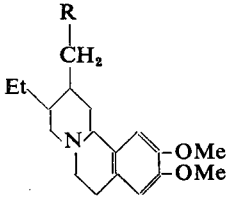
ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

Alkaloids of *Rauwolfia* Species. Studies on *Rauwolfia Cambodiana*. D. A. A. Kidd. (*Chem. Ind.*, 1957, 1013.) Dried roots, collected during March in Bangkhen, Thailand, were extracted with cold and hot methanol. The concentrated extract, acidified with dilute acetic acid, was defatted with *n*-hexane. Basification with ammonia and chloroform extraction gave the bulk of the alkaloids (3·5 per cent). Further basification with sodium hydroxide gave only a minute yield of a second alkaloid fraction: water-soluble alkaloids were precipitated from the mother liquors with ammonium reineckate. The major weakly basic fraction was separated by paper electrophoresis into reserpine (0·01 per cent yield) and a second alkaloid, fluorescent in ultra-violet light, m.p. 211–210), $[\alpha]_D^{12} - 111°$). The infra-red spectrum showed two peaks at 5·88 and 6·16 μ consistent with the presence of the ROOC−C=C−O−C−chromophore (compare ajmalicine). J. B. S.

Ipecacuanha Alkaloid, New, and a Partial Synthesis of Emetine. A. R. Battersby, G. C. Davidson and B. J. T. Harper. (*Chem. Ind.*, 1957, 983.) A new alkaloid has been isolated in 0·002 per cent yield from the alkaloid bases of ipecacuanha root, by countercurrent distribution. The alkaloid, $C_{19}H_{27}O_3N$ (two OMe, one C-methyl) showed ultra-violet absorption characteristic of veratrole: the infra-red spectrum indicated the presence of an aldehyde group, confirmed by the reduction of Tollen's reagent, and hydrogenation. The basic strength indicates that the nitrogen is common to two rings. On this evidence and Robinson's proposals for the biogenesis of emetine, structure I, (R = CHO) is advanced for the new alkaloid. This was confirmed by converting the aldehyde, through its oxime, to the nitrile I, (R = CN) and hence to the corresponding acid, identical with that known to have the structure I, (R = CO_2H) from *O*-methylpsychotrine. A partial synthesis of emetine is described from the acid I, (R = CO_2H), the acid chloride of which was condensed with homoveratrylamine to give the amide (II). The latter treated with $POCl_3$ gives *O*-methylpsychotrine, identical with the natural alkaloid, the reduction of which to emetine has already been described. J. B. S.



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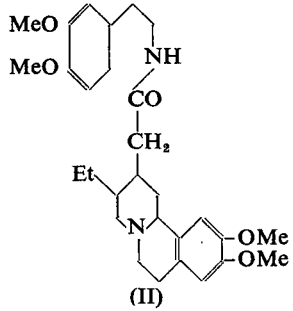


(II)

ANALYTICAL

β-Bromallylbarbiturates, Detection of, on Paper Chromatograms. A. S. Curry. (*Acta pharm. tox. Kbh.*, 1957, **13**, 357.) The 5:5-disubstituted barbiturates

can be distinguished from the 1 : 5 : 5-substituted barbiturates and the thiobarbiturates by observation of the changes in the ultra-violet absorption spectrum with pH. Identification of the individual members is made by paper chromatography with selective spray reagents for detecting the spots. Thus 5 : 5-disubstituted barbiturates with fully saturated side chains do not react with aqueous solutions of potassium permanganate, but compounds that have an allyl radical in the molecule react immediately. Other barbiturates with side chain radicals also containing a double bond can be divided into two further groups, depending on their speed of reaction with this spray reagent. However because this is a subjective measurement of rate of reaction, it was thought necessary to devise another test to distinguish those barbiturates with β-bromallyl radical in the molecule. Chromatography, using *n*-butanol/5 N ammonia as the solvent and a saturated solution of soluble fluorescein in glacial acetic acid and hydrogen peroxide with a trace of copper acetate, as the spray reagent, was employed. The copper catalyses the hydrolysis of the β-bromallyl barbiturates and the floresceineosin reaction can then be used. With such a method good separation between Noctal, Pernocton and Sigmodal is obtained, and quantities as small as 50 μg. can be detected. M. M.

***Digitalis purpurea*, Chemical and Biological Assay of.** K. B. Jensen. (*Acta pharm. tox. Kbh.*, 1957, **13**, 381.) 25 digitalis leaf specimens of varying origin were assayed biologically by the guinea pig method and the amounts of the individual cardio-active substances were determined chromatographically and fluorimetrically. It was found that there was marked agreement between the percentages that the individual substances constituted of the total amount, in the various specimens analysed, provided that they fulfilled the requirements made in the Scandinavian Pharmacopoeias for Folium Digitalis as to collection and drying. In a few drug specimens dried in a different way the quantitative composition of the glycoside complex was different. The observed uniformity of composition of the glycoside complex in the analysed specimens of Folium Digitalis justifies the presumption that the total glycoside content can be regarded as a measure of the potency of these specimens. A comparison of the results achieved by the biological and the paper-chromatographic and fluorimetric methods showed a marked agreement for most of the drug specimens examined. However, for a few of the specimens the differences were so great that a fixed relationship between the two methods seems unlikely. These differences are assumed to be due to the biological method being not sufficiently specific and including in the assay cardiotoxic substances that do not have the character of cardiac glycosides. It is suggested that the potency of a Scandinavian drug specimen can be estimated by chemical assay of the total content of cardio-active substances—by means of the paper-chromatographic and fluorimetric or an equally specific method. By fermentative decomposition of primary into secondary glycosides before paper chromatography it should be possible to restrict to a practical limit the number of substances that must be determined to give an adequately accurate estimate of potency. M. M.

Mercaptoaneurine and Aneurine, Determination of. B. Buděšínský and E. Vaníčková. (*Československ. Farm.*, 1957, **6**, 308.) Aneurine is precipitated as $(C_{12}H_{18}N_4OS)(BiI_4)_2$ in acid solution and the excess of precipitant is determined complexiметrically. A weighed sample (120 to 300 mg.) of aneurine hydrochloride is dissolved in 25 ml. of water and 2 ml. of conc. hydrochloric acid are added, then 5 ml. of a 20 per cent solution of potassium iodide and

exactly 10 ml. of 0·25M potassium iodobismuthite. The volume is made up to 50 ml. and the liquid is filtered through a dry filter. The first 10 ml. of the filtrate are rejected and about 1 ml. of 0·1N sodium thiosulphate and 10 ml. of acetate buffer are added to a 25-ml. quantity of the remainder. This solution is then titrated against 0·05M Complexone III until its yellow colour disappears. A blank experiment is carried out at the same time: 1 ml of 0·05M Complexone III corresponds to 8·432 mg. of anhydrous aneurine hydrochloride. Mercaptoaneurine is determined by potentiometric titration against potassium bromate in acid solution. E. H.

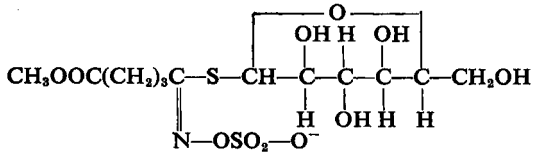
Salicylic Acid and Benzoic Acid in Mixtures, Determination of by Differential Nonaqueous Titration. M. I. Blake. (*J. Amer. pharm. Ass., Sci. Ed.*, 1957, **46**, 287.) For the analysis of ointments containing benzoic and salicylic acids, a 5-g. sample (containing 2–3 m.eq. of benzoic acid and 1–2 m.eq. of salicylic acid) was dissolved in neutralised dimethylformamide with the aid of a magnetic stirrer. The solution was titrated rapidly with 0·1N sodium methoxide, the end points being determined electrometrically. The first end point was due to salicylic acid and the second to benzoic acid. This method was satisfactory for the U.S.P. XV ointment which is made with a macrogol basis. Whitfield's ointment, U.S.N.F. IX, which has a basis of wool fat and soft paraffin did not dissolve readily in the dimethylformamide. In this case good results were obtained by dissolving the ointment in a little chloroform and adding the dimethylformamide before carrying out the titration. G. B.

Sulphonamides, Analysis of Mixtures of, by Paper Electrophoresis. S. Ljungberg. (*Svensk farm. Tidskr.*, 1957, **61**, 529.) Mixtures of sulphonamides were dissolved in 5 M acetic acid and separated by electrophoresis on paper. After drying, the position of the sulphonamides on the paper was detected in ultra-violet radiation. The appropriate areas were cut from the paper and digested for 1 hour with hydrochloric acid, and the quantity of sulphonamide in the resulting solution determined by the colorimetric method of Bratton and Marshall, or by measuring the ultra-violet absorption. The error of the method was about 5 per cent. Mixtures of sulphadiazine, sulphamerazine and sulphamethazine were separated in 20 hours' electrophoresis, but mixtures of sulphadiazine, sulphamerazine and sulphathiazole required 40 hours. G. B.

GLYCOSIDES

Methyl 4-*iso*thiocyanatobutyrate, a New Mustard Oil as a Glucoside (Glucoerypestrin) in *Erysium* Species. A. Kjaer and R. Gmelin. (*Acta chem. scand.*, 1957, **11**, 577.) Seed extracts of *Erysimum rupestre* DC yield a glassy glucoside fraction, which on acetylation gives crystalline glucoerypestrin tetra-acetate monohydrate. De-acetylation with methanolic ammonia furnished the alkali labile glucoerypestrin. Enzyme hydrolysis with myrosinase at pH 6·7 gave a mustard oil, which in turn yielded the thiourea $H_2N{\cdot}CS{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}COOMe$ on treatment with methanolic ammonia. Reaction of the *iso*thiocyanate with aniline and 1-naphthylamine in methanolic solutions afforded the crystalline phenylthiourea $C_6N_5NH{\cdot}CS{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}COOMe$ and the 1-naphthylthiourea $1\text{-}C_{10}H_7NH{\cdot}CS{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}COOMe$ respectively. The structure of the new mustard oil which follows as methyl 4-*iso*thiocyanatobutyrate was confirmed by synthesis from methyl 4-aminobutyrate hydrochloride

and thiocarbonyl chloride. Strong acid hydrolysis of glucoerypestrin yields hydroxylamine in accordance with the structure (I) for the glucoerypestrin anion.



(I)

J. B. S.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

8-Azapurines, Metabolism of. J. D. Smith and R. E. F. Matthews. (*Biochem. J.*, 1957, **66**, 323.) Growth of *E. coli* is inhibited by 8-azaguanine (I), 8-aza-adenine (II), 8-azahypoxanthine (III) and 5(4)-amino-1*H*-1 : 2 : 3-triazole-4(5)-carboxyamide (IV). (I) and 8-azaxanthine (V) inhibit the growth of *B. cereus*, whilst development of the tobacco leaf virus is inhibited by (I), (II) and (IV). A number of 8-azapurines and substituted triazoles were not inhibitory. In all cases those which are inhibitory are incorporated as 8-azaguanine in the organism's ribosenucleic acid. In *B. cereus* this occurs in amounts up to 40 per cent of the ribosenucleic acid guanine, the highest ratio being found in the terminal purine nucleoside 2′ : 3′-(monohydrogen phosphate) residues liberated by pancreatic ribonucleases. *B. cereus* ribosenucleic acid containing (I) has been fractionated and the shorter nucleic acid chains shown to contain more 8-azaguanine than the longer chains. They also contain a greater proportion of the cyclic-8-azaguanylic acid residues. Assimilation of (I) by *B. cereus* can be readily reversed by addition of guanine. Ethanol extracts of *B. cereus* grown in the presence of (I) have been shown to contain 8-azaguanosine and 8-azaxanthosine. Some (I) is incorporated into *B. cereus* dexoxyribonucleic acid, and 8-azaguanine desoxyribonucleoside has been tentatively identified in hydrolysates of the nucleic acid. J. B. S.

Di*iso*propyl Phosphorofluoridate and other Anticholinesterases, Action of, on Amino Acids. R. F. Ashbolt and H. N. Rydon. (*Biochem. J.*, 1957, **66**, 237.) The action of di*iso*propyl phosphorofluoridate dyflos, di*iso*propyl phosphochloridate (DC1P) and other phosphorus-containing anticholinesterases on a number of amino acids has been studied under "physiological" conditions. Dyflos differs markedly from DC1P in that it reacts appreciably with the phenolic hydroxyl group of tyrosine under "physiological" conditions, causing *O*-di*iso*propylphosphorylation, the product being identified by comparison with a synthetic specimen. Tyrosine is able to compete with water in its reaction with dyflos at pH 7-8. Di*iso*propylphosphorylation of the α-amino group occurs to a small extent with tyrosine and phenylalanine. DC1P is even less reactive in this respect. Tetraethylpyrophospate (TEPP) is much less specific but more reactive than dyflos towards amino acids. It reacts equally readily with the phenolic and α-amino groups of tyrosine, with the α-amino group of phenylalanine, and the ε-amino group of lysine. It is slightly less reactive with the α-amino and β-hydroxy groups of serine. The significance of the results in relation to the mode of action of di*iso*propylphosphorofluoridate and other anticholinesterases is briefly discussed. J. B. S.

Poliomyelitis Vaccine: Safety and Antigenic Potency Testing. Report from the Biological Standards Control Laboratory, M.R.C. Laboratories. (*Brit. med. J.*, 1957, **2**, 124.) The British poliomyelitis vaccine is prepared by the formalin-inactivation method introduced by Salk (1953) but differs in its type I component from that produced in North America. The Mahoney strain has been replaced by the partially attenuated Brunenders strain. As in America, strains MEF-I and Saukett are used in preparing the type II and III components of the British vaccine. The general regulations for the testing of the British vaccine have been laid down in the T.S. Amendment Regulations No. 1131 (1956) and are based on the present American ones, but the introduction of an attenuated strain in this country has necessitated some modification of the American methods of testing. In Britain concurrent tests are made on each batch of trivalent vaccine by the control laboratory and the manufacturer, after the latter has shown that the tests for safety and potency on the individual type components are satisfactory. In the final tests the vaccine is examined for the presence of live virus by the inoculation of cell cultures and monkeys, and for its antigenic potency in monkeys. The three tests are described in detail. S. L. W.

BIOCHEMICAL ANALYSIS

Adrenaline, Estimation of, in Peripheral Blood. B. V. Franko, A. D. Bragg and D. T. Watts. (*Arch. int. pharmacodyn.*, 1957, **111**, 123.) This method is a modification of that used by Gaddum and Lembeck. It involves the use of the isolated uterus of the rat, suspended in a calcium and glucose deficient Ringer solution. An organ bath of 3 ml. capacity, of the overflow type was used. All apparatus was constructed in polyethylene to prevent haemolysis when whole blood was used for the assay. Lysergic acid diethylamide, 5 μg./l., was added to the Ringer solution in order to prevent stimulation of the tissue by the 5-hydroxytryptamine in the blood. These modifications permit the estimation of adrenaline in the peripheral arterial blood of the dog. Although insufficiently sensitive to estimate the adrenaline level under basal conditions, it could be used for this purpose under conditions of stress. The adrenaline could be estimated in whole blood provided that the assay was conducted within one minute of the blood being shed. The method is rapid and simple, and blood samples as small as 0·3 ml. can be used. At least 95 per cent of the adrenaline added could be recovered at the end of one minute. If the blood samples could not be assayed immediately the plasma was separated from the cells and used for assay. The method described here has been utilised for the determination of adrenaline in peripheral arterial blood of the dog under conditions such as haemorrhagic hypotension, anoxia and after the administration of such drugs as nicotine, histamine and acetylcholine. It was found that the maximum blood adrenaline level observed during haemorrhagic hypotension is approximately 100 times that of the basal level of less than 1 μg./l.

M. M.

Adrenaline, Noradrenaline and Hydroxytyramine, Separation of. N. Kirshner and McC. Goodall. (*J. biol. Chem.*, 1957, **226**, 207.) A procedure is described in which the weak cation exchange resin Amberlite IRC–50 is used to separate adrenaline, noradrenaline and hydroxytyramine in less time than that required by previous methods and in amounts which vary from 0·02 to 1·0 mg. Extracts of adrenal glands were prepared in 10 per cent trichloroacetic acid. After filtration the acid was removed by extraction with ether and the pH of the resultant solution was adjusted to 6·1. This solution was

then passed through the resin column and eluted with ammonium acetate buffer solution at pH 5·0. The amines were determined by their absorption at 279 mμ. In 3 experiments with pure solutions the per cent recovery of adrenaline was 85–95, noradrenaline 95–97 and hydroxytyramine 83–95. In 5 experiments with trichloroacetic acid extracts of adrenal glands the recovery of adrenaline, calculated from the optical density at 279 mμ, ranged from 88 to 103 per cent and the recovery of noradrenaline from 73 to 103 per cent. This separation of adrenaline, noradrenaline and hydroxytyramine is dependent upon the pH of the resin and the pH of the eluting fluid. Increasing the pH of the resin to 6·6 greatly enhanced the separation of adrenaline from noradrenaline but decreased the separation of noradrenaline from hydroxytyramine. Decreasing the pH of the resin below 6·0 increased the resolution of the hydroxytyramine and noradrenaline fractions but decreased the separation of adrenaline from noradrenaline. Changing the pH of the eluting buffer caused similar shifts in the resolving capacity of the resin. Increasing the ionic strength of the eluting buffer increased the rate at which the compounds migrated down the column. Increasing the molarity of the buffer beyond 0·4 M caused increased losses of adrenaline, noradrenaline and hydroxytyramine and decreased the resolution for all 3 compounds. M. M.

Dextran in Plasma, Estimation of. R. E. Semple. (*Canada J. Biochem. Physiol.*, 1957, **35**, 383.) When dextran is used to estimate plasma volume, concentrations of 60–150 mg./100 ml. of plasma have to be measured accurately and fairly rapidly. The methods that are already in use are accurate only for amounts greater than 300 mg./100 ml. The method described here is satisfactory for 50–150 mg. of dextran/100 ml. of plasma. First the plasma protein is removed with trichloroacetic acid. The supernatant fluid is then dialysed against water to remove the glucose. The carbohydrate concentration of the resulting aqueous extract is determined by a modified anthrone technique. Anthrone solution is added to the extract and the optical density of the solution is read in a spectrophotometer against the distilled water-anthrone blank at $\lambda = 625$ mμ. The results show that mean recoveries were between 99·8 and 100·1 per cent. When single plasma samples were analysed the standard deviations from the means varied, with the dextran concentration, from 1·7 to 2·5 per cent. These deviations were reduced to 1·4 to 1·7 per cent by the use of duplicate plasma samples. The whole procedure takes 3–4 hours.

M. M.

Noradrenaline and Adrenaline, Urinary Excretion of. N. T. Kärki. (*Acta physiol. scand.*, Supp. 132.) This paper gives a detailed account of the adrenaline and noradrenaline content of normal human urine. In order that the adrenaline and noradrenaline can be estimated quantitatively by a biological method the amines are first extracted from the unhydrolysed urine. This is done by adsorption on to aluminium oxide at pH 8·5. To minimise inactivation of the amines the pH is allowed to remain at this high value for not longer than 25 minutes. The amines were then eluted with 1 N sulphuric acid. The recovery of adrenaline and noradrenaline added to urine was approximately 73 per cent. The stability of the extracts was good: no reduction in biological activity being observed during storage at + 4° for 10 days. In the study of the stability of noradrenaline added to urine, no variation in the content occurred when the urine was stored in the cold (+ 4°) at either pH 4 or pH 6·5. The content did not change when the urine of pH 4 was stored for 2 days at room temperature, but a marked decrease occurred when the pH of the urine was 6·5 during the

storage at room temperature. The biological activities of the extracts were determined using the blood pressure of the hexamethonium—treated cat or rat and the rectal caecum of the hen as test preparations. The adrenaline and noradrenaline content was then determined by the use of a suitable formula. To determine the normal excretion of noradrenaline in men, women and children 356 twenty-four urine samples from 291 subjects were used. To determine the adrenaline excretion 240 samples from 182 subjects were used. In the group of children from 1·5 to 6 years old, the mean 24-hour excretion of noradrenaline in the urine was 5·6 μg. and that of adrenaline 1·3 μg. In the children of 7–16 years the mean noradrenaline excretion was 14·5 μg./24 hours and that of adrenaline 2·8 μg. The excretion levels in this group were approximately twice those of the preceding group, and a highly significant regression was established between the amount of noradrenaline excreted and the weight of the child. In those subjects from 17 to 29 years the mean excretions were 24·5 μg. of noradrenaline and 5·1 μg. of adrenaline per 24 hours. In the group from 30 to 59 years the mean excretions were 25·2 μg. of noradrenaline and 5·4 μg. of adrenaline per 24 hours. In the group from 60 to 96 years the mean excretion of noradrenaline was 23·1 μg. and that of adrenaline 4·4μg./24 hours. When the amounts of noradrenaline were calculated per kilogram of body weight it was found that the mean noradrenaline output was highest for both sexes in the 7 to 16 year old group and that it decreased with increasing age. No differences in the 24 hour noradrenaline excretion were observed between the sexes when the mean excretions for the various age groups were compared. No statistically significant differences in the urinary excretion of adrenaline, calculated per kilogram of body weight were found between the different age groups and between the sexes. The urine volumes excreted by the children were large but the mean concentration was low, being only about half that of the urine of adults. The amounts of noradrenaline excreted by 85 subjects from 17 to 29 years were not found to bear any relationship to the urine volume. The excretion of the two amines was found to vary with the time of day. With both adrenaline and noradrenaline the amount excreted during the night was considerably lower than the amount excreted during the day. Muscular work was found to cause a very large increase in the amounts of both amines excreted. The greatest increase was 35 times the normal level. M. M.

CHEMOTHERAPY

Erythromycin Group of Antibiotics. L. P. Garrod. (*Brit. med. J.*, 1957, **2**, 57.) A series of *in vitro* experiments were undertaken to determine (1) the activity of oleandomycin, alone and in combination, with tetracycline, and (2) the closeness of the relationship between erythromycin, oleandomycin, and spiramycin from which might be deduced how far acquired resistance to each involves the others. The *in vitro* antibacterial activity of oleandomycin was found to be somewhat less than that of erythromycin, and the claims that a 2:1 mixture of tetracycline and oleandomycin exerts a synergic action *in vitro* were not confirmed. Spiramycin was shown to have a considerably lower activity *in vitro* than erythromycin. Studies of cross-resistance among the members of this group showed that, whereas complete cross-resistance develops in strains of staphylococci habituated *in vitro*, erythromycin-resistant strains isolated from patients may or may not be resistant to oleandomycin and spiramycin. To what extent the clinical use of these two antibiotics may produce bacterial resistance to erythromycin remains uncertain, but it would be safer to assume that cross-resistance may sometimes follow the use of any of the three. S. L. W.

Glyoxals, Antiviral Activity of. C. A. de Bock, J. Brug and J. N. Walop, (*Nature, Lond.*, 1957, **179**, 706.) The antiviral activity of some compounds with an $\alpha\beta$-dicarbonyl structure, and closely related substances was studied. Influenza virus A-USA-47 (A′ strain) was used and was cultured in eleven-day-old chick embryos. The eggs were inoculated with the seed virus and incubated at 36° for 48 hours. After this time the haemagglutination titre was tested. For estimation of antiviral activity the compounds were injected into the allantoic fluid of the eggs one hour before inoculation and the titre measured in the usual way. A compound was considered active if the difference between the logarithm of the haemagglutination titre of the eggs inoculated with virus only and those treated with the drugs was greater than + 0·6. A number of α-keto-aldehydes appeared to be active in the concentration used (0·1M solution or suspension in saline). *In vitro* investigations on some of the more active compounds showed a direct action on the virus. The virus particles lost their infective power when incubated with concentrations as low as 0·002M for 5 hours at 37°. Somewhat higher concentrations destroyed the enzymic activity of the virus against urinary mucin as substrate. Haemagglutinating power of the virus was destroyed by still higher concentrations or by prolonged incubation with one of the active compounds in a concentration of 0·004M at 37°. The virucidal action *in vitro* is strong enough to explain the activity in the allantoic test. G. P.

PHARMACOLOGY AND THERAPEUTICS

Hypoglycaemic Agent, Clinical Report of. J. Pomeranze, H. Fujiy and G. T. Mouratoff. (*Proc. Soc. exp. Biol. N.Y.*, 1957, **95**, 193.) A new synthetic oral hypoglycaemic drug, *N*-β-phenylethylformamidyliminourea (DBI) causes in doses of 100 mg. a significant decrease in the blood sugar concentration in normal adults and in diabetics. The configuration of the glucose tolerance curve was altered, unlike the sulphonylurea drugs which lower the fasting blood sugar but do not alter the glucose tolerance curve. DBI adequately replaced 40 units of the 70 required units in a young severe labile diabetic patient and totally replaced insulin in a less severe diabetic patient under 40 years of age and in a 68 year old patient whose diabetes had been present for 28 years. G. F. S.

Indole Carboxamidines and Aminomethylindoles as Antimetabolites of Serotonin. E. Shaw and D. W. Woolley (*J. Amer. chem. Soc.*, 1957, **79**, 3561.) A number of 6-aminomethyl-1 : 2 : 3 : 4-tetrahydrocarbazoles and 1 : 2 : 3 : 4-tetrahydrocarbazole-6-carboxamidines have been synthesised as potential antimetabolites of serotonin. The antiserotonin action of 1 : 2 : 3 : 4-tetrahydrocarbazole-6-carboxamidine and -6-*N*-phenylcarboxamidine, 6-aminomethyl-, 6-*NN*-dimethylaminomethyl-, and 9-benzyl-6-*NN*-dimethylaminomethyl-1 : 2 : 3 : 4-tetracarbazoles has been measured on carotid artery segments, on isolated rat uterus, and against the pressor action of serotonin in dogs. 1 : 2 : 3 : 4-Tetrahydrocarbazole-6-*N*-phenyl carboxamidine caused a sharp fall in the blood pressures of anaesthetised dogs when administered intravenously in doses of 2–7 mg./kg. 9-Benzyl-6-dimethylaminomethyl-1 : 2 : 3 : 4-tetrahydrocarbazole in daily doses of 25 mg./kg. administered orally to dogs caused refusal of food and behavioural changes after 3–4 days treatment. J. B. S.

Iron-Dextran; Treatment of Iron-deficiency Anaemia in Children. R. O. Wallerstein and M. S. Hoag. (*J. Amer. med. Ass.*, 1957, **164**, 962.) Iron-deficiency anaemia in 24 infants from 5 to 36 months was treated by intramuscular injection of solutions of an iron-dextran complex (Imferon). Dosage

was at the rate of 50 to 100 mg. of Fe daily (1 to 2 ml. of Imferon), and the total dosage varied according to age: under 6 months, 100 mg.; 6 to 12 months, 200 mg.; 12 to 24 months, 300 mg.; over 24 months, 400 mg. Haemoglobin values rose to about 11 g./100 ml. in 3 weeks. Rises of 4 per cent/day were seen in several infants with severe anaemia. Reticulocyte response occurred early and correlated fairly well with the degree of anaemia in patients with severe anaemia, though it was inconstant in patients with moderate anaemia. The injections caused no local tenderness, redness or swelling, but slight brownish discoloration of the subcutaneous tissues, lasting for several weeks, occasionally occurred. There were no systemic reactions. There is a wide margin of safety, and a total dosage of at least 1 g. may be given to infants. It is emphasised, however, that failure to respond to the proper intramuscular dose of iron is never an indication for giving more iron. S. L. W.

Iron, Intravenous, Toxic Reactions to. I. P. Ross. (*Lancet*, 1957, **2**, 77.) Patients given 100-mg. doses of saccharated iron oxide preparation (Ferrivenin) intravenously, following initial doses of 25–50 mg. showed toxic reactions in about 7·5 per cent of the cases, about half of these being serious enough to require the treatment to be discontinued. Massive doses (500–600 mg. by intravenous infusion) gave rise to a much larger proportion of toxic reactions. Reactions were least common in pure iron-deficiency anaemias and more frequent in the presence of fever, toxaemia or metabolic disturbance. Great care appears to be necessary with patients having disorders of the pulmonary capillary bed, who may be given doses of 25 to 50 mg. very slowly. As, even with careful selection of cases, the incidence of toxic reactions to 100-mg. doses is about 5 per cent, the development of less toxic preparations is desirable.

G. B.

Peganone; A Clinical Evaluation. C. H. Carter and M. C. Maley. (*Amer. J. med. Sci.*, 1957, **234**, 74.) After a control period of one year on established therapy, 38 chronic, refractory epileptics, suffering from mixed grand and petit mal epilepsy, were treated with peganone (3-ethyl-5-phenylhydantoin). Of the total of 38, 23 were children and 15 adults. In 9 cases peganone was used alone, and in the remainder it was combined with the previous medication. No incompatibilities were found with other anti-epileptic drugs. Dosage was commenced at 0·5 g. daily and gradually increased to a total of 3 to 4 g. daily in divided doses; in a few adults dosage was increased to a maximum of 5 or 6 g. daily. Thirteen of the patients were studied for more than one year, 10 for from 6 to 9 months and the remainder for short periods. In the group as a whole there was an overall improvement of 62 per cent in the number of seizures; 71 per cent of the cases showed a reduction of more than 50 per cent in the number of seizures. Routine blood studies, liver function tests and urinalyses were carried out on all patients. There were no deviations from normal and no evidence of other toxic effects such as skin rash or gum hyperplasia. The only side-effect noted was drowsiness in a few patients daily. The authors consider peganone to be a valuable addition to the available anti-epileptics because of its effectiveness and lack of toxicity. S. L. W.

Proclorperazine; Antiemetic Properties. D. G. Friend and G. A. McLemore. (*Arch. intern. Med.*, 1957, **99**, 732.) Proclorperazine, a new chlorpromazine congener, gave excellent or good results in 23 out of 25 cases of nausea and vomiting of various etiologies. It was given in a dose of 10 mg. by mouth or intramuscularly every 4 to 6 hours or as a rectal suppository of

50 mg. once daily. Several of the cases of nausea and vomiting had previously failed to respond to chlorpromazine therapy. In 2 cases with Ménière's syndrome with severe vertigo it effectively relieved the dizziness. Two cases of hiccough were also relieved. Slight drowsiness was a common but usually desirable side-effect. On long-continued therapy mild gastric irritation may occasionally occur, and in doses higher than 60 mg. a day it may cause confusion, dizziness or fainting. No jaundice, agranulocytosis or other serious toxic effects were observed. S. L. W.

Rauwolfia, the Total Alkaloids of, and Reserpine, Sites of Action of, on the Sleep Centre. E. Frommel and P. Gold. (*Acta pharm. tox. Kbh.*, 1957, **13**, 345.) A comparison is made of the action of an extract containing all the active principles of rauwolfia with that of a specific member of the group, namely reserpine, on the sleeping time of various animals. It has previously been suggested that the action of reserpine involves a sleep centre which is different from that affected by phenobarbitone. This has been confirmed by showing that reserpine does not potentiate significantly barbiturate-induced sleep in guinea pigs. In contrast, the total alkaloids of *Rauwolfia serpentina* appear to overlap the site of action of phenobarbitone since these alkaloids potentiate its sleep-producing effect. Neither the total alkaloids of rauwolfia nor reserpine modified the hypnosis produced by sodium thiopentone in rabbits. Atropine was found to significantly enhance the sleep-inducing effect of thiopentone in rabbits, previously treated with the total alkaloids of rauwolfia. This action was less marked in those animals which had received reserpine. Although the administration of phenobarbitone significantly augmented the duration of thiopentone-induced sleep in rabbits treated with the total alkaloids, this effect was much smaller in animals given reserpine. The administration of atropine and phenobarbitone to rabbits treated with the total alkaloids produced the longest duration of thiopentone-induced sleep. There was less effect in the reserpine treated animals. These results indicate that the action of the total alkaloids of rauwolfia differ from reserpine on the sleep centres affected by phenobarbitone and thiopentone. However this distinction does not apply to the centres of nikethamide excitation because here both the total alkaloids and reserpine neutralised the agitation produced by nikethamide in guinea pigs and enhanced the sedative effect of phenobarbitone against nikethamide. M. M.

Ro 2-7113, Analgesic Activity and Toxicity of. W. M. Benson, D. J. Cunningham, D. L. Hane and S. Van Winkle. (*Arch. int. Pharmacodyn*, 1957, **109**, 171.) By intravenous or subcutaneous injection Ro 2–7113 [(±)-1-methyl-3-allyl-4-phenyl-4-propionoxy-piperidine hydrochloride] had the same order of toxicity in mice as alphaprodine (the corresponding 3-methyl derivative) and levorphanol, but was considerably more active as an analgesic. Orally the ratio of toxic dose to analgesic dose LD50/AD50 for all three drugs was much less, but was still more favourable in the case of Ro 2–7113. In rats Ro 2–7113 was twice as toxic by intravenous injection as alphaprodine and levorphanol, but more than twelve and seven times as active, respectively. Duration of activity of Ro 2–7113 by this route, like that of alphaprodine, was less than that of levorphanol. Subcutaneously in rats the ratio of LD50/AD50 was twelve times more favourable for Ro 2–7113 than for alphaprodine, and twice that of levorphanol. By the oral route the ratio for Ro 2–7113 was twice that for the other two. Similar results were obtained for rabbits and dogs. In dogs, sedation and respiratory and cardiac depression was seen with sufficiently large

doses. Peripheral cholinergic effects were also noted. The increased potency of the new analgesic is interesting since altering the position of the allyl group to the nitrogen gives a compound with much diminished, if not antagonistic, action. G. P.

Senna, Standardized, as a Laxative in the Puerperium, a Clinical Assessment. A. S. Duncan. (*Brit. med. J.*, 1957, **1**, 439.) Senna has been regarded for many years as a safe laxative for pregnant and puerperal women, but its use has lapsed because of variability of the potency of preparations. The introduction of a stabilised consistent preparation, Senokot, has led to a revaluation of its use, and in the present trial the preparation was compared for laxative effect with cascara. As a preliminary step spontaneous bowel movements in 100 consecutive puerperal women were recorded; of these only 26 occurred by the third day, and in 23 an enema was required after the eighth day. Two further groups received either 0·4 g. of tab. extract cascara B.P. or two teaspoonsful of Senokot granules (equivalent to 0·7 g. of senna pod) on the morning of the third puerperal day. With the doses used the senna preparation was the more effective of the two, bowel movement occurring in about 85 per cent of the patients within 24 hours, whereas with cascara the figure was about 55 per cent. Also the proportion of normal stools was higher with the senna. No untoward side effects were noted with the laxatives, apart from gripes, which were more frequently observed with the senna preparation. A few patients complaining of severe morning sickness improved dramatically after Senokot, but this requires further investigation. Of the 290 women in the trial, 66 had been taking laxatives regularly before they became pregnant and 43 had taken liquid paraffin regularly during pregnancy. G. P.

Tolbutamide; Clinical and Biochemical Studies. M. F. Crowley, F. W. Wolff and A. Bloom. (*Brit. med. J.*, 1957, **2**, 327.) Tolbutamide was used in the treatment of 42 patients on standard diets whose diabetes was neither so mild as to be controlled by diet alone nor so severe as to need insulin immediately. Patients were maintained for a total of 6 weeks on tolbutamide and then for a further 6 weeks on dummy tablets unless relapse occurred, in which case tolbutamide was re-introduced. The dosage was 3 g. on the first day and 2 g. daily thereafter. Of the 42 patients treated 30 responded well, with a return to normoglycaemia, and a complete or almost complete disappearance of glycosuria. Twelve responded poorly or not at all. The majority who responded were middle-aged or elderly. Seven of the 30 who responded relapsed when the drug was stopped, six within the first 2 months; six of the 7 responded well when the drug was restarted and remained satisfactorily controlled on 2 g. daily. The remaining 23 remained well controlled on dietary regime alone. No toxic effects were recorded in any of the patients. The majority showed no weight change while on tolbutamide, but when it was discontinued there was a mean reduction of 3 lb. in weight in patients observed over the next 2 months. When tolbutamide 1 g. was given twice daily the blood concentration differed from that following a single dose of 2 g., but the effect on the blood and urine sugars was the same. This suggests that the level of blood tolbutamide is not the determining factor in the fall in blood and urine sugar. The fact that the plasma inorganic phosphorus did not fall during tolbutamide therapy and that the drug had no effect on the amino acid nitrogen levels indicates that tolbutamide does not act in the same way as insulin. S. L. W.