ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

***Pausinystalia Mayumbensis*, New Alkaloid from.** R. Hamet. (*C.R.Acad. sci. Paris*, 1951, **232**, 2354.) An alkaloid was extracted from the bark of *Pausinystalia* (Pseudocinchona) *mayumbensis* (Rubiacae). It contained 1 methoxy group. Several of the characters and colour reactions resembled those of yohimbine isomers, but the absorption spectrum indicated the presence of a different chromogenic complex. The new alkaloid has been named mayumbine. Its characters suggest that it is a representative of a new type of alkaloids of the yohimbine group. G. M.

***Strychnos Toxifera*, Rob Schomb, Some Alkaloids of.** H. King. (*J. chem. Soc.*, 1949, 3263.) Chromatography of the alkaloidal reineckates from *Strychnos toxifera* bark on three successive columns of alumina followed by various crystallisation processes effected a separation into 12 crystalline quaternary alkaloids, the toxiferines I-XII. Their properties and characteristic colour reactions are recorded; the latter suggested that the alkaloids may be indole derivatives. Of the 12 alkaloids, only 2, toxiferine-I chloride and toxiferine-II picrate, appear to have been isolated previously. The absorption spectra of toxiferine-I chloride and of toxiferine-III chloride have been determined in water. The results of a preliminary determination of the paralysing activities of 8 of the alkaloids are given. J. B. S.

ANALYTICAL

Thiouracil Derivatives, Detection of. K. Bucher. (*Pharm. Acta Helvet.* 1951, **26**, 145.) Of the thiouracil derivatives, *n*-propylthiouracil is the only one which has a satisfactory m.pt. suitable for identification. Suitable derivatives are the benzylthio-ethers, prepared by the following method: 0·1 g. of substance is dissolved on the water-bath in 0·15 ml. of a mixture of equal volumes of concentrated sodium hydroxide and water: if necessary, slightly more alkali is added to produce a clear solution. To the hot solution 4 drops of benzyl chloride are added, the mixture is emulsified by shaking, and heated for a further 1 minute, with continual shaking. After the addition of 2·5 ml. of alcohol, the mixture is heated until it begins to boil, and cooled in ice. 2 ml. of water is added and, after re-cooling, the mixture is filtered. The crystals are dissolved in 2·5 ml. of alcohol, the solution is filtered and concentrated to half bulk, and cooled in ice. The crystals obtained are dried at 103° to 105°C. Corrected m.pts. for benzylthio-ethers of thiouracil derivatives are as follows: thiouracil 192° to 192·5°C.; methylthiouracil 183·5° to 184°C.; *n*-propylthiouracil 131° to 132·0°C. Derivatives obtained by coupling of thiouracil derivatives with diazotised aniline have also been described in the literature. This reaction is however troublesome and less convenient for the present purpose. G. M.

FIXED OILS, FATS AND WAXES

***Oenothera Biennis* L., Seed Fat of.** J. P. Riley. (*J. chem. Soc.*, 1949, 2728.) The mixed acids from the seed oil of *Oenothera biennis* L. have been examined by low temperature crystallisation from solvents together with

a determination of the component acids by alkali isomerisation. The most soluble fraction containing the trienoic acid has been ozonised to products which include adipic acid, thus confirming the deductions of Eibner, Widenmeyer and Schild that the acid is octadeca-6:9:12-trienoic acid. A pure specimen of the acid was obtained by bromination to the hexabromide followed by debromination of the pure hexabromide with zinc and pyridine. Alkali isomerisation and spectographic examination of the pure acid gave results in good qualitative agreement with those for linolenic acids (octadeca-6:9:15-trienoic acid). The oleic and linoleic acids present in the oil are those normally occurring in vegetable fats. The composition of the oil is shown to be: palmitic acid 8·8, stearic acid 1·3, higher saturated acids 1·0, oleic acid 7·0, linoleic acid 71·7 and octadeca-6:9:12-trienoic acid 10·2 per cent. J. B. S.

Unsaponifiable Matter in Indian Edible Oils. K. Ramamurti and B. N. Banerjee. (*Indian J. med. Res.*, 1950, **38**, 377.) The effects of rancidity on the unsaponifiable fractions of ground-nut, sesame and coconut oils were investigated. With increasing rancidity the content of alcohol-soluble matter was decreased and the alcohol-insoluble matter increased. The iodine values of both fractions were diminished by rancidity and the hydrolysis of fresh cow ghee was inhibited by it. The protective action of the three oils against the oxidation of cow ghee was reduced. Rancidity reduced the content of sterols and tocopherols in the oils but the degradation products could not be identified. A. D. O.

GLYCOSIDES, FERMENTS AND CARBOHYDRATES

Digitalis Glycosides, New Colour Reaction for. M. Frerejacque. (*C.R.Acad. sci. Paris*, 1951, **232**, 2369.) A number of nitro derivatives give colours with the heterosides of digitalis: a new reaction with 1:3-dinitronaphthalene is superior to those previously described as it is very sensitive and the colour is stable. A drop of the solution to be examined is dried on paper which has previously been soaked in dinitronaphthalene and dried, and is then sprayed with N alcoholic potash. In presence of more than 1 to 2 μg. of digitalis heterosides, a stable red stain appears. Unlike the reaction with *m*-dinitrobenzene, a positive reaction is given by all the heterosides, and also by a number of ketosteroids (œstrone, testosterone, pregnelonone, progesterone and cortisone). G. M.

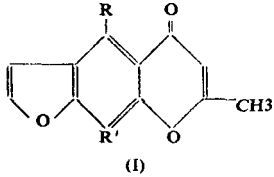
ORGANIC CHEMISTRY

Phenobarbitone, Solubility of, in Ethanol-Water-Glycerin Systems. G. M. Krause and J. M. Cross. (*J. Amer. pharm. Ass., Sci. Ed.*, 1951, **40**, 137.) The solubility of phenobarbitone in mixtures of ethanol and water, glycerin and water, and ethanol, glycerin and water, was determined by adding a slight excess of phenobarbitone to the solvent, immersing the container in a constant temperature bath at 25°C. and rotating for 48 hours. At the end of this time, two 15-ml. portions of the clear supernatant liquid were withdrawn and titrated potentiometrically with 0·1N sodium hydroxide. The solubility in water was found to be 0·12 per cent., in absolute ethanol 12·30 per cent., and in glycerin 1·16 per cent. Glycerin and glycerin-water solutions were poor solvents, but glycerin enhanced the solubility in ethanol. In the absence of glycerin, phenobarbitone was most soluble in ethanol (90 per cent.), to the extent of 13·38

per cent.; if the water were replaced by glycerin the solubility increased to 15·30 per cent. The greatest solubility, 16·27 per cent., occurred with a mixture of 4 parts of absolute ethanol, and 1 part of glycerin. G. R. K.

Quassin and Neoquassin. E. London, Alexander Robertson, and (in part) H. Worthington. (*J. chem. Soc.*, 1950, 3431.) Quassin $C_{20}H_{22}O_4(OMe)_2$, m.pt. 22°C., and neoquassin $C_{20}H_{24}O_4(OMe)_2$, m.pt. 228°C. were isolated and separated from crude extracts of *Quassia amara* Linn. by two procedures: (a) chromatography on alumina from chloroform solution, (b) solution in 5 per cent. methanolic potassium hydroxide and then dilution with water to precipitate neoquassin only. This latter method also led to the isolation of a small amount of a new alkali-soluble compound, m.pt. 246° to 248°C.(d), with apparent empirical formula $C_{19}H_{20}O_4(OMe)_2$. Quassin is a (+) unsaturated lactone containing two (and possibly three) C-methyl groups, a tertiary hydroxyl, and a ketonic group. Upon hydrogenation with a palladium-charcoal catalyst in alkaline solution it yields dehydroquassin, a neutral saturated compound. Some neoquassin was obtained by reduction with a highly active Raney nickel catalyst and hydrogen at atmospheric pressure. With hot mineral acid quassin is demethylated giving, under mild conditions, norquassin $C_{20}H_{23}O_5$ (OMe) behaving like a monohydric phenol, and under more vigorous conditions, bisnorquassin. With aqueous-ethanolic sodium or postassium hydroxide, solutions of the corresponding salts of quassinic acid are produced, which, upon acidification, regenerate quassin. Upon boiling with 5 per cent. ethanolic potassium hydroxide, however, quassin yields a stable unsaturated monobasic acid, isoquassinic acid, $C_{20}H_{24}O_5(OMe)_2$, together with a small amount of a second monobasic acidic product. Neoquassin is an unsaturated neutral compound containing one double bond, two, and possibly three, C-methyl groups, a ketonic group and two hydroxyl groups of which one reacts to form a monomethyl and a monoethyl ether. It may be distinguished from quassin by giving a positive Tollens and a negative Legal reaction in pyridine, giving a magenta colour in the Libermann-Burchardt test, and not being affected by boiling 5 per cent. ethanolic potassium hydroxide. It is partly demethylated by hot mineral acid to give alkali-soluble norneoquassin, $C_{20}H_{25}O_5(OMe)$. Upon oxidation with chromic acid neoquassin is converted to quassin, identical with the natural product. Dehydrogenation yields a mixture from which the monoethyl ether of an alkyl-dihydroxybenzene was isolated. A. H. B

Visnagin as Source of Khellin. A. Schönberg and N. Badran. (*J. Amer. chem. Soc.*, 1951, **73**, 2960.) A method for the conversion of visnagin (I; R = OCH_3 R′= H) to khellin (I; R = OCH_3; R′= OCH_3) is reported. The methoxy group in visnagin was converted to an −OH group with dilute hydrochloric acid, and the resulting compound nitrated to produce (I; R= -OH; R′ = $-NO_2$). Reduction with tin and hydrochloric acid converted the $-NO_2$ group to the $-NH_2$, and subsequent oxidation with chromic acid gave a quinone which was reduced to the dihydric compound (I; R = OH; R′ =OH) with sulphur dioxide. Methylation of this compound in acetone solution with methyl iodide in presence of potassium carbonate produced khellin (I; R = $-OCH_3$; R′ = OCH_3). The above conversion is important because visnagin is a by-product in the manufacture of khellin. A. H. B.

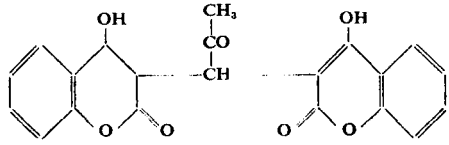


(I)

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Blood Anticoagulant, A New. K. Fučik, Ž. Procházka, L. Lábler and J. Štrof. (*Nature*, 1950, **166**, 830.) Di(4-hydroxycoumarinyl-3)



propanone was prepared by the condensation of two molecules of 4-hydroxycoumarin with one molecule of *iso*nitrosoacetone in aqueous solution. It has a powerful anticoagulant activity in rabbits and a low toxicity. Using oral administration, it produced hypoprothrombinæmia of earlier onset and shorter duration than dicoumarol. A. H. B.

Vitamin B_{12} Group of Factors. E. Lester Smith. (*Brit. med. J.*, 1951, **1**, 151.) It has now been found possible to obtain in crystalline form two further members of the vitamin B_{12} group of factors, namely vitamins B_{12c} and B_{12d}. These new factors were isolated from *Streptomyces griseus* fermentation liquors and were separated by partition chromatography. Vitamin B_{12c} can be distinguished from the other factors by its characteristic absorption spectrum and partition behaviour. The absorption spectrum of vitamin B_{12d} is identical with that of vitamin B_{12b}, but they can be separated chromatographically. In addition, vitamins B_{12c} and B_{12d} behave differently from the other factors in the microbiological plate assay technique, since they tend to give fuzzy rings of bacterial growth, whereas vitamins B_{12} and B_{12b} give sharp clear-cut rings. Vitamin B_{12b} is probably identical with B_{12a} the reduction product of vitamin B_{12}. It would thus appear that the new factors are not conjugates of vitamin B_{12} with peptides but represent slight chemical modifications of the vitamin B_{12} molecule. It is now known that the vitamin B_{12} molecule contains a cyanide group co-ordinated with the cobalt atom. Vitamin B_{12b} differs only in the absence of this cyanide group and is readily converted into vitamin B_{12} by treatment with potassium cyanide. There is now little doubt that Castle's extrinsic factor is simply vitamin B_{12}. When administered orally to cases of pernicious anæmia the pure vitamin is ineffective, except in enormous doses, but it is strongly potentiated by normal gastric juices. There are indications that vitamin B_{12} has a number of functions in living organisms. A growth-promoting action has been clearly demonstrated in pigs, chicks and turkeys. It has been shown that it is concerned in transmethylation reactions; thus, chicks on a deficient diet can utilise homocystine as an alternative to methionine only when vitamin B_{12} is given. It has also been suggested that it has an antihistamine and anti-anaphylactic effect. S. L. W.

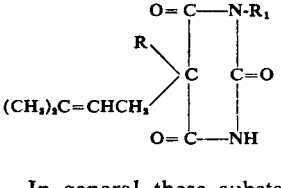
BIOCHEMICAL ANALYSIS

Ethanol and Ether in Biological Products and Air, Simultaneous Determination of. R. Fabre, R. Thuhaut and P. Chéramy. (*C.R.Acad. sci. Paris*, 1951, **232**, 2266.) By using two successive absorption tubes, containing suitable chromic acid solutions, it is possible to determine both ethanol and ether in the same sample. The reagents are: for ethanol, 4·90 g. of potassium dichromate dissolved in nitric acid (d = 1·33) to 1 l. and

diluted with water to 2 l.; for ether, equal volumes of this nitro-chromic acid solution (not diluted) and sulphuric acid (d=1·84). The vapours are aspirated through these solutions in succession, the quantity of reagent being determined by a preliminary trial. After the absorption, the solutions are allowed to stand for 30 minutes, diluted with water, treated with potassium iodide, and titrated with 0·1 N sodium thiosulphate. One ml. of 0·1 N. sodium thiosulphate corresponds to 1·15 mg. of ethanol, or 0·9256 mg. of ether. This method may be applied directly to the determination of ethanol and ether in air. Biological products are minced in a saturated solution of picric acid at 0°C. G. M.

CHEMOTHERAPY

Barbiturates Containing the 3-Methyl-2-Butenyl Group. H. Walton, J. Doczi and J. A. King. (*J. Amer. chem. Soc.*, 1950, **72**, 4319.) Because it had been previously reported that the replacement of an alkyl group on 5:5-dialkylbarbituric acids by an alkyl group frequently led to an increase in effectiveness, together with a lower degree of increase in toxicity, the effect of the replacement of an alkyl group by a γ, γ-dimethylallyl group was investigated. Compounds of the type shown were prepared where R=$(CH_3)_2CH$-, CH_2=CH CH_2-, C_2H_5- or H, and R_1=H, CH_2=CH CH_2-, or CH_3-.



In general these substances, with the exception of R = $(CH_3)_2CH$- and R_1 = CH_2 =CH CH_2-, have a rather excitory effect on experimental animals. A. H. B.

***N*-(3-Phenylpropyl)-amines and 3-Amino-1-phenyl-1-propanols as Antispasmodics.** A. W. Ruddy and J. S. Buckley. (*J. Amer. chem. Soc.*, 1950, **72**, 718.) *N*-(3-Phenylpropyl)-amines and 3-amino-1-phenyl-1-propanols have been prepared in order to determine the effect on spasmolytic activity of altering the structure of *N*-(3:3-diphenylpropyl)-piperidine (I). The following general structural modifications are described. (a) replacement of one phenyl group by hydrogen, *iso*-propyl, *iso*-butyl, *n*-hexyl, *cyclo*-hexyl or thienyl radicals, (b) substitution of the hydrogen of the propyl chain by methyl, ethyl and hydroxyl groups, and (c) replacement of piperidine by dimethylamine, diethylamine and morpholine. A new route to *N*-(3-phenylpropyl)-piperidine is described in which 1-phenyl-3-(1-piperidyl)-1-propanol is converted to *N*-(3-chloro-3-phenylpropyl)-piperidine with thionyl chloride and then hydrogenated to remove the halogen. *N*-(2-methyl-3-phenylpropyl)-piperidine was prepared similarly. 3-Amino-1-phenyl-1-propanols were conveniently obtained *via* the Mannich reaction with alkyl aryl ketones and various tertiary bases. The resulting diethylaminoalkyl aryl ketone on reaction with various Grignard reagents gave the required 3-amino-1-phenyl-1-propanols. The latter were converted in good yield to the corresponding *N*-(3-phenylpropyl)-amines by reduction with red phosphorus and hydriodic acid. Spasmolytic activity of compounds of type I is decreased by branching of the propyl chain; substitution of *cyclo*hexyl for one phenyl group increases both musculotropic and neurotropic activity and introduction of a hydroxyl group increases the neurotropic activity. J. B. S.

2-Phenyl-4-thiazolidone Derivatives as Local Anæsthetics. F. P. Luduena and J. O. Hoppe. (*J. Amer. pharm. Ass., Sci. Ed.*, 1951, **40**,

132.) 36 members of a series of 3-(alkyl, dialkyl or *cyclo*alkylaminoalkyl)-2-phenyl-4-thiaolidone derivatives possessed local anæsthetic activity when tested by the external canthus and sciatic nerve block methods in rabbits and guinea-pigs. 2 compounds, 3:4-methylenedioxy-2-phenyl-3-*iso*butylaminopropyl-4-thiazolidone (WIN 2661) and 3:4-methylenedioxy-2-phenyl-3-(2-*cyclo*hexylaminoethyl)-4-thiazolidone (WIN 2663) were 2 to 4 times as active as procaine in producing sciatic nerve block in guinea-pigs. When injected intraspinally in rabbits they were twice as active as procaine and were also more active in man when injected intradermally. By the trypan blue test, WIN 2663 was the most irritating and procaine the least. Toxicity tests showed that WIN 2661 was twice and WIN 2663 about 3·5 times as toxic as procaine when given subcutaneously in mice; by intravenous injection in guinea-pigs both compounds were about three times as toxic as procaine.

G. R. K.

2-Substituted-1 : 3-propanediols, Anticonvulsant Action of. F. M. Berger. (*Proc. Soc. exp. Biol, N.Y.*, 1949, **71**, 270.) A series of 2-substituted-1:3-propanediols of the type $CH_2OH{\cdot}CR_1\ R_2{\cdot}CH_2OH$ has been examined for anticonvulsant activity in mice. Intraperitoneal injections of metrazol, which causes convulsions and death, were made into groups of mice together with graded doses of the substances under test. The degree of protection assessed in terms of that dose which prevented a reaction in 50 per cent. of the animals, was compared with that of 3-*o*-tolyl-1:2-propanediol (myanesin). Substances in which at least one of the groups R_1 and R_2 are either ethyl, *n*-propyl or *iso*-propyl are of equivalent or greater activity than myanesin. When both R_1 and R_2 are methyl or *n*-butyl the substance is inactive; phenyl and phenoxy groups considerably decrease activity. 2:2-Diethyl-1:3-propanediol was by far the most outstanding anticonvulsant of the substances examined, being about twice as effective as myanesin. It resembles the latter in causing transient paralysis of the skeletal muscles, though this latter effect was of a much lower order. Its acute toxicity is low and it has no effect on the blood pressure and respiration when administered intravenously to cats. J. B. S.

Thiophene Nucleus, Antihistaminic Agents Containing. L. P. Kyrides, F. C. Meyer, F. B. Zienty, J. Harvey and L. W. Bannister. (*J. Amer. chem. Soc.*, 1950, **72**, 745.) A number of compounds of general formula $RR'N{\cdot}CH_2.CH_2.N(CH_3)_2$ (I) containing thenyl and substituted thenyl radicals have been prepared for testing as potential antihistaminics. The most potent of these substances was *N N*-dimethyl-*N'*-(5-chloro-2-thenyl)-*N'*-phenylethylene diamine, which was approximately 125 per cent. as active as antergan in animal tests. Such chloro substituted phenyl compounds, like their corresponding pyridine analogues, show enhanced activity over those substances in which the heterocyclic ring is unsubstituted. Chlorine substituents in the phenyl group on the other hand cause a reduction of activity. Replacement of the thenyl group by methyl or methoxybenzyl groups reduces the activity to negligible values. 2-(*N*-benzylanilinomethyl)-1, 4, 5, 6-tetrahydro-pyrimidine and 2-(*N*-benzylanilinomethyl)-2-thiophene, analogues of antistin, were without significant activity. J. B. S.

Thiosemicarbazones, Tuberculostatic Action of. M. Welsch, N. P. Buu-Hoï, G. Dechamps, N. Hoań, H. LeBihan and F. Binon (*C.R.Acad. Sci. Paris*, 1951, **232**, 1608.) The tuberculostatic activity of over

300 new thiosemicarbazone derivatives was determined, *in vitro*. A small proportion of these show a very high activity, greater than that of streptomycin. Products showing an activity 100 times that of the thiosemicarbazone of 4-acetaminobenzaldehyde (Conteben, thiacetozone) are listed. They have in general heavier molecules than those previously described. There is no relation between the activity and toxicity; thus the thiosemicarbazone of the cinnamyl ether of *p*-hydroxybenzaldehyde is 100 times as active as thiacetozone, while the toxicity to mice is only four-tenths. G. M.

PHARMACY

DISPENSING

Bacteriostatic Effects of Chemicals. J. D. Kohli, I. C. Chopra and K. Chandar. (*Indian J. med. Res.*, 1950, **38**, 413.) The bacteriostatic effects of various chemicals under the conditions of the B.P. tests for sterility for injections were investigated. The tests were carried out in meat-infusion broth containing 1 per cent. of peptone and 0·5 per cent. of sodium chloride adjusted to *p*H 7·2 to 7·8. A 24-hour culture of *Staphylococcus aureus* was used for the inocula and the cultures were incubated for 48 hours at 38°C. The following substances were not bacteriostatic at the percentage concentrations stated: strychnine sulphate 0·002, yohimbine 0·008, iron cacodylate 0·13, ephedrine hydrochloride and hyoscine hydrobromide 0·66, congo red 1·0, iodine solution 1·25, calcium chloride 5, caffeine sodium benzoate, calcium gluconate and sodium iodide 10, glucose 25. The two calcium salts at these concentrations give turbid solutions which may interfere with the reading of the end points. Other preparations were tested as follows (the figures in parentheses indicate the recommended volume of medium for diluting-out the substance): emetine hydrochloride, bacteriostatic range 1 in 750 to 1,000 (40 ml.), emetine gr. ½ with strychnine gr. 1/60 in 1 ml., 1 in 250 to 260 (150 ml.), sodium salicylate, 1 in 250 to 360 (75 ml.), hexamine, 1 in 300 to 400 (200 ml.) sodium salicylate gr. 7½ with sodium iodide gr. 10, 1 in 120 to 180 (200 ml.) sodium antimonyl tartrate, 1 in 17,500 to 20,000 (400 ml.) quinine bihydrochloride, 1 in 980 to 2,040 (700 ml.). A. D. O.

Heat Sterilisation, Chemical and Bacteriological Effects of. S. A. Schou. (*Acta pharm. int.*, 1950, **1**, 117.) By applying the temperature coefficient to the velocity constant for the hydrolysis of procaine it was calculated that heating at 80°C. for 2 hours, at 100°C. for 19 minutes and at 120°C. for 3 minutes produced the same amount of hydrolysis. Similarly, by applying the temperature coefficient to the velocity constant for the process of killing resultant spores, it was calculated that heating at 80°C. for 2 hours, at 100°C. for 5 minutes and 120°C. for about 1½ seconds produced the same bacteriological effect. These results showed that a short heat treatment at a high temperature was preferable both from a chemical and bacteriological point of view to more prolonged heating at a lower temperature. G. R. K.

Procaine, Effect of *p*H on the Stability of Solution of. L. Marchesi. (*Boll. chim. farm.*, 1951, **90**. 135.) When procaine is diazotised and the diazo compound united with α-naphthylamine a fairly stable colour is obtained which can be used for estimating the quantity present. *p*-Aminobenzoic acid, which is formed by the hydrolysis of procaine, gives a similar colour,

but this can be removed by shaking with ether, in which the procaine compound is insoluble. By this means the effect of heat in decomposing procaine in solutions at various *p*H can be studied. The method is as follows. To 4 ml. of a buffer solution add 1 ml. of a 1 in 10,000 solution of procaine hydrochloride. Heat this solution to the temperature desired for the desired time. Then add distilled water to make 8 ml., 2 ml. of 15 per cent. trichloracetic acid, and 1 ml. of 1 in 1,000 solution of sodium nitrite (freshly prepared). After 5 minutes add 1 ml. of 30 per cent. solution of urea and after another 3 minutes, 1 ml. of 1 in 1,000 solution of α-naphylamine hydrochloride. After half an hour extract with 10 ml. of ether and read the colour in a colorimeter. With known mixtures of procaine and *p*-aminobenzoic acid this gave accurate results. The experiments showed that procaine was most stable at *p*H 6 and any increase over *p*H 7 caused rapid decomposition. Heating to 70°C. for 1 hour at *p*H 6 caused little decomposition and this could be repeated, as in tyndallization. Heating to 100°C. for 15 minutes at *p*H 6 caused a little more, but at *p*H 10 half is decomposed. H. D.

NOTES AND FORMULÆ

Bethanechol Chloride (Urecholine Chloride). (*New and Nonofficial Remedies; J. Amer. med. Ass.*, 1951, **145,** 1067.) Bethanechol chloride is β-methylcholine carbonate chloride and occurs as a white, crystalline solid with an amine-like odour, m.pt. 217° to 220°C. with decomposition, soluble in water and alcohol and almost insoluble in benzene, chloroform and ether; a 0·5 per cent. aqueous solution has *p*H 5·5 to 6·3. It is distinguished from salts of choline by the following tests. With sodium hydroxide it yields the odour of ammonia, with nitric acid and silver nitrate, a white, curdy precipitate, and with cobaltous chloride and potassium ferrocyanide, an emerald green colour which fades rapidly. It loses, when dried over phosphorus pentoxide *in vacuo* for 24 hours, not more than 1·0 per cent. of its weight, and yields not more than 0·1 per cent. of ash. Bethanechol chloride contains 14·0 to 14·8 per cent. of nitrogen (determined by semi-micro Kjeldahl), 17·7 to 18·6 per cent. of chloride (determined by adding an excess of silver nitrate and back titrating with ammonium thiocyanate) and 95·0 to 105·0 per cent. of bethanechol chloride, determined by treating an aqueous solution with ammonium reineckate, dissolving the precipitate in acetone and measuring the light absorption at 5260Å spectrophotometrically. The amount of chloride present is read from a standard curve prepared by heating in a similar manner a series of solutions of choline chloride. G. R. K.

Piperoxan Hydrochloride (Benodaine Hydrochloride). (*New and Nonofficial Remedies; J. Amer. med. Ass.*, 1951, **145,** 1135.) Piperoxan hydrochloride is 2-(1-piperidylmethyl)-1 : 4-benzodioxan hydrochloride, $C_{14}H_{19}NO_2$,HCl. It is a white, crystalline, odourless powder, m.pt. 232° to 236°C., soluble in water, alcohol and chloroform and slightly insoluble in benzene and ether. It is identified by the picrate, which melts at 165° to 160°C. after drying at 105°C. for 2 hours. A 0·005 per cent. solution in water exhibits an ultraviolet absorption maximum at about 2740Å and a minimum at about 2430Å. When dried at 105°C. for 4 hours, it loses not more than 0·5 per cent. of its weight; sulphated ash, not more than 0·1 per cent. It contains 98·0 to 102·0 per cent. of piperoxan hydrochloride and is assayed by measuring the optical activity at 2740Å; the extinction coefficient

($E^{1\ per\ cent.}_{1\ cm.}$) is 80·0. It is administered intravenously as a diagnostic test for the presence of adrenaline-producing tumours. G. R. K.

PHARMACOGNOSY

Cascara, Indian. ***Rhamnus virgatus*** **Roxb.** I. C. Chopra, J. D. Kohli and K. L. Handa. (*Ind. J. med. Res.*, 1950, **38,** 473.) The bark used in this study was collected from the Gandarbal side in the Kashmir valley. It is known as chato or chadua. The powdered bark is greenish yellow and has a slightly bitter taste. Its total ash is 11·2 (B.P. drug, 6 per cent.) and the water-soluble extractive is 19·2 per cent. (B.P.C. drug, 23 to 28 per cent.). Only traces of hydroxymethyl anthraquinones could be detected and ethereal or aqueous extracts did not give the reaction for cascara sagrada when treated with ammonia. When given to puppies, guinea-pigs, rabbits and human beings, the bark and its extract had little purgative effect. A. D. O.

Senna, Synergistic Effect of a Third Active Glycoside. J. W. Fairbairn and M. R. I. Saleh. (*Nature,* 1951, **167,** 988.) The biological activities of the pure sennosides do not account for the total activity of the crude drug. Samples of leaf which contained much less sennoside than samples of the fruit had the same biological activity. This discrepancy is explained by the existence of a third glycoside which is present in small amount but which exerts a marked synergistic effect when present at about 15 per cent. of the total glycosidal content. In the samples of leaf referred to above, the third glycoside represented 12 to 15 per cent. of the total content whilst in the fruit it represented only 2 to 4 per cent. A. D. O.

PHARMACOLOGY AND THERAPEUTICS

Pentobarbitone Sodium; Physiological Performance following a Hypnotic Dose. R. E. Goodnow, H. K. Beecher, M. A. B. Brazier, F. Mosteller and R. Tagiuri. (*J. Pharmacol.*, 1951, **102,** 55. This study is part of a continuing effort to develop criteria for appraising the sedative agents, both narcotic and hypnotic. Little exact information is available concerning the nature and duration of the neuromuscular effects of the usual hypnotic dose of pentobarbitone sodium (0·1 g.). The after-effects of 0·1 g. of pentobarbitone sodium given by mouth were investigated in 30 healthy male college students by means of 4 tests, representing a range of functions. *Tapping speed:* the number of taps a subject could make in 10 seconds, using a telegraph key; *Auditory reaction time;* the speed with which a subject could react to an auditory stimulus by pressing a key; *Naming of opposites:* the time required to name the opposite of a common word of one or two syllables; *Memory for digits:* the number of digits a subject could recall in reverse order after a list of digits had been read to him. The tests showed a significant deterioration in performance at 6 a.m., 4 hours after the barbiturate had been given. The effect observed at 6 a.m. diminished after breakfast, but was found to continue in a highly suggestive (qualitative trend), but not statistically significant, degree until after 4 p.m., 14 hours after medication. S. L. W.

Procaine Amide; Physiological Disposition and Cardiac Effects of. L. C. Mark, H. J. Kayden, J. M. Steele, J. R. Cooper, I. Berlin,

E. A. Rovenstine and B. B. Brodie. (*J. Pharmacol.*, 1951, **102,** 5.) Procaine amide is *N'*-(2-diethylaminoethyl)-*p*-aminobenzamide. It is relatively stable in the body and is rapidly and completely absorbed from the gastro-intestinal tract. Plasma levels in man decline only 10 to 20 per cent. per hour. Metabolic transformation accounts for part of the decrease but urinary excretion accounts for the larger part. Organ tissues reversibly localise considerable amounts of the drug which are released to the plasma as the drug is lost by metabolic transformation or urinary excretion. Procaine amide is an effective agent against ventricular arrhythmias. Given in doses of 0·4 to 1 g. orally or intravenously to 54 patients who had frequent ventricular premature contractions, the contractions in all cases were suppressed for variable periods. Of 15 patients with ventricular tachycardia, intravenous administration of the drug successfully abolished the tachycardia in 13, 6 of whom had previously received quinidine to the point of toxicity without therapeutic effect. In 7 patients with chronic auricular flutter and 12 with chronic auricular fibrillation intravenous injection of 1 g. did not revert the arrhythmia but slowed the auricular rate. The drug is relatively non-toxic. On intravenous administration in therapeutic dosage it does not cause the central nervous stimulation typical of procaine in conscious subjects. Intravenous injections may cause a moderate but transient hypotension. In some cases of prolonged ventricular tachycardia where arterial pressure is low, the drug causes a further fall, which disappears promptly with the termination of the tachycardia. Untoward effects have not been seen with daily oral dosage continued up to three months. Procaine amide seems more effective and less toxic than quinidine for the treatment of ventricular tachycardias.

S. L. W.

Sulphonamides in the Treatment of Cholera. S. C. Lahiri. (*Brit. med. J.*, 1951, **1,** 500.) A total of 268 patients, admitted to hospital during the period May to July, 1950, were under clinical observation for this study. At the time of admission, 133 of the patients were in a very bad state of collapse. Powdered sulphaguanidine, formosulphathiazole and formosulphacetamide (the last two, condensation products of formaldehyde and sulphonamides) were given orally to successive patients in order of their admission, the fourth patient admitted receiving no chemotherapeutic drug and serving as a control. The dosage was the same for all three compounds, namely, 4 g. initially, followed by 2 g. every 4 hours throughout the day and night for an adult till the symptoms subsided or the stools became vibrio-free. All patients received saline transfusion till the specific gravity of the blood came down to normal level; atropine sulphate, 1/100 gr. hypodermically was given to all adult patients on admission and repeated after 8 to 12 hours as necessary. All patients received dextrose intravenously. Niketh-amide was extensively used as an analeptic and compounds of theophylline intravenously to stimulate urination. To combat collapse a number of patients received plasma or 6 per cent. intravenous gelatin. The use of the sulphonamides did not reduce the mortality rate and cases treated with these compounds compared unfavourably with those where no chemotherapy was given. No special vibriocidal effect of these compounds was apparent *in vivo*. Once the disease is fully developed, the most important part of treatment is to replace quickly the fluid and salt lost and to prevent the development of the irreversible condition of circulatory collapse. The peripheral circulatory failure is an important cause of persistent anuria occurring as a

result of failure of adequate glomerular filtration pressure, which ultimately leads to complete renal failure. Chemotherapeutic drugs, to be of any real value in cholera, must have a quicker action than any of the sulphonamides tested in this series, and should not be toxic. S. L. W.

Trypanocidal Compounds, Efficacy of. A. J. Duggan and M. P. Hutchinson. (*Trans. roy. Soc. trop. Med. Hyg.*, 1951, **44**, 535.) Melarsen, melaminylphenyl-arsanilate, has proved as effective in trypanosomiasis, in courses of 8 intravenous injections of 15 mg./kg. at 5-day intervals, as 12 × 3-g. injections of tryparsamide. It proved to be much more toxic than tryparsamide and is not suitable for use on a large scale in unselected cases. The incidence of toxic reactions bore no relation to the stage of injection or the clinical picture. Melarsen oxide (0·1 mg./kg. intravenously, 7 doses at 24-hour intervals) gave results which appeared to be comparable with those obtained with intravenous injections of mapharsen (0·4 mg./kg., 7 doses at 24-hour intervals). Toxic reactions from melarsen oxide were also very common, and were serious. The alkyl-mercapto derivative, known as Mel B, was also used and did not appear to give significantly better results than any of the other drugs employed. The toxicity is greater than the other two melarsen compounds and it bears a direct relation to the severity of the disease and its widespread use under field conditions is precluded. In "intermediate" cases pentamidine isethionate (0·3 g. intravenously, 7 doses at 24-hour intervals) gives results as good as those obtained with tryparsamide and is almost non-toxic. When combined with tryparsamide it was superior to suramin-tryparsamide mixture in the intermediate group, but this combination failed to cure 3 out of 10 early cases. A. D. O.

Vitamins B_{12c} and B_{12d}, Hæmopoietic Activity of. J. N. M. Chalmers. (*Brit. med. J.*, 1951, **1**, 161.) Nine cases of pernicious anæmia in relapse were treated with crystalline vitamin B_{12c} and 5 cases with crystalline vitamin B_{12d}. Both vitamins were given in a single dose of 20 μg. intramuscularly and a satisfactory hæmatological response was obtained in all the cases. Marked clinical improvement, with considerable relief of glossitis and lessening or disappearance of subjective nervous symptoms occurred. It is too early for conclusions to be drawn but, at the time of writing, the cases being investigated showed progressive clinical and hæmatological improvement on doses of 20 μg of vitamin B_{12d} at fortnightly intervals. S. L. W.

Xenon and Krypton, Anæsthetic Properties of. S. C. Cullen and E. G. Gross. (*Science*, 1951, **113**, 580.) A mixture with oxygen of 80 per cent. of a gas containing 95 per cent. of krypton and 5 per cent. of xenon in a closed circuit was ineffective as a narcotic in mice, rats and rabbits. 80 per cent. of pure krypton with oxygen also failed to produce narcosis in rabbits. Inhalation of this mixture from a closed circuit (with oxygen replacement and carbon dioxide elimination) by human beings caused discomfort but no significant narcosis. Pure xenon, with 20 per cent. of oxygen, however, in a closed system in rabbits (75 to 100 ml./minute for a 2·5 kg. rabbit for 15 minutes) caused some loss of eyelid reflex, slight diminution of reaction to pain, a tendency to remain in induced unnatural postures and a slowing of the respiration. After premedication with morphine these signs were increased. In human beings, xenon-oxygen mixture (50-50) produced narcosis equivalent to that obtained with nitrous oxide and oxygen (50-50), and a

70-30 mixture caused loss of consciousness after 3 minutes inhalation. Recovery was prompt. An orchidectomy was successfully carried out on a 81-year old patient, who had been premedicated with 0·2 mg. of atropine, using an 80-20 mixture. The patient was maintained in light anæsthesia and satisfactory muscular relaxation was obtained. He fully recovered consciousness 5 minutes after the withdrawal of the anæsthetic. The same mixture was also successfully used in a 38-year old woman during ligation of the Fallopian tubes. The anæsthetic effects of xenon were equivalent to those of ethylene.

A. D. O

BACTERIOLOGY AND CLINICAL TESTS

Aureomycin, Sensitivity of Strains of *Staphylococcus aureus* to. K. Anderson. (*J. clin. Path.*, 1951, **4**, 355.) Sensitivity tests were conducted on 100 strains of *Staphylococcus aureus* isolated from 132 swabs taken from fresh septic lesions in patients seen for the first time. The strains were all subjected to 4 accepted tests for pathogenicity, namely pigment production, coagulase production, liquefaction of gelatin and ability to ferment mannitol. Bacterial culture media are normally slightly alkaline and aureomycin is unstable in alkaline solution, but it was found that the strains of *Staph. aureus* grew vigorously in glucose broth at *p*H 6·8. Dilution tests showed that the strain adopted as test organism was regularly inhibited by a concentration of 0·625 μg./ml. of aureomycin hydrochloride both at 20°C. and 37°C. and the stability of the aureomycin hydrochloride in the broth solution at *p*H 6·8 was thus confirmed. Of the 100 strains, 81 were inhibited by concentrations of 0·625 μg./ml. or less and 19 were inhibited by 1·25 μg./ml. The lowest effective concentration was 0·078 μg./ml. H. T. B.

Irradiation, Response of Mice to Avirulent Bacteria after Exposure to. I. L. Shechmeister and V. P. Bond. (*Proc. Soc. Biol., N.Y.*, 1951, **77**, 77.) It has been observed that whole-body X-irradiation markedly lowers the resistance of mice to infection, and the appearance of bacteræmia following the treatment has been demonstrated. This bacteræmia has been identified with normal bowel inhabitants. In these experiments bacteræmia and death were induced in animals exposed to sublethal doses of irradiation and subsequently inoculated with live avirulent or even dead organisms generically different from the bacteria normally present in the intestines of these animals (namely, *Pasteurella pestis* and *Escherichia coli*). This observation may be of importance under conditions where irradiation is a factor and vaccination is indicated. S. L. W.

Pleuropneumonia-like Organisms, Isolation of. P. F. Smith and H. E. Morton. (*Science*, 1951, **113**, 623.) The media used for the isolation of these organisms were prepared with bacto-beef heart infusion with the addition of crystal violet, bacto-Chapman tellurite solution and 25 per cent. of ascitic fluid. In many cases 1 per cent. of a recently characterised serum fraction was used instead of the ascitic fluid, and adjustment was made to maintain the concentrations of crystal violet and potassium tellurite at the required concentrations for the inhibition of other organisms. Swabs taken from tonsils and back of the throat of 11 patients were incubated in the broth for 2 days at 37°C. and inocula from the liquid cultures were incubated anaerobically on tellurite-crystal violet agar plates enriched with ascitic fluid for 2 days at 37°C. 6 patients had pleuropneumonia-like organisms present in the throat; 32 out of 103 healthy medical students also showed the presence of these organisms. A. D. O.