of reagent but an excess of reagent gives an orange to yellow colour. The following may be used quantitatively. Place 2 ml. of the amidone hydrochloride solution in a large test tube immersed in cold water and add 8 ml. of sulphuric acid containing 0·5 per cent. w/w of potassium nitrate, shaking after the addition of 10 drops. Heat in a boiling water bath for exactly 2 minutes, cool with cold water for 15 minutes and determine the spectrophotometric absorption at 525 mμ. Using 1-mg. samples, errors up to 6·5 per cent. were experienced. G. B.

p-Aminosalicylic Acid, Estimation of m-Aminophenol in. A. Kirschbaum. (*Pharm. Acta Helvet.*, 1952, **27**, 26.) It has been suggested that the amount of *m*-aminophenol present in solutions of *p*-aminosalicylic acid should be estimated by shaking 10 ml. of solution at *p*H 8 to 8·5 six times with 10 ml. of ether, evaporating off the ether and drying *in vacuo* and weighing the residue. The residue is tested for m.pt. 120° to 122° C. and its solution should give a yellow to brown colour with aqueous solution of ferric chloride (*p*-aminosalicylic acid gives a red colour) and if to 2 ml. of solution 1 ml. of saturated solution of potassium iodate and then 2 ml. of glacial acetic acid are added, a characteristic reddish violet colour is formed in a short time, and this can be used for colorimetric estimation. The author investigated the extraction of *m*-aminophenol with ether, using a 20 per cent. solution of anhydrous sodium *p*-aminosalicylate (A) and the same with the addition of 2 per cent. of *m*-aminophenol (B). Solution B was extracted 6 times with ether, but only 80 per cent. of the *m*-aminophenol was obtained, a further 6 extractions only recovered another 15 per cent. and the latter residue was coloured and impure. Commercial ether was used in these experiments; using anæsthetic ether 93 per cent. was extracted in 6 shakings and the residue was much purer, showing that the peroxides present in the commercial ether had caused decomposition. The solutions were allowed to stand 5 months without special precautions and then tested again. Solution A had become reddish-brown and the *p*H was more alkaline and when extracted with anæsthetic ether a residue of 0·060 g. (from 2 g. of original sodium *p*-aminosalicylate) was obtained; this was impure *m*-aminophenol. Solution B had become brownish-black and opaque, ether extracted 0·225 g. as against 0·186 g. for the fresh solution. Although the aqueous solutions were deeply coloured the ether extracts were practically colourless. When solutions were kept in ampoules sealed from air, even when 50 per cent. of the *p*-aminosalicylate was decomposed by heat, no discoloration was caused and no change of *p*H, and extraction with ether gave pure *m*-aminophenol. Decomposition can be approximately measured by acidifying and determining the carbon dioxide evolved, in the cold, from the sodium carbonate formed, or by direct titration of the latter. H. D.

Barium in Calcium Salts, Limit Test for. A. Askgaard and F. Reimers. (*Dansk. Tidsskr. Farm.*, 1952, **26**, 32.) A seeding reagent is prepared by precipitating the barium chloride in 2 drops of a solution containing 100 μg. of Ba^{++} per ml. with 1 ml. of 0·1 M sulphuric acid. To this seeding reagent is added 10 ml. of test solution and after 1 minute's standing the mixture is vigorously shaken. The turbidity produced, after 30 minutes standing, is compared with a standard liquid. If no barium is allowed a blank using the seeding reagent and 10 ml. of water is prepared for comparison. If a positive reaction for barium is allowed the turbidity produced by 4 drops of the barium chloride solution, 1 ml. of 1 M sulphuric acid and 10 ml. of water is recommended

for comparison. The turbidity of this standard is only slightly altered on standing for 30 minutes. J. R. F.

Chloramphenicol, Colour Reaction for. R. Truhaut. (*Ann. pharm. franc.*, 1951, **9**, 347.) Chloramphenicol, in common with trihalogen compounds and a series of halogen derivatives was found to give a colour reaction, when heated with pyridine in an alkaline medium. 5 ml. of a solution of the drug in purified pyridine was heated with 2 ml. of a 50 per cent. w/w solution of potassium hydroxide at 100° C. for 5 minutes. The solution was cooled in iced water for 90 seconds, when a rose to red colouration developed in the pyridine layer, the depth of colour depending on the concentration. Attempts to use this reaction for quantitative estimation and determination of the drug in urine and blood have failed owing to the development of an opalescence. J. R. F.

Salicylates and Derivatives, Estimation of Salicylic Acid in. G. Scandellari (*Boll. chim.-farm.*, 1951, **90**, 387.) The method of assay based on the formation of Lautemann's Red (tetriodiphenylquinone) may be used when there are no other substances present which react in the same way with iodine. It can also be used for estimating acetylsalicylic acid, salol, phenol and salicylamide, but cinchophen, *p*-aminosalicylic acid and sodium gentisate react irregularly. Place about 0·3 g., accurately weighed, of the substance previously dried at 100° C. in a 250 ml. beaker. Add 5 ml. of 2 N sodium hydroxide and 100 ml. of water and heat on a water bath to about 95° C. for 20 minutes. Then add concentrated solution of iodine (iodine 12·70 g., potassium iodide 20 g., water to 100 ml.) until the liquid is deep brown. An abundant precipitate is formed. Leave on the water bath for an hour, keeping free iodine always in excess, and cool. Remove the excess of iodine by cautiously adding sodium bisulphite and collect the red precipitate on a double tared filter paper 11 cm. in diameter. Wash until free from iodide, dry at 100° C. and weigh. 1 g. of the precipitate corresponds to 0·4017 g. of salicylic acid. Sodium salicylate showed 86·40 and 86·31 per cent. of salicylic acid (theory 86·25 per cent.); acetylsalicylic acid, 76·25 per cent. (theory 76·66 per cent.); salol, 125·22 per cent. (theory 64·48 per cent. for one molecule and 128·95 for two molecules); phenol, 147·79 per cent. (theory 146·86 per cent.); cinchophen does not form a red precipitate; sodium *p*-aminosalicylate showed 41·59 per cent. (theory 78·41 per cent.); sodium gentisate gave a black crystalline precipitate equivalent to 12·05 per cent. of salicylic acid (theory 77·97 per cent.); salicylamide, 74·90 per cent. (theory 100·72 per cent.). H. D.

GLYCOSIDES, FERMENTS AND CARBOHYDRATES

Cardiac Glycosides, Aglycones and Acetates, Paper Chromatography of. E. Heftmann and A. J. Levant. (*J. biol. Chem.*, 1952, **194**, 703.) Data are given relating to the relative mobility in benzene-formamide and toluene-propylene glycol systems and on the sensitivity to Tollens' and trichloroacetic acid reagents of a series of cardiac glycosides, aglycones and acetates. Details of procedure are quoted for the preparation of the chromatographic cabinet, the preparation of the filter paper and for the development. After completion of the development, the sheets were dried and sprayed with either Tollens' reagent or trichloroacetic acid solution. Tollens' reagent gave black or dark brown spots after use of benzene-formamide and reddish-brown spots after toluene-propylene glycol; trichloroacetic acid gave either yellow or green spots, which turned brown on prolonged heating, visible in daylight and fluorescing

around the edges in ultra-violet light or invisible in daylight but fluorescing brightly in ultra-violet light. The sensitivities of the spot tests are recorded for 22 cardiac glycosides, aglycones and acetates. The results are discussed in an attempt to correlate structure and chromatographic behaviour. R. E. S.

ORGANIC CHEMISTRY

Saccharin, Hydrolytic Stability of. O. DeGarmo, G. W. Ashworth, C. M. Eaker and R. H. Munch. (*J. Amer. pharm. Ass. Sci. Ed.*, 1952, **41**, 17.) A method for the determination of the amount of decomposition in saccharin depends upon measurements of the optical densities of solutions in 0·1N sodium hydroxide solution. Under these conditions, saccharin and its hydrolytic decomposition products, *o*-sulphamylbenzoic acid and (ammonium *o*-sulpho) benzoic acid exhibit absorption maxima at 267·3 mμ, the absorption coefficients of the two decomposition products being about equal and much lower than that for saccharin itself. Using optical density measurements at 267·3 mμ the decomposition of saccharin at temperatures used in cookery was shown to be negligible.

DECOMPOSITION OF SACCHARIN SOLUTIONS

Solvent	*p*H	Percentage decomposition after 1 hour at		
		100° C.	125° C.	150° C.
Water	2·0	2·9	8·5	18·6
Buffer	3·3	0	1·0	1·9
Buffer	7·0	0·3	0·3	1·6
Buffer	8·0	0	0	0

G. B.

TOXICOLOGY

Amphetamine in Viscera, Determination of. E. Rathenasinkam. (*Analyst*, 1952, **77**, 135.) A scheme is described for the isolation, identification and determination of amphetamine; the isolation is first achieved by extracting with ethanol acidified with tartaric acid according to the Stas-Otto process. The residue is steam-distilled from alkaline solution, the distillate evaporated to low bulk made alkaline with sodium hydroxide and the base extracted into chloroform; the hydrochloride is then produced by extraction into hydrochloric acid. Methods of identification are reviewed and a further colour reaction of the nitro-compounds formed by the nitration of amphetamine is described. A number of processes for the determination of the substance are discussed and a new method depending on the precipitation of the amphetamine as oxalate is given; a comparison of the results obtained by this method with those obtained by a volumetric method is shown. R. E. S.

Blood Stains, Spectrophotometric Detection of. A. A. Khalifa and M. K. Salah. (*Nature, Lond.*, 1952, **169**, 461). A test for the identification of blood stains is described depending on the fact that potassium cyanide, with hæmoglobin, methæmoglobin or hæmatin, gives cyanohæmoglobin which is characterised by an absorption curve with a maximum at 422 mμ and smaller bands at 360 and 550 mμ respectively; the maximum at 422 mμ has 10 times the intensity of the visual band at 550 mμ making the ultra-violet examination more sensitive than the visual. The test was applied by soaking a suspected stain (as small as 2 sq. mm.) in 0·5 per cent. potassium cyanide solution for 15 minutes, filtering, and determining the absorption curve from 300 to 600 mμ. The method can be adopted for quantitative estimation. The test has been applied to blood stains obtained

from a variety of materials; leather, painted wood, walls, soil, sand and stains from cloth either washed with soap and water or contaminated with vegetable juices or rust. A graph is given of absorption curves obtained. R. E. S.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Dextran Sulphate, A Synthetic Heparin Analogue. C. R. Ricketts. (*Biochem. J.*, 1952, **51**, 129.) A series of sulphuric esters of dextran, differing widely in molecular weight and in the number of sulphate groups, were prepared. Three main molecular weight types of dextran sulphate were prepared, two from unfractionated hydrolysates and the third from the low molecular fraction of a hydrolysate with intrinsic viscosity 0·24. Intrinsic viscosity was used as a measure of molecular weight, the average molecular weight of the first two dextrans being about 200,000 and 20,000; allowing for the introduction of 1·3 sulphate groups per glucose unit, the average molecular weight of the dextran sulphates would then be very approximately 300,000 and 30,000. The third type of dextran sulphate had an estimated molecular weight of less than 20,000 allowing for the introduction of 1·3 sulphate groups per glucose unit. Biological testing of the preparations showed that the third series of dextran sulphates (lowest molecular weight) were free from toxic effects although the higher molecular weight series were found to be toxic. Details are given of the preparation of a non-toxic dextran sulphate. When prepared the dextran sulphate decomposed on boiling in aqueous solution with the formation of inorganic sulphate and reducing substances; such decomposition, for example, on autoclaving, could be prevented by buffering the solution with sodium chloride and sodium bicarbonate. Maximum blood anticoagulant activity was found when the number of sulphate groups exceeded an average of 1·3 per glucose unit. R. E. S.

Pancreatin with High Enzymatic Activity. C. W. Bauer and A. J. Vazakas. (*J. Amer. pharm. Ass., Sci. Ed.*, 1951, **40**, 552.) Pancreatin prepared by defatting fresh pancreas with acetone and drying with ether, according to the method of Willstätter and Waldschmidt-Leitz, had a high lipase content and contained 3 times the amount of trypsin and twice the amount of amylase required by the U.S.P. The lipolytic activity was destroyed by exposure to an acidity equal to that of the stomach. The lipase content of fresh hog pancreas was reduced by immersion in ethanol ranging in strength from 20 to 95 per cent. for 11 days. Hog intestine was investigated as a source of lipase by cutting into several sections, grinding a piece from each section with sand and water and assaying the resulting suspensions; all samples gave low results. When a portion of the intestine was ground together with a piece of fresh pancreas, the lipase content of the resulting suspension was found to be no greater than the sum of the lipase contents of the constituents, indicating that if the intestine contained a lipase precursor, it was not activated by fresh pancreas.

G. R. K.

***Saccharomyces cerevisiae*, Effects of Cocaine on the Metabolism of.** B. E. Ryman and E. O'F. Walsh. (*Biochem. J.*, 1952, **50**, 570.) The glucose fermenting properties of *Saccharomyces cerevisiæ* at *p*H 7 have been studied in the presence of cocaine and added vitamin B_1. *S. cerevisiæ* grows quite well in the presence of cocaine, provided that the concentration is not greater

than 0·004 M (0·005 M inhibits growth completely); the organism appears to acquire a tolerance for the drug, and yeast which has been grown in the presence of cocaine grows quite well in its absence. Experiments with vitamin B_1 indicated that changes occurred in the cells as a result of growth in the presence of cocaine; a difference in behaviour towards added vitamin B_1 between the normal yeast and the cocaine-grown yeast was noted. Cocaine, in concentrations sufficient to arrest growth (0·005 M) at *p*H 7, inhibited completely the carboxylase system of *S. cerevisiæ*; the carboxylase systems of yeast grown in the presence and in the absence of cocaine were inhibited by cocaine to a similar extent. Growth in the presence of cocaine at *p*H 7 did not show any quantitative adaptation of the carboxylase system of *S. cerevisiæ*. R. E. S.

Streptomycin, A New Colour Reaction of. W. J. Halliday. (*Nature, Lond.*, 1952, **169**, 335.) When streptomycin and diacetyl are mixed in aqueous alkaline solution, a pink colour is produced by virtue of the guanidine groupings in the antibiotic. This colour can be greatly intensified by the further addition of α-naphthol, and the modification increases the sensitivity only. The following facts are noted: (1) the colour was slow to develop, and faded after reaching a maximum intensity; (2) oxygen was necessary both for colour development and for the fading process; (3) strong absorption was found at the shortest wavelengths of visible light, with a characteristic band in the green region (peaks at 504 mμ for the first reaction and at 515 mμ for the modification). The sensitivity was limited to about 50 μg. of free base in a total of 15 ml. Many guanidine derivatives interfered with the test, and dihydrostreptomycin gave a similar reaction. A. H. B.

Terramycin, Fluorimetric Behaviour of. M. Serembe. (*Arch. Ital. Sci. Farmacol.*, 1951, **1**, 244.) Terramycin in the solid state gives a yellow fluorescence under Wood's light. In solution, with *p*H 1 to 5 there is no fluorescence, in distilled water (*p*H 5 to 6) there is a yellow fluorescence which becomes brighter as the *p*H increases up to a maximum at *p*H 9 to 10. On standing, the fluorescence becomes greenish and this appears more rapidly with greater alkalinity and higher temperature. Lithium chloride, disodium hydrogen phosphate, calcium chloride and magnesium chloride increase the fluorescence notably, other salts have less action. The yellow fluorescence can be used for estimating the amount present. With biological material the solubility of terramycin in *n*-butanol can be used for removing other substances which fluoresce. 1 ml. of blood serum, pulped organs, urine or bile is brought to *p*H 9 to 10 with 0·1N sodium hydroxide and shaken thoroughly with 2 ml. of *n*-butanol for serum or pulped organs and 1 ml. for urine or bile, and then centrifuged. The intensity of fluorescence in the butanol solution is proportional to the amount of terramycin present within the limits of 5 mμ and 50 mμ per ml. Aureomycin also gives a fluorescence, which can be distinguished from that of terramycin as it is yellow at *p*H 6 to 8·5 and blue at higher figures. It is also blue in the presence of lithium chloride, sodium bicarbonate, sodium sulphate and disodium hydrogen phosphate. The change of colour of the fluorescence of terramycin to greenish and aureomycin to blue is accompanied by loss of activity. H. D.

Terramycin in Serum and Urine after Ingestion of Terramycin Base. J. D. Carlile, A. C. Kester, C. B. McDonald and C. F. Clancy. (*J. Amer. pharm. Ass., Sci. Ed.*, 1951, **40**, 535.) 15 males were given a single dose of 2 g. of terramycin base on a fasting stomach. After 1 hour the average serum level was 0·9 μg./ml., although not all subjects showed a measurable level.

After 2 hours the level was 1·8 μg./ml., all subjects having a demonstrable level of drug. The highest level, 2·4 μg./ml., was reached after 4 hours; the drug had disappeared by the 24th hour. The levels in 5 control subjects receiving terramycin hydrochloride followed a similar course except that the highest level, also reached after 4 hours, was 4·8 μg./ml. In a similar series of experiments, in which the drugs were given in doses of 0·5 g. every 6 hours, some of the subjects receiving the base showed demonstrable serum levels after 8 hours; after 24 hours the test and control groups showed 1·1 and 1·6 μg./ml. respectively. Urine analyses after the administration of a single dose of 2 g. of base and hydrochloride showed that all subjects were excreting the drug by the end of the first hour and also after 24 hours. In general, the levels attained in subjects receiving the hydrochloride were greater than those in subjects receiving the base. It appears that the rate of absorption of terramycin from the alimentary tract is independent of whether the base or the more soluble hydrochloride is administered, but that after ingestion of the base the concentration in the urine is less than that following ingestion of the hydrochloride.

G. R. K.

Thiochrome Solutions under Various Lighting Conditions. L. J. DeMerre and M. A. Seibold. (*J. Amer. pharm. Ass., Sci. Ed.*, 1951, **40**, 566.) Direct sunlight and ultra-violet light produced total destruction in thiochrome solutions. Natural daylight also produced total destruction but at a slower rate. Exposure to dim daylight in intensities not higher than 10 foot candles produced no destruction in 120 minutes. Artificial light from an incandescent bulb had a marked destructive effect for intensities above 600-foot candles. With monochromatic light, destruction was greater in the short wavelength region. In the green region (485 mμ) and above, no destruction occurred. G. R. K.

BIOCHEMICAL ANALYSIS

Ethanol in Blood or Urine, Determination of. F. J. Scandrett. (*Analyst*, 1952, **77**, 132.) A method is described for the micro-determination of ethanol in blood or urine by means of a new micro-diffusion procedure; after numerous trials the method and the quantities and concentrations of reagents used by Widmark were found to be the most suitable. A new micro-diffusion apparatus that permits the separate temperature control of the two chambers, is illustrated and described in detail; a lower vessel, which contains the sample for determination, has a flat base and is attached to the chimney part of a "mushroom" which is surrounded by a simple form of condenser that allows water at 50° C. to circulate over and under it. Accurate results were obtained over the range of 80 to 300 μg. of ethanol per 0·1 ml. of blood and urine, the standard deviation being less than ± 3·0 μg. per 0·1 ml. of blood. It is claimed that the method reduced the time for a single diffusion to 30 minutes, and that as a result of the large excess of water in the "mushroom" receiver there is no possibility of loss of the liberated iodine, that the end-point is not so abrupt and the subsequent titration and shaking are, therefore, easy to control and manipulate. An increase of the temperature gradient of the absorption made possible an increase in the range over which diffusion techniques could be used; experiments with blood containing 300 mg. of ethanol per 100 ml. stored at room temperature for one week, did not show any diminution of ethanol concentration. R. E. S.

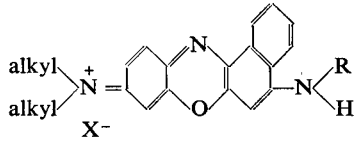
Penicillin, Effect of Sugars on Plate Assay of. C. R. Bond. (*Analyst*, 1952, **72**, 118.) An examination was made on the effect of dissolved substances in penicillin test solutions; such substances often yield larger zones, giving

fictitiously high assay results, if normal simple solutions of penicillin are used as standards. Preliminary investigation of this phenomenon showed that the causal agent was sucrose; work was carried out to determine more precisely the effects of the commonly used sugars (sucrose, lactose and dextrose), on the size of the zones of inhibition, and on the definition of the zone edges. Sucrose produced the largest effect and dextrose a somewhat smaller effect, while up to 0·4 per cent. of lactose was almost without effect on the size of the zones. In the assay of penicillin lozenges or other samples containing sugars it was considered that the standards used must be compensated by addition of the appropriate sugars. The presence of sucrose in assay solutions gave improved zone edges in an ordinary nutrient agar media, this also being obtained by incorporating 0·1 per cent. of sucrose into the nutrient agar. The accuracy of the method could thus be increased and the curvature of the regression line for zone diameter on the logarithm of the concentration in the sucrose medium was sufficiently small over the range 2 to 8 units per ml. to allow calculation of results on a theoretically linear relationship without introducing serious error (maximum about 3 per cent.). In the assay of penicillin lozenges the concentrations of sugars in the standards must be the same as in solutions under test. R. E. S.

Urinary 17-ketosteroids, Estimation of. E. R. Cook. (*Analyst*, 1952, **77**, 34.) A method is described for the rapid estimation and fractionation of urinary 17-ketosteroids based on the routine procedure of Reiss, Hemphill, Gordon and Cook, by which the crude extract from 250 ml. of urine may be rapidly purified and partitioned into 3(α)-hydroxy- and 3(β)-hydroxy-17-ketosteroids. Attempts were made to reduce the experimental work to a minimum by separating smaller quantities of material and by a direct estimation of the β-ketosteroid component as its digitonide. Details of the method and of the precautions necessary to obtain quantitative results are given. Known amounts of pure 17-ketosteroids added to urine gave recoveries of at least 93 per cent.; the procedure is recommended as a rapid and satisfactory routine determination for use in the estimation of fractional 17-ketosteroids. R. E. S.

CHEMOTHERAPY

Chemotherapeutic Dyes. I. 5-Aralkylamino-9-alkylaminobenzo[a]phenoxazines. M. L. Crossley, P. F. Dreisbach, C. M. Hofman and R. P. Parker. (*J. Amer. chem. Soc.*, 1952, **74**, 573.) A series of 5-amino and 5-aralkylamino-9-(mono- and di-)-alkylaminobenzo[a]phenoxazonium salts of general formula I—



where R = a benzyl or ring-substituted benzyl group and X is the anion of a salt, were prepared. Their differential tissue staining and tumour growth-retarding actions were investigated, and the effect of structural modifications upon these actions are discussed. Some of the derivatives showed a marked differential fat-staining effect when administered orally either to normal mice or to tumour-bearing mice. In the latter case, the tumour was stained blue

and the fatty tissue red. Many of the compounds exhibited strong antituberculous activity when administered orally to infected mice, and 20 members of the series possessed activity equivalent to, or greater than, that of streptomycin given subcutaneously at optimum dosage. Compounds with an unsubstituted amino group in the 5-position were inactive. The presence of one, or preferably two, alkyl radicals on the 9-amino nitrogen seems to be necessary for activity. Maximum effect was obtained in the 9-di-*n*-propylamino and 9-di-*n*-butylamino series. The presence of a substituent in the benzyl ring is unnecessary for high activity. An acidic group in the molecule lowers the antituberculous effect.

A. H. B.

Chemotherapeutic Dyes. II. 5-Arylamino-9-dialkylaminobenzo [a] phenoxazines. M. L. Crossley, R. J. Turner, C. M. Hofmann, P. F. Dreisbach and R. P. Parker. (*J. Amer. chem. Soc.*, 1952, **74**, 578.) A series of 5-aryl amino-9-(mono- and di-)-alkylaminobenzo[a]phenoxazines was prepared and the compounds tested for tumour growth-retarding action and antituberculous action. The alkyl groups were varied from methyl to *n*-hexyl, and maximum antituberculous activity resulted when two propyl groups were present on the 9-amino group. Substitution by chloro or methyl groups in the 5-position of the aryl ring maintained or increased activity, but larger alkyl groups decreased activity. Introduction of electronegative substituents such as nitro, carboxy, carbethoxy or acetyl produced a sharp decrease in activity. 26 of the compounds of this series, when administered orally to mice, possessed activity equivalent to or greater than that of streptomycin administered subcutaneously at optimum dosage.

A. H. B.

Chemotherapeutic Dyes. III. 5-Heterocyclicamino-9-dialkylaminobenzo[a]-phenoxazines. M. L. Crossley, C. M. Hofmann and P. F. Dreisbach (*J. Amer. chem. Soc.*, 1952, **74**, 584.) A series of 9-dialkylamino-5-heterocyclicaminobenzo[a]phenoxazines was prepared and tested for tumour growth-retarding and antituberculous action. Those compounds possessing a 9-diethylamino group showed a growth-retarding effect on tumour transplants, the most active compound being the 9-diethylamino-5-(2-pyridylamino)benzo[a]phenoxazine derivative. None of the compounds of the series possessed significant antituberculous activity.

A. H. B.

PHARMACY

NOTES AND FORMULÆ

Choline Gluconate. (*New and Nonofficial Remedies, J. Amer. med. Ass.*, 1952, **148**, 744.) Choline gluconate is 2-(hydroxyethyl)trimethylammonium D-gluconate. It is commercially available as a 58 to 62 per cent. aqueous solution. The following tests and standards apply to a 95 per cent. sample, which occurs as a straw-coloured highly viscous mass with an amine-like odour and a bitter taste; soluble in water, sparingly soluble in ethanol, very slightly soluble in ether and practically insoluble in benzene and chloroform; the *p*H of a 50 per cent. solution is between 5·0 and 6·0. Choline gluconate gives a pale yellow precipitate with mercuric potassium iodide, and an emerald-green colour with cobaltous chloride and potassium ferrocyanide. The yellow colour of an aqueous solution is intensified by ferric chloride. The crystals of gluconic acid phenylhydrazide formed by heating a 10 per cent. solution with glacial acetic acid and phenylhydrazine melt at 199° to 202° C. Choline gluconate

contains less than 5 per cent. of water, when determined by the Karl Fischer method, and yields less than 0·05 per cent. of ash. It is assayed spectrophotometrically by measuring the light absorption at 5260 Å of a solution in acetone of the reineckate obtained by treating an aqueous solution with ammonium reineckate. The content of choline gluconate is obtained from a standard curve prepared with Choline Chloride U.S.P. Reference Standard, and is not less than 95·0 and not more than 105·0 per cent. G. R. K.

Cyclocumarol (Cumopyran). (*New and Nonofficial Remedies, J. Amer. med. Ass.*, 1952, **148**, 939.) Cyclocumarol is 3 : 4-dihydro-2-methoxy-2-methyl-4-phenyl-2H,5H-pyrano[3,2-c][1]-benzopyran-5-one and occurs as a white crystalline powder with a slight odour, m.pt. 164° to 168° C., insoluble in water, and slightly soluble in ethanol. A 0·015 per cent. solution in ethanol exhibits ultra-violet absorption maxima at 2710 and 2820 Å and a minimum at 2760 Å. The ratio of the extinction coefficients at 2760 and 2820 Å is not less than 0·856 and not more than 0·956. It loses not more than 1·0 per cent. of its weight when dried at 105° C. for 2 hours, yields not more than 0·2 per cent. of ash, and complies with a test for heavy metals. It is assayed by dividing the extinction coefficient at 2820 Å of a 0·015 per cent. ethanolic solution by the factor 396; it contains 97·0 to 103·0 per cent. of cyclocumarol. Cyclocumarol is an anticoagulant. G. R. K.

PHARMACOGNOSY

Colchicum, Alkaloid Content of. A. Mastnak-Regan. (*Acta pharm. Jug.*, 1951, **1**, 67.) After the seeds and corm, the flower has the highest content of alkaloids, while the leaves have the lowest. In the dried plant the corm is the richest part, followed by the leaves, the seeds, the fruit and the flower. During growth the percentage of alkaloids in the corm is lowest in the autumn; in old corms, the percentage is greatest in the spring. In the stem the alkaloidal content diminishes during May and June when the leaves begin to wither. Unripe seeds contain less alkaloid than ripe seeds. Fresh corm and seeds are poorer in alkaloidal content than dried corm and seeds. The iodimetric method of assay was used in these determinations. The method of the U.S.P. XIII, P. Helv. V and D.A.B. VI for the extraction of the alkaloids often produced strong emulsions, whereas the method of P. Ned. V modified by Uffelie was free from this objection. Results obtained by the iodimetric method were often very low. Those obtained by the P. Ned. V and the U.S.P. methods were in agreement. G. R. K.

Digitalis Leaf Glycoside Yields, Effects of Freezing Temperature Storage on. H. W. Youngken, Jr., E. H. Djao and D. P. N. Tsao. (*J. Amer. pharm. Ass., Sci. Ed.*, 1951, **40**, 569.) First year digitalis leaves stored at −18° to −12° C. for two years packed in manila envelopes or cloth bags were of excellent green appearance and had dried considerably; those stored in the envelopes had dried more than those stored in the bags, but in both the moisture content was still considerably more than the U.S.P. maximum. Tinctures made by the U.S.P. method modified to allow for the higher moisture content had glycoside contents consistently higher (usually more than 20 per cent.) than tinctures made from leaves from the same source which had been dried immediately after collection by heating at 29° to 38° C. in a current of air. When the frozen material was dried in the same way before preparation of the tincture, all samples but one gave lower yields than the undried material, indicating that

the method of drying destroyed part of the glycosides, although the loss was less when the material had been previously frozen. The disadvantages of storage at low temperature are the longer time taken to prepare official tinctures due to the necessity of determining the moisture content and adjusting the composition of the solvent, and the larger storage space required. G. R. K.

***Digitalis purpurea*, Effects of Season, Temperature and Plant Age on Glycoside Production in.** D. P. N. Tsao and H. W. Youngken, Jr. (*J. Amer. pharm. Ass. Sci. Ed.*, 1952, **41**, 19.) Plants were raised from seeds of known strains of *Digitalis purpurea* L. and grown in carefully controlled field experiments or in hydroponic culture in greenhouses. Dried leaves were assayed for glycoside content against the U.S.P. reference standard, by a modified Knudson–Dresback method using a spectrophotometer. Some samples were also assayed by the U.S.P. pigeon method. In field experiments the highest glycosidal yield was obtained at the end of 141 days' growth after which the glycoside content declined. This maximum corresponded to collection of the plants in August. For plants grown for 6 to 7 weeks in the greenhouse, the glycoside content was highest in August-September and January-March. The highest glycosidal yield was achieved after 120 to 136 days' growth in hydroponic culture. Discrepancies between the colorimetric and biological assays were observed, the colorimetric method giving higher and more consistent results.

G. B.

PHARMACOLOGY AND THERAPEUTICS

Antibiotics: *in vitro* Effect on Typhus Rickettsiæ. A. Karp and J. C. Snyder. (*Proc. Soc. exp. Biol., N.Y.*, 1952, **79**, 216.) Aureomycin and terramycin in concentrations of 100 to 300 μg./ml. were found to inhibit markedly the respiration of murine and epidemic typhus rickettsiæ *in vitro*, as measured by the rate of oxygen uptake by the Warburg method. Chloramphenicol in concentrations up to 300 μg./ml. produced only slight inhibition. The inhibition of respiration was correlated with a decrease in the number of viable rickettsiæ as determined by toxicity and infectivity for white mice. S. L. W.

Blood Coagulation, Influence of Drugs on. D. I. Macht. (*J. Amer. med. Ass.*, 1952, **148**, 265.) A number of widely used drugs have been found to exert a thromboplastic or coagulation promoting influence on the blood of animals and humans. The digitaloid drugs and the antibiotics, penicillin, streptomycin and aureomycin, are amongst these; also included are the mercurial diuretics, metallic antisyphylitics, amphetamine and some opium derivatives. Although there is usually a wide margin of safety for accommodating fluctuations in coagulation time, attention is drawn to the possible deleterious effects of the administration of these drugs. J. R. F.

Citrovorum Factor in the Treatment of Megaloblastic Anæmia. L. S. P. Davidson and R. H. Girdwood. (*Lancet*, 1951, **261**, 1193.) A good clinical and hæmatological response was obtained in 6 cases of Addisonian pernicious anæmia and 2 cases of the megaloblastic anæmias of pregnancy from the administration of leucovorin (a synthetic form of citrovorum factor, stated to have the structure 5-formyl-5:6:7:8-tetrohydropteroyl-glutamic acid). Good results were obtained from administration either by mouth or by intramuscular injection of a dose of 3 to 12 mg. daily, the dosage schedule being varied according to the response. The effects produced in one case of idiopathic steatorrhœa were much less striking. S. L. W.

Colchicine, Natural Resistance of the Golden Hamster to. M. W. Orsini and B. Pansky. (*Science*, 1952, **115**, 88.) Rats and mice were killed by the intraperitoneal injection of 0·25 and 0·5 mg. of colchicine per 100 g. of body weight, respectively. In similar experiments, hamsters survived 7 mg. per 100 g. and showed no toxic effects. Their fertility and normal weight increase continued. When the animals were fed on a diet containing colchicum seed, 33 per cent., mice and rats died but hamsters survived and increased in weight. This resistance resembles that shown by rabbits towards aconite and it is suggested that it may have been acquired from a close association with *Colchicum* sp. in the animal's normal habitat, where the plants may possibly be eaten as food by hamsters. G. B.

Dihydrostreptomycin; Deafness following use in Tuberculous Meningitis. J. T. Naismith. (*Brit. med. J.*, 1952, **1**, 796.) The results obtained in a series of 26 cases of tuberculous meningitis treated with streptomycin are compared with those in a series of 51 cases treated with dihydrostreptomycin. While the latter showed a 67 per cent. recovery rate as compared with 50 per cent. in the former, 50 per cent. of the survivors (i.e., 17 out of 34) in the second series were deaf, whereas only 1 out of 13 survivors in the first series had impairment of hearing. In both series of cases the drug was given intramuscularly and intrathecally, though in the second series the intrathecal dosage was increased. The average time of onset of deafness was 5 months from beginning of treatment and most patients appeared to have fully recovered or to be steadily improving when their hearing began to be impaired. It is unlikely therefore that the deafness is caused by the meningitis, but rather that it is a toxic manifestation—apparently irreversible—of the drug used. While dihydrostreptomycin appears to be at least as effective as other forms of streptomycin in the treatment of tuberculous meningitis, there is enough evidence to warrant caution in its use and to indicate the desirability of a controlled investigation of its advantages and disadvantages compared with other forms of streptomycin. S. L. W.

Dimercaprol in Lead Poisoning. E. C. Vigliani and N. Zurlo. (*Brit. J. industr. Med.*, 1951, **8**, 218.) An investigation was carried out of the effect of injections of dimercaprol in 27 patients with occupational lead poisoning of whom 14 were suffering from acute lead colic on admission to hospital. The average lead content of the blood before treatment was 122 μg. per cent. The greatest reduction in the blood level was attained 8 to 10 hours after the injection of 2 to 5 mg./kg. of body weight, the average value being about 50 μg. per cent. 24 hours after the injection, the amount of lead in the blood had returned to near the previous level. A single injection of 50 mg. of dimercaprol raised the urinary excretion during the first hour from 6 to 25 times the rate before the injection. After the second hour, the rate of excretion fell rapidly. A series of 1 to 3 injections daily for several days, the total daily dose being 50 to 450 mg., produced an increase in urinary lead for the first 3 to 5 days, followed by a reduction to pre-treatment levels. On stopping treatment, both blood and urinary lead tended to return to the initial levels. In some cases, administration during lead colic aggravated the symptoms and caused them to re-appear even after they had disappeared for several days. The principal pharmacological effect of dimercaprol is the transfer of lead from the blood and certain tissues to other tissues. The authors conclude that the de-leading effect is relatively small when the unfavourable effects of changes in the internal distribution of lead are taken into consideration. H. T. B.

αα-Diphenyl-γ-dimethylaminovaleramide hydrogen sulphate, a Synthetic Atropine Substitute. A. Wollum and H. M. Pollard. (*J. Lab. clin. Med.*, 1951, **38**, 238.) This report is a summary of studies undertaken to evaluate the effect of αα-diphenyl-γ-dimethylaminovaleramide hydrogen sulphate (BL-139) on certain phases of fasting gastric secretion and gastric and small bowel motility. It is very similar to atropine in its effect on gastric secretory volume, free hydrochloric acid, and *p*H. The effect of both this drug and atropine on gastro-intestinal motility (gastric as measured by balloon studies and roentgenogram, and small bowel as measured by roentgenogram) appears similar, that is, a moderate but not complete or sustained inhibition of motility. Clinical side-reactions are similar to those of atropine, and the incidence of these side-reactions suggests that the dosage in clinical use should be similar to that of atropine in the majority of patients, namely, 0·5 mg. The available evidence does not suggest this is a better parasympatholytic agent than atropine.

S. L. W.

Hydroxyethylcarbamyl Group, Pharmacology of Compounds containing. R. Hazard, J. Cheymol, P. Chabrier, Y. Gay and M. P. Muller. (*Ann. pharm. franc.*, 1951, **9**, 390.) The authors give methods of preparing compounds containing the β-hydroxyethylcarbamyl group from benzylamine, phenylethylamine and phenyl*iso*propylamine and also compounds in which the carbamyl group is replaced by an amido group. They tested their pharmacological actions as to:—(1) toxicity to white mice, (2) local anæsthetic action on the cornea of the rabbit, (3) effect on the nervous system of the rat (excitement, depression, sleep), (4) changes in the arterial pressure of the chloralised dog. Compared with the amines the β-hydroxyethyl carbamates have less toxicity, possess a very marked anæsthetic action, produce depression instead of excitement and reduce instead of increasing the blood pressure. The anæsthetic action is notable, β-hydroxyethyl benzylcarbamate ($C_{10}H_{13}O_3N$) has an anæsthetic action equal to that of procaine, with a toxicity of one quarter, β-hydroxyethyl phenylethyl carbamate ($C_{11}H_{15}O_3N$) has twice the anæsthetic action and half the toxicity, and β-hydroxyethyl-phenyl *iso*propyl carbamate has twice the anæsthetic action and two-thirds of the toxicity. They are soluble in water and lipids and are neither basic, nor ionisable nor hydrolysable like esters. They have considerable chemical stability, and their hypotensive action is less than that of procaine. The esterification of the carbamates by succinic or maleic acids noticably increases the toxicity and diminishes their anæsthetic action, suppresses the action on the central nervous system and weakens the hypotension. The sodium salts of the corresponding succinamides show reduction in the toxicity and complete disappearance of anæsthetic action and of effects on the central nervous system and on blood pressure.

H. D.

Mepacrine Hydrochloride in Tæniasis. W. A. Sodeman and R. C. Jung. (*J. Amer. med. Ass.*, 1952, **148**, 285.) The use of mepacrine hydrochloride in the elimination of *Tænia saginata* in 11 cases of tæniasis has been investigated. A dose of 0·6 to 0·8 g. was administered by giving 2 tablets of 0·1 g. every 5 minutes, with water, until the entire dose was taken. If the drug had previously produced nausea and vomiting, sodium bicarbonate was added to the water and the medication repeated. The drug was effective in 10 patients on initial trial, and in the 11th when treatment was repeated. The only toxic reactions of importance were the nausea and vomiting which in general were easily controlled.

J. R. F.

Mephenesin Carbamate, Pharmacology of. P. E. Dresel and I. H. Slater. (*Proc. Soc. exp. Biol., N.Y.*, 1952, **79**, 286.) Mephenesin carbamate, 3-*o*-toloxy-2-hydroxypropyl carbamate (MC2303) is similar to mephenesin in potency and activity, but appears to have a longer duration of action, using the effectiveness of the two compounds against the extensor phase of maximal electric shock pattern as a criterion. Studies in animals were made to ascertain whether the mode and site of action of the compounds were comparable. In mice given the drug the pinna reflex disappeared before the corneal, a sign considered characteristic of mephenesin-like activity, and anti-convulsant actions in mice appeared similar. In spinal and anæsthetised cats both compounds showed a selective depression of the multisynaptic flexor reflex. In rabbits doses of both compounds causing a smooth reversible paralysis caused comparable slowing in the brain-wave frequency with an increase in amplitude. The action is not considered to be the result of degradation to mephenesin. S. L. W.

Mephenesin, Effect of on Spastic Paralysis. D. R. Laurence. *Lancet*, 1952, **262**, 178.) Mephenesin given by mouth, in the form of an elixir containing 1 g. in 15 ml., to the limit of tolerance was of benefit to only 2 out of 27 patients with various types of spastic paralysis, though it altered neurological signs in many cases without improving the patients' performance. Mephenesin intravenously, in a dose of 1 g. in 5 per cent. solution, produced good muscular relaxation of short duration in each of 10 cases of spastic paralysis without diminishing voluntary power, but it is useless for therapeutic purposes not only because of the brevity of its action but also because of the side-effects such as sleepiness and dizziness which are severe enough to prevent the patient taking advantage of his temporary release from spasticity. Nystagmus was also invariably present for a few minutes after each injection. S. L. W.

Mercurial Diuretics, Pharmacology of New. C. A. Handley, D. Chapman and J. H. Moyer. (*Proc. Soc. exp. Biol., N.Y.*, 1951, **78**, 433.) The compounds selected for investigation from a new series of diuretics were 3-chloromercuri-2-methoxypropylurea (compound I), 3-carboxymethylmeraptomercuri-2-methoxypropylurea (II) and 3-(α-carboxyethylmercaptomercuri)-2-methoxypropylurea (III). Diuretic activity and effect on sodium excretion were studied on dogs after intravenous injection, the urine being collected from a retention catheter at 20 minute intervals. Meralluride (mercuhydrin) was used as the standard diuretic. Sodium determinations were made by a flame photometer. Acute cardiac effects were measured by the electrocardiogram. Chronic toxicity was investigated by measuring the glomerular filtration rate at monthly intervals after doses of 1 mg. of Hg./kg. of body-weight 3 times weekly. Tubular function was determined from the maximal rate of tubular reabsorption of dextrose. Diuretic activity of each compound was 3 to 4 times as much as that of meralluride; the maximum effect was slightly delayed but the duration of action was about the same. The rates of excretion of mercury approached that of meralluride. The chronic toxicity and the rate of excretion were about the same for the four compounds. Of 6 animals given large doses of compound III, one developed ventricular fibrillation but the other 5 showed no significant cardiac changes. 2 out of 6 animals given compound I also developed ventricular fibrillation and all showed some cardiac effects. Dogs given compound II showed no cardiac changes and all the compounds had a lower acute toxicity than meralluride. H. T. B.

Methoxamine, Clinical Observations on. M. H. Nathanson and H. Miller. (*Amer. J. med. Sci.*, 1952, **223**, 270.) Methoxamine, a synthetic

sympathomimetic compound is β-(2:5-dimethoxyphenyl)-β-hydroxy*iso*propylamine hydrochloride. It differs from adrenaline, noradrenaline and most other pressor amines in that it does not induce ventricular fibrillation or other arrhythmias even in the *cyclo*propane-sensitised heart of the experimental animal. This study was undertaken to determine its action on the rhythmic function of the human heart. Its effect was studied in 6 patients in whom it was possible to induce cardiac standstill of 5 seconds or longer by compression of the right carotid sinus, in 6 patients with complete heart block, and in 20 patients with sinus rhythm. The drug was given by intravenous injection in a dose of 5 to 10 mg. and the rhythm was studied from the electrocardiogram. It was concluded that methoxamine in doses producing a pronounced pressor reaction does not increase the rhythmic function of the human heart. This is shown by the following: (*a*) it does not prevent the carotid sinus-induced cardiac standstill; (*b*) it does not increase the ventricular rate in heart block; (*c*) there is a definite slowing of the heart rate following intravenous administration of the drug. The bradycardia is abolished or prevented by atropine. The pronounced vagal effect induced by the drug can be employed in the treatment of supraventricular tachycardia. Because of the absence of a cardiac stimulating action it may be of value in the treatment of certain hypotensive states.

S. L. W.

Nisin in Experimental Tuberculosis. E. M. Bavin, A. S. Beach, R. Falconer and R. Friedmann. (*Lancet*, 1952, **262**, 127.) Crude and purified preparations of nisin, the antibiotic produced by *Streptococcus lactis*, were dissolved in 0·02N hydrochloric acid, and the solutions after adjustment to *p*H 4 were administered by injection in the treatment of experimental tuberculosis in mice. Previous work had shown that *in vitro* nisin compares favourably with streptomycin against *Mycobacterium tuberculosis* under the conditions of the experiments. The results of the experimental *in vivo* tests were assessed by the increase in survival time and by the protection against corneal inoculation of *Myco. tuberculosis* when the antibiotic was given by intraperitoneal injections twice daily, each of 25,000 units, for 18 days. Only one of 5 groups of 10 animals showed any significant increase in survival time and in none of 18 mice was any protection demonstrable by the corneal method. Further tests were carried out *in vivo*/*in vitro* by the Brownlee method. Guinea-pigs were given a large dose and when signs of serious distress were apparent, or after 2 hours, blood was taken from the heart and part was assayed for nisin, the remainder being tested against *Myco. tuberculosis* by serial dilution. The supernatant liquors from preparations of lungs, spleen and liver homogenised with 0·02N hydrochloric acid were also assayed. In these tests the heart blood suppressed the growth of *Myco. tuberculosis* in only one instance; the blood contained 500 units/ml. and this was sufficiently toxic to kill the animal. The tissue extracts contained only 50 to 70 units/ml. The authors conclude that the activity of nisin is reduced by serum so that *in vitro* results are not repeated *in vivo*. The best nisin-producing organism so far obtained produces only about one-thirtieth of the quantity of antibiotic produced by organisms yielding penicillin and streptomycin. As the cost is appreciably higher, nisin is unlikely to find a place in therapeutics.

H. T. B.

Pheniodol; Elimination in Normal Subjects. H. O. Bang and J. Georg. (*Acta Pharmacol. Toxicol.*, 1951, **7**, 321.) Experiments on three healthy persons showed that pheniodol given orally (3 g.) is very readily absorbed from the intestine and then mainly excreted in the urine. The major part is excreted

in a few days but the excretion continues for several days. In this it differs from iodophthalein, which is excreted mainly in the fæces. The reason for this difference is not clear, though it may be that attachment to the plasma protein has some bearing on the problem, iodophthalein being completely bound to the proteins, whereas in these experiments about 14 per cent. of pheniodol was found ultrafiltrable. After intravenous injection of pheniodol (1 mg./kg. of body weight was given to 7 healthy persons) a plasma concentration of about 2 mg./100 ml. was obtained, which decreased to about half this value in 4 to 6 hours. Measurable amounts of pheniodol were present for 48 to 96 hours after injection. Quantitative balance tests were made in 2 healthy persons given 3 g. pheniodol orally and in 1 given 500 mg. intravenously. After oral administration 64 and 72 per cent. were recovered, after intravenous injection 80 per cent. S. L. W.

Phenylboric Acid, Toxicity of. F. Caujolle, C. Franck, P. Gayrel and G. Roux. (*Thèrapie*, 1951, **6**, 366.) Phenylboric acid may be prepared by the condensation of butyl borate with phenyl magnesium bromide, hydrolysis with dilute acid and purification to remove products of side reactions (for example, diphenyl). The LD50 for mice was found to be 560 mg./kg. and for guinea pigs, 284 mg./kg., both by intraperitoneal injection. For dogs, the toxicity by slow intravenous injection depends upon the speed with which the injection is given. The lethal dose administered during 1 hour was 450 mg./kg. Phenylboric acid has previously been shown to augment the action of hypnotics such as barbiturates and thiobarbiturates. It appears that its toxicity is small enough to permit its pharmacological use. G. B.

Prantal, A New Parasympathetic Blocking Agent, Pharmacology of. S. Margolin, M. Doyle, J. Giblin, A. Makovsky, M. T. Spoerlein, I. Stephens, H. Berchtold, G. Belloff, and R. Tislow. (*Proc. Soc. exp. Biol., N.Y.*, 1951, **78**, 576.) Prantal is the methyl sulphate of *N*:*N*-dimethyl-4-piperidylidene-1:1-diphenylmethane, one of a new series of quaternary compounds having autonomic ganglion blocking properties and therefore of possible interest in the management of peptic ulcer. Prantal appears to act primarily upon that portion of the parasympathetic nervous system which is associated with gastric secretion and motility. In doses eliciting this selective action it produces no mydriasis in animals and rarely produces mydriasis or xerostomia in man, even in doses inhibiting gastric motility for several hours. The intravenous sympathetic ganglion blocking dose is 50 to 100 times that required for parasympathetic ganglion blocking. After oral administration to dogs it delays the gastric emptying time more effectively and for a longer period than methantheline bromide; it also reduces the volume and titratable total acid of the gastric secretion. In rabbits, the minimum mydriatic concentration on topical application to the eye is 2 per cent. whereas 0·1 per cent. of methantheline bromide is mydriatic. Intravenously, doses of up to 8 mg./kg. of body weight produce no mydriasis in rabbits whereas methantheline bromide is mydriatic in doses of 1 mg./kg. of body weight. H. T. B.

Streptomycin, *p*-Aminosalicylic acid and Thiacetazone in Genito-Urinary Tuberculosis. J. Cosbie Ross, J. G. Gow and C. A. St. Hill. (*Lancet*, 1951, **260**, 1033.) The effects of streptomycin alone, streptomycin and *p*-aminosalicylic acid, and streptomycin, *p*-aminosalicylic acid and thiacetazone on tuberculosis of the genito-urinary tract were investigated. Genito-urinary tuberculosis was divided into 5 types, according to the Medical Research

Council classification, and the criteria for diagnosis and control of disease (as opposed to cure) were carefully laid down. Since streptomycin resistance develops rapidly in an acid medium, efforts were made to keep the urine alkaline with potassium citrate, although this proved difficult. Streptomycin alone in this series was given in a total dosage of 90 g. as 0·5 g. twice daily for 90 consecutive days. Results were disappointing as were those when streptomycin, in the same dosage, and *p*-aminosalicylic acid, 15 g. daily, were given. There was a slight improvement when streptomycin and *p*-aminosalicylic acid were given alternately for 6 months, each being given for a month alone, streptomycin 0·5 g. twice daily, and *p*-aminosalicylic acid 15 g. daily. 6 patients with the most severe type of genito-urinary tuberculosis were treated with streptomycin, *p*-aminosalicylic acid and thiacetazone combined. Streptomycin and *p*-aminosalicylic acid were given alternately as before and thiacetazone 50 mg. daily initially, gradually increasing to 200 mg. daily, the whole course lasting 6 months. Results with this regime showed an encouraging improvement and the authors intend to use it for all future cases. 5 g. of potassium iodide was added to the alkaline mixture given with the streptomycin, following reports of its value in increasing the effectiveness of streptomycin against the tubercle bacillus in laboratory animals and in pulmonary lesions. The three drugs mentioned should be used as an adjunct, not a substitute, for surgery. Every case should have sanatorium treatment, and surgery should be performed under streptomycin cover. Tabulated results are given of the various regimes employed.

G. R. B.

Streptomycin in Ophthalmology. A. Sorsby, J. Ungar and N. L. Bailey. (*Brit. med. J.*, 1952, **1**, 119.) The clinical results obtained with streptomycin in 53 cases of ocular infection seen during the past 3 years are recorded. In 6 cases of acute conjunctivitis due to penicillin-resistant organisms, mainly *Proteus vulgaris*, local applications including drops, 0·5 g./ml. used half-hourly, ointment, 0·1 g./g., and subconjunctival injection, 0·5 g. in 10 ml. with 0·3 ml. adrenaline solution, rapidly effected a cure. Several cases of infected corneal ulcer were successfully treated with daily subconjunctival injections of 0·5 g. of streptomycin in a solution containing atropine sulphate 1·6 mg., cocaine hydrochloride 8 mg., water to 0·6 ml., 0·3 ml. of adrenaline solution being added immediately before the injection was given. One case each of tuberculous conjunctivitis and of dacryocystitis due to *Pr. vulgaris*, and 3 of tuberculous keratitis were cured by systemic treatment with streptomycin. Among the conditions believed but not proved to be of tubercular origin, Eales's disease, iridocyclitis and scleromalacia perforans were not significantly affected by systemic streptomycin. In phlyctenular ophthalmia, systemic streptomycin cut short severe attacks and appeared to reduce the frequency and the severity of relapses. Experimental evidence from the use of subconjunctival injections in the treatment of *Pseudomonas pyocyanea* infection of the eye in rabbits showed that the intraocular streptomycin levels are higher and are maintained for a longer period if the injection contains adrenaline. H. T. B.

Terramycin in Treatment of Gonorrhœa. R. R. Willcox. (*Brit. med. J.*, 1951, **2**, 527.) Only 2 relapses were observed in 19 cases given 2 oral doses, each of 1 g., of terramycin spaced 6 hours apart. Single doses of 1 to 2 g. of terramycin orally were unsuccessful however in 3 out of 6 cases. In this small series terramycin, in double doses, was shown to be not quite as effective as penicillin at its best, though more prolonged schedules remain to be tried. While it may not perhaps replace penicillin in the treatment of gonorrhœa,

it is likely to have a considerable application for those who dislike, or are unable to obtain, injections, for cases resistant to penicillin, and as an "emergency kit" for both treatment and prophylaxis of travellers and soldiers. Like penicillin, however, it may mask undeclared syphilis. S. L. W.

Triethylene Melamine in the Treatment of Neoplastic Disease. D. A. Karnofsky, J. H. Burchenal, G. C. Armistead, Jr., C. M. Southam, J. L. Bernstein, L. F. Craver and C. P. Rhoads. (*Arch. intern. Med.*, 1951, **87**, 477.) Triethylene melamine (2:4:6-triethylenimino-*s*-triazine) is a new compound which closely resembles the nitrogen mustards both in its effects on normal and neoplastic tissues and in the essential chemical grouping necessary for its specific biological activity. It is a white, crystalline powder, readily soluble in water. Solutions should be prepared in water or normal saline solution, since triethylene melamine reacts with many substances to lose its pharmacological activity. In contrast to methyl-bis-(2-chlorethyl) amine, the nitrogen mustard in general use, it is relatively stable in an alkaline medium, but it will react rapidly at an acid *p*H. Intravenous injection of triethylene melamine produced evidence of transient improvements similar to those obtained with nitrogen mustard in Hodgkin's disease, lymphosarcoma and chronic lymphatic and myelogenous leukæmia. The daily intravenous dose was about 2 to 3 mg., diluted with normal saline to a concentration of 0·5 mg./ml., immediately before use, and a total course of treatment for an adult was 5 to 20 mg. In this dosage it rarely caused nausea or vomiting, or venous thrombosis. Careful control of treatment is necessary to prevent depression of hæmopoietic function. Oral administration produced temporary clinical improvement in Hodgkin's disease, lymphosarcoma, chronic lymphatic and myelogenous leukæmia and mycosis fungoides. It produced slight nausea with infrequent vomiting or no gastro-intestinal symptoms. Dosage varied widely but a course of triethylene melamine usually consisted of 20 to 40 mg. given in a 3 to 5 week period. If properly used, triethylene melamine orally appears to be a valuable addition to the chemical palliatives now being used for the treatment of certain types of neoplastic disease. G. R. B.

Tromexan, Clinical Experience with. M. R. Bronstein and E. Witkind. (*Amer. J. med. Sci.*, 1951, **222**, 677.) Tromexan was used in 50 cases of hæmorrhagic disease. Doses 6 times as high as for dicoumarol were required to reach therapeutic levels in 24 hours. Wide fluctuations in prothrombin time occurred especially in the first 7 days, and for this reason daily determination of the prothrombin time was essential. It is recommended that a reliable thromboplastic substance such as thromboplastin A be used and that results be expressed as prothrombin times in seconds. A single daily dose is generally satisfactory, but no correlation could be observed between dose and body weight. Cumulative phenomena were observed but were more rapidly dissipated than for dicoumarol, either by withdrawing the drug or by administering a water-soluble derivative of vitamin K. Tromexan should not be given when there is renal insufficiency, and resistance to the drug occurs occasionally. G. B.

Tromexan, Toxicology and Anticoagulant Action of. C. M. Gruber, Jr., K. S. Lee, Z. T. Lasziczenko and C. M. Gruber. (*Arch. int. Pharmacodyn.*, 1951, **87**, 402.) Oral and intraperitoneal administration of lethal doses of the drug produced death in mice, rats and some rabbits within 12 hours (immediate death). In other rabbits death was delayed, taking between 12 and 72 hours.

Immediate deaths were not characterised by hæmorrhagic complications in the three species, but by primary cardiac arrest. Delayed death in rabbits was due apparently to hæmorrhage into the cæcum. The dose and route of administration appear to influence the type of death in rabbits. Orally the drug produced immediate and delayed deaths. Intraperitoneally, with one exception, death was immediate. No sign of chronic toxicity developed in rats or dogs when the drug was given daily by the oral route over 3 months. In dogs, production of hypoprothrombinæmia and return to normal prothrombin levels was more rapid with tromexan than with bishydroxycoumarin. No absolute evidence that vitamin K_1 and menaphthone sodium bisulphite antagonise the hypoprothrombinæmia produced by tromexan was obtained. J. R. F.

Unsaturated Carbinols, a New Class of Hypnotics. S. Margolin, P. Perlman, F. Villani and T. H. McGavack. (*Science*, 1951, **114**, 384.) The simple unsaturated aliphatic alcohols were found to possess high hypnotic activity, desirable duration of action, and low toxicity, and 3-methyl-pentyne-ol-3 was considered suitable for extensive pharmacodynamic, biochemical, and clinical study. The hypnotic effect was characterised by the reaction pattern—sedation, loss of righting reflex, and sleep. Its hypnotic activity was compared with that of amylene hydrate, paraldehyde, phenobarbitone, phenobarbitone sodium, and presidon when oral doses were given to mice, dogs and man. A high selectivity of hypnotic action was shown by 3-methyl-pentyne-ol-3, because neither analgesic, anæsthetic nor antispasmodic activity could be demonstrated. It did not depress respiration, and caffeine given parenterally caused rapid recovery from the deep hypnotic state induced by overdoses. No undesirable after effects were observed on animals following overdoses, and the drug was also shown to possess low toxicity. The results of metabolic studies are recorded. In a clinical study of 134 subjects it was found to be highly active, without toxic effect, and free from undesirable side effects. A number of patients were given daily doses of the compound for more than 6 months without any untoward effects. Clinical laboratory tests indicated the absence of any pathological changes attributable to the drug. A. H. B.

Veratrine, Veratridine and Cevadine, Cardiac Stimulation by. M. de V. Cotten and R. P. Walton. (*Arch. int. Pharmacodyn.*, 1951, **87**, 473.) Injection of the alkaloids into open-chest vagotomised dogs produced cardiovascular effects which resembled those due to adrenaline discharged from the adrenals. Large doses of dibenamine hydrochloride blocked, and adrenalectomy reduced, these effects. Several successive doses of the alkaloids caused the death of some animals by ventricular fibrillation. Veratrine showed the greatest activity in this respect. A dose of 0·35 mg./kg. of veratrine, 0·07 mg./kg. of veratridine and 0·5 mg./kg. of cevadine produced similar effects to a dose of 3 μg./kg. of adrenaline and was called the "heart stimulant dose." With single "heart stimulant doses" each alkaloid produced strong skeletal muscle spasms despite the condition of deep barbiturate anæsthesia. Hypotensive effects may be produced with initial injections, but do not usually occur with repeated dosage. Single "heart stimulant doses" of veratrine and cevadine in intact dogs produce convulsive effects, parasympathetic manifestations and depression of external respiratory movement. Adrenaline-like effects without cardioacceleration were produced on isolated rabbit heart indicating a direct action by the drugs. The heart stimulant effects, however, are only obtained by doses which produce marked side effects and prospective clinical application seems remote. J. R. F.

LETTER TO THE EDITOR

The Determination of Santonin in Artemisia—Solubility Correction

SIR,—With reference to the letter of Mr. J. Isaacs published in your June number, I have to express regret for the mistake in the solubility correction to be added in the assay of santonica as described in my paper.[1] The figure should have been 0·046 g., and not 0·0064 g. as recorded. It was a clerical mistake, which unfortunately escaped my notice. In my earlier publication[2] the solubility correction was rightly recorded as 0·046 g., and this figure was used in later papers.[3,4] Minute traces of santonin are absorbed by the mixture of animal charcoal and kieselguhr used for removing the resinous colloidal impurities in the final purification of the santonin. Taking into consideration the solubility at 15° to 17° C. and the adsorption factor, I suggest 0·046 g. as the correction factor to be added to the final weight of refined crystals of santonin. I am most grateful to Mr. Isaacs for pointing out the error.

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ABSTRACTS (*Continued from page* 510)

Vitamin B_{12} from Fish, Hæmopoietic Effect of. K. Hausmann and K. Mulli. (*Lancet*, 1952, **262**, 185.) Concentrates of high microbiological vitamin B_{12} activity were prepared from fish solubles and parenterally administered to 4 patients with pernicious anæmia in relapse. The doses were equivalent to 100 and 120 μg. of vitamin B_{12} as microbiologically determined. There was no improvement in the clinical condition of any of the patients and no increase in the numbers of reticulocytes and red cells; the megaloblastic state of the bone marrow remained unchanged. After being treated with potassium cyanide for 8 days the concentrates became completely soluble in butanol and yielded the absorption spectra of vitamin B_{12}. Administration to 3 of the patients of doses equivalent to 50 and 60 μg. of vitamin B_{12} from this preparation resulted in rapid clinical improvement in the clinical condition, high reticulocytosis and increase in the number of red cells to normal levels within 3 weeks; the megaloblasts and giant myelocytes of the bone marrow disappeared. It is concluded that the hæmopoietically inactive red pigments are peptide conjugates of vitamin B_{12} which can be utilised for the growth of lactic acid bacteria but not in the intermediate metabolism of patients with pernicious anæmia, and that treatment with potassium cyanide releases vitamin B_{12} from peptide linkage. S. L. W.