ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

Reserpiline, Alkaloid of *Rauwolfia serpentina* Benth. M. W. Klohs, M. D. Draper, F. Keller and W. Malesh. (*Chem. Ind.*, 1954, 1264.) Reserpiline was isolated by subjecting the fraction remaining, after the crystallisation of *py*-tetrahydroserpentine, to a 24-plate countercurrent distribution employing benzene-0·25M acetate buffer (*p*H 4·3) as the solvent system. It was purified *via* its crystalline oxalate. The base has the empirical formula $C_{23}H_{28}O_5N_2$, equivalent weight 410, $[\alpha]_D^{24^\circ C.} = -38 \pm 4^\circ$ (c, 1·0 in ethanol). The infra-red spectrum shows free NH absorption at 3·0 μ and strong bands at 5·99 and 6·20 μ indicating the presence of a CH_3—O—CO—C=C—O system. Reduction with lithium aluminium hydride and the infra-red spectrum of the product gave support for the presence of the above chromophore. The ultra-violet spectrum of reserpiline, and the reduction product, besides showing diminished absorption in the region of 250 mμ due to the reduction of the CH_3—O—CO—C=C—O-chromophore, was identical with that of 2:3-dimethyl-5:6-dimethoxyindole. A tentative structural formula for reserpiline is proposed. A. H. B.

ANALYTICAL

Ergot, Assay of. E. Graf and E. Neuhoff. (*Arzneimit.-Forsch.*, 1954, **4**, 397.) The method of separation is based on distribution chromatography. The buffered column is prepared from silica gel (Merck), which is ground, sieved (0·15 mm. mesh) and dried for 3 hours at 120° C. The hot powder is bottled, and after cooling is rubbed down thoroughly with 7 per cent. of water: 20 g. of the powder is then rubbed down with 10 ml. of phosphate-citrate buffer of *p*H 7 (Sorensen), the gel being added in small portions. This mixture should only be kept for a few days. For the assay, 0·5 g. of powdered ergot (0·30 mesh), which need not be defatted, is rubbed down with 1 ml. of concentrated ammonia, followed by 2 ml. of methanol, then 5 g. of the silica gel preparation (without buffer) is added. The chromatograph tube (2 cm. diam.) is filled with 5 g. of the buffered gel, which is tapped down, followed by the ergot-silica gel mixture. It is then percolated with 120 to 150 ml. of chloroform-trichlorethylene (1:1) under slight suction at 1 to 2 drops per second. A narrow yellow zone is allowed to pass through the column, and the receiver is changed. Elution is continued with the rest of the solvent until all blue fluorescence has passed through. Solvent is removed from the two eluates *in vacuo*, and the residues are dissolved each in 2 ml. of methanol and mixed, the first one with 25 ml. and the second with 10 ml., of 5 per cent. solution of tartaric acid. After a brief warming, and cooling again, the solutions are defatted by shaking with 50 ml. of ether-light petroleum (1:9), this extraction being repeated. To 5 ml. of the solution is added 10 ml. of metaldehyde reagent, prepared by dissolving 0·1 g. of metaldehyde in a cooled mixture of 35 ml. of water and 65 ml. of sulphuric acid. After 30 minutes the absorption is measured at 590 mμ. The determinations are standardised against pure ergometrine and ergotamine respectively. It is claimed that this metaldehyde reagent is more specific and sensitive than the reagents previously used. G. M.

***Rauwolfia serpentina*, Determination of Alkaloids in.** L. Hörhammer and S. B. Rao. (*Arch. Pharm. Berl.*, 1954, **287**, 75.) About 3 g. of the powdered drug is extracted in a Soxhlet with 95 per cent. ethanol. After removal of the ethanol, the residue is extracted repeatedly with 20 ml. portions of hot water until a test with Mayer's reagent is negative. The filtered aqueous extracts are made alkaline with ammonia and extracted with 4 × 20 ml. of chloroform. The chloroform solution is washed with 10 ml. of water, filtered and evaporated, and the residue dried to constant weight. The results obtained compare with those given by the method of the Indian Pharmaceutical Codex 1953, but the new method is considerably quicker. G. M.

Sulphates, Titrimetric Determination of. J. S. Faber. (*Pharm. Weekbl.*, 1954, **89**, 705.) A suitable quantity of the sulphate (about 1 milliequivalent of SO_4) is dissolved in 40 ml. of water and 2 ml. of ammonia-ammonium chloride buffer solution (*p*H 10) is added. After heating to 50° C., the mixture is titrated with 0·1N disodium ethylenediaminetetra-acetate using eriochrome black T as indicator, to a blue end-point. After the addition of 3 ml. of 4N hydrochloric acid, the mixture is brought to the boil and treated with 25 ml. of 0·1N barium chloride solution. After heating gently for 5 minutes, and allowing to stand for 5 minutes, 0·1 g. of magnesium dipotassium ethylenediaminetetra-acetate is added, and the excess of barium is titrated with 0·1N ethylenediaminetetra-acetate until the colour is blue: 10 ml. of 0·1N magnesium chloride is added and the titration is continued until the colour has again become blue. The percentage of base (e.g., magnesium) may be calculated from the first titration; that of sulphate from the 25 ml. of standard barium chloride solution plus 10 ml. of standard magnesium chloride solution minus the second titration. G. M.

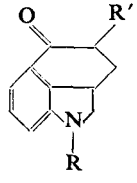
GLYCOSIDES, FERMENTS AND CARBOHYDRATES

Dextran, Depolymerisation of, in Non-aqueous Solutions. E. Hultin and L. Nordström. (*Acta chem. scand.*, 1954, **8**, 1296.) It was found that dextran could be successively depolymerised by alcoholysis in organic solvents with free hydroxyl groups. The monovalent aliphatic alcohols were poor solvents for dextran. However, at temperatures above 140° C., dextran dissolved rapidly in polyvalent alcohols, e.g., ethylene glycol, glycerol and sorbitol. The dextran slowly reacted with the solvent, but when the solution was heated to a higher temperature (up to about 200° C.), or if a small quantity (about 0·1 to 1 per cent.) of an acid catalyst (phosphoric acid, trichloroacetic acid or acid sodium sulphate) was added the reaction proceeded more rapidly. Dextran reacted with phenols, e.g. resorcinol, in the same way. The depolymerisation reaction can easily be followed by measuring the viscosity of samples taken out at intervals, as the intrinsic viscosity of dextran is approximately proportional to its average molecular weight. By controlling temperature, catalyst and time in carrying out the alcoholysis, it is possible to obtain dextran glycosides with any desired average molecular weight. The dextran glycosides can be fractionally precipitated. By a partial depolymerisation of dextran in glycerol solution, and fractionation of the reaction products to give a preparation with an average molecular weight of about 70,000, a product was obtained which proved to be excellent for the manufacture of blood plasma substitute. A. H. B.

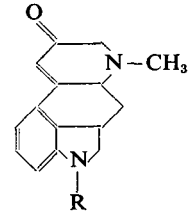
Digitalis and Strophanthus Glycosides, Dinitrobenzoic Acid Reaction of. J. A. C. van Pinxteren and A. L. O. M. Smithuis. (*Pharm. Weekbl.*, 1954, **89**, 741.) The increase in extinction observed after digitalis and strophanthus glycosides are boiled with hydrochloric acid in ethanol, and then subjected to the 3:5-dinitrobenzoic acid reaction, is the result of conversion of the glycosides into anhydro or dianhydro compounds with the disappearance of the hydroxyl groups in positions 14 or 14 and 16. The hydroxyl group is responsible for the lower molar extinction of the original glycosides. The difference in behaviour between the two groups of glycosides is probably due to *cis-trans*-isomerism with respect to the hydroxyl group in position 14 and the lactone ring in position 17. G. M.

ORGANIC CHEMISTRY

Lysergic Acid and Ergonovine, Total Synthesis of. E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, R. G. Jones and R. B. Woodward. (*J. Amer. chem. Soc.*, 1954, **76**, 5256.) An outline of the first total synthesis of lysergic acid is recorded. The reaction of *N*-benzoyl-3-(β-carboxyethyl)-dihydroindole with thionyl chloride, followed by aluminium chloride, gave (I, R = $-COC_6H_5$, R′ = H) which

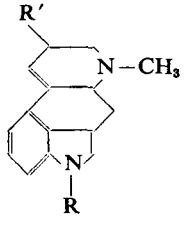


I

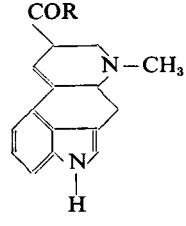


II

was brominated to give (I, R = $-COC_6H_5$; R′ = Br). The bromo-derivative was converted to (I, R = COC_6H_5; R′ = $-N(CH_3)CH_2C(CH_3)OCH_2CH_2O$) by reaction with methylaminoacetone ethylene ketal, and hydrolysis of this compound yielded the diketone (I, R = H; R′ = $-N(CH_3)CH_2COCH_3$) which, on treatment with sodium methoxide gave the tetracyclic ketone (II, R = H). Acetylation of the ketone afforded (II, R = $COCH_3$) which on reduction with sodium borohydride gave the alcohol



III



IV

(III, R = $COCH_3$, R′ = OH). The hydrochloride of the latter was treated with thionyl chloride followed by sodium cyanide in liquid hydrogen cyanide to give the nitrile (III, R = $-COCH_3$; R′ = $-CN$). Methanolysis of the nitrile gave the ester (III, R = H; R′ = $COOCH_3$). Alkaline hydrolysis of the latter, followed by catalytic dehydrogenation in water using a deactivated

Raney nickel catalyst gave (±)-lysergic acid (IV, R = $-OH$). The synthetic (±)-lysergic acid was converted to the corresponding ester by means of diazomethane and thence with hydrazine to (±)-*iso*lysergic acid hydrazide (IV, R = $-NHNH_2$). Both the acid and hydrazide were identical with the corresponding sample derived from natural ergot alkaloids in melting point, mixture melting point, ultra-violet spectrum, infra-red spectrum, paper chromatographic behaviour and X-ray diffraction pattern. A. H. B.

BIOCHEMISTRY

BIOCHEMICAL ANALYSIS

Gentisic and Salicylic Acids, Determination of, in Blood. R. Rutkowski. (*Arzneimit.-Forsch.*, 1954, **4**, 453.) Gentisic acid may be determined in presence of salicylic acid by the following method: 0·5 ml. of serum is treated with 0·5 ml. of hydrochloric acid and, after 10 minutes, with 1 ml. of 20 per cent. solution of trichloracetic acid. After a further 10 minutes, the mixture is made up to 10 ml. and filtered: 5 ml. of the filtrate plus 1 drop of *p*-nitrophenol solution is neutralised with ammonia, acidified slightly with sulphuric acid and treated with 0·1 ml. of 2·5 per cent. solution of ferric chloride. After 5 minutes 0·1 ml. of 4 per cent. solution of potassium fluoride is added, followed by 1 ml. of 0·25 per cent. solution of *o*-phenanthroline. After 18 hours the gentisic acid is determined colorimetrically at 480 mμ against standard solutions. It is essential to allow for a blank determined at intervals on the same serum plus the reagents. For the determination of gentisic acid with salicylic acid, 0·5 ml. of the serum is treated with 1 ml. of trichloracetic acid solution, and filtered: 5 ml. of the filtrate is treated with 0·2 ml. of caustic soda solution and, after 1 hour, with 0·5 ml. of Folin and Ciocalteu reagent and about 3 ml. of water. The mixture is made alkaline with 0·6 ml. of sodium hydroxide and, after 20 minutes, the blue colour is determined colorimetrically at 540 mμ. A further method for the determination of gentisic acid uses the green colour obtained with Folin and Ciocalteu reagent in acid solution. For a 1 cm. cell, the concentrations (c) are calculated from the formula $E = 20 \times 10^{-6} \times k \times c + E$ (blank), where k has the following values:—

Method	Substance determined	k
o-Phenanthroline	gentisic acid	$1{\cdot}6 \times 10^2$
Folin–Ciocalteu reagent (blue colour)..	salicylic acid	$5{\cdot}77 \times 10^2$
do. (green colour)	gentisic acid	$2{\cdot}2 \times 10^2$
do. (blue colour)	gentisic acid	$1{\cdot}2 \times 10^2$

G. M.

Phenylbutazone in Blood, Estimation of. D. G. Moss. (*J. clin. Path.*, 1954, **7**, 344.) The method is based on the hydrolysis of phenylbutazone to benzidine with sulphuric acid and the subsequent coupling of the benzidine with *n*-sulphatoethyl-*m*-toluidine. One ml. of serum is added to 4 ml. of acetone in an 8 ml. glass-stoppered centrifuge tube, well shaken, set aside for 30 minutes and then centrifuged. Duplicate portions of 1 ml. of the supernatant solution are removed and transferred to conical graduated 10 ml. centrifuge tubes. A duplicate standard is also set up using 1 ml. of standard phenylbutazone solution. The bulk of the acetone is now cautiously evaporated in a hot water bath, N sulphuric acid 1 ml. is added to each tube and they are placed in a water bath for four hours. At half-hourly intervals distilled water is added to maintain a volume of 1 ml. in each tube. The tubes are now placed

in ice water and 0·5 ml. of ice cold sodium nitrite solution, and 2 ml. of *n*-sulphatoethyl-*m*-toluidine added. The purple colours are allowed to develop for 30 minutes at room temperature. Turbidity is removed by the addition of 0·2 ml. of light petroleum (40 to 60°), shaking and centrifuging. Three ml. of the aqueous phase is removed and read in a spectrophotometer at 525 mμ, or in a colorimeter with the appropriate filter. The standards correspond to serum level of 15 mg./100 ml. From a series of 50 estimations the average error was ± 3 per cent. Examination of the distribution of phenylbutazone showed only traces to be present in the red cells. G. F. S.

Progesterone in Human Blood and Tissues. J. Zander. (*Nature, Lond.*, 1954, **174**, 406.) A sensitive micromethod for the estimation of progesterone has been used to investigate the progesterone content of human peripheral blood. Progesterone was extracted from the blood, partitioned between solvents, isolated by paper chromatography and determined by measurements of its ultra-violet absorption spectrum. Definitive identification of the product measured was carried out with colour tests, infra-red spectra and also ultra-violet absorption in sulphuric acid. In this way concentrations as low as 0·05 μg./ml. of blood may be determined. The blood samples examined were taken from the cubital vein of women from the sixth month of pregnancy onwards. The presence of progesterone in these samples at an average concentration of 0·078 μg./ml. was definitely established. Concentrations ranging between 0·020 and 0·151 μg./ml. were observed. The method was used to study the speed of elimination of progesterone from human blood. The concentration of progesterone in the placenta, corpora lutea, corpus luteum cysts and follicle cysts was also investigated. A high concentration of progesterone was detected in a mature Graafian follicle immediately before ovulation. J. B. S.

CHEMOTHERAPY

Natural Constituents of the Body, Chemotherapeutic Experiments with. H. Meyer-Döring. (*Nature, Lond.*, 1954, **174**, 555.) The preparation of cysteylascorbic acid is described. Its purification has only been partly successful though both physical constants and analytical data are given. The following were examined for their action on intraperitoneal pneumococcal infections of the mouse: (1) an equimolecular mixture of cysteine hydrochloride and sodium ascorbate, (2) the residue obtained by evaporating an equimolecular mixture of cysteine hydrochloride and sodium ascorbate, (3) the same product stirred with light petroleum for several hours, (4) cysteine hydrochloride, (5) the first residue obtained from the synthesis of cysteylascorbic acid, and (6) the residue obtained by evaporating the final solution after precipitation of the cysteyl-ascorbic acid with ether, (7) cysteyl ascorbate. The latter, only, gave a large measure of protection, and against one particular strain of *pneumococcus* at concentrations as low as 5 mg./ml. *In vitro* cysteinylascorbic acid inhibited the growth of the *pneumococcus* employed down to a concentration of 450 μg./ml. as compared with inhibitory concentrations of aureomycin and streptomycin of 25 to 250 μg./ml. Cysteinylascorbic acid guaranteed the survivial of mice infected with *Staph. aureus* (penicillin resistant) at concentrations of 0·075 mg./ml. Preliminary experiments with *Streptococcus* and *Escherichia coli* indicated a similar degree of chemotherapeutic activity. The ultra-violet absorption spectrum and polarographic analysis suggest that cysteinylascorbic acid is a cysteyl ester of ascorbic acid, the attachment of the cystine residue being at C_2 or C_3. J. B. S.

_iso_Nicotinyl Hydrazones as Antitubercular Agents and Derivatives for the Identification of Aldehydes and Ketones. P. P. T. Sah and S. A. Peoples. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 513.) Of 106 aldehydes and ketones treated with *iso*nicotinyl hydrazide, 93 yielded crystalline *iso*nicotinyl hydrazones suitable for identification purposes. Melting points are given. The majority of the derivatives were obtained by dissolving *iso*nicotinyl hydrazide in warm water, heating with a slight excess of aldehyde or ketone dissolved in ethanol and allowing to stand for 24 to 72 hours, when crystals of the *iso*nicotinyl hydrazone separated. Volatile aldehydes and ketones were shaken with *iso*nicotinyl hydrazide, allowed to stand, the solvent evaporated and the residue recrystallised. Hydrazones which did not crystallise readily were converted into their hydrochlorides and recrystallised from dehydrated ethanol. A large number of *iso*nicotinyl hydrazones, when tested in mice, were at least as active antitubercular substances as isoniazid, and were less toxic than the parent substance. The most active compounds were derived from D-galacturonic acid, D-glucuronolactone, 2-hydroxy-5-chlorobenzaldehyde, salicyldieneacetone, 4-methoxybenzalacetone, salicylaldehyde, 4-methoxypropiophenone and 4-diethylaminobenzaldehyde. The addition of 0·05 per cent. to the diet of mice infected with *Mycobacterium tuberculosis* H37Rv for 4 to 5 weeks prevented death and cured the disease, as shown by autopsy. G. B.

PHARMACY

NOTES AND FORMULÆ

Complex Formation between Macromolecules and Pharmaceuticals. T. Higuchi and R. Kuramoto. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 393, 398.) Complex formation was assessed by a method involving dialysis and, in the case of phenobarbitone, by a solubility method in addition. A solution of polyvinylpyrrolidone containing a proportion of the drug under study was placed in a thin sausage casing and tied in so as to prevent excessive imbition of water. The casing was placed in a solution containing the same concentration of the drug in water at 0° C., and agitated so as to achieve equilibrium rapidly. Any increase in the concentration of drug in the polyvinylpyrrolidone solution was interpreted as indicating the formation of a complex. The analyses were carried out by measuring the spectrophotometric absorption at wavelengths where the absorption due to polyvinylpyrrolidone could be neglected, or by titration. The following decreasing order of complex formation with polyvinylpyrrolidone was established: sulphathiazole, 3-hydroxybenzoic acid, 4-hydroxybenzoic acid, 4-aminosalicylic acid, salicylic acid, phenobarbitone, benzoic acid, sodium salicylate, mandelic acid and chloramphenicol. The presence of carboxylic, phenolic or amino groups appeared to lead to association with the polymer. The introduction of polar groups into benzoic acid increased the tendency for complex formation, which may be due to interaction between dipoles, involving the amido groups of the polyvinylpyrrolidone. There is a marked similarity between complex formation with polyvinylpyrrolidone and with caffeine. Complex formation was not observed with procaine hydrochloride, benzylpenicillin, caffeine, theophylline and cortisone. G. B.

Hexylcaine Hydrochloride (Cyclaine Hydrochloride). (*New and Nonofficial Remedies, J. Amer. med. Ass.*, 1954, **155**, 908.) Hexylcaine hydrochloride is 1-*cyclo*hexylamino-2-propyl benzoate hydrochloride, $C_6H_5.CO_2.CH(CH_3).CH_2.NH.C_6H_{11},HCl$, and occurs as a white, bitter, slightly aromatic powder, m.pt. 182° to 184° C., freely soluble in ethanol and chloroform, almost insoluble in

ether, and soluble in about 16 parts of water at 25° C.; *p*H of a 5 per cent. solution, 4·1 to 4·7. When treated with trinitrophenol and a few drops of sulphuric acid, it yields a picrate melting at 129° to 133° C. A 0·001 per cent. w/v solution in 0·1 N hydrochloric acid exhibits an ultra-violet absorption maximum at about 232mμ ($E^{1\text{ per cent.}}_{1\text{ cm.}}$, about 422). A solution of 1 g. in 25 ml. of water requires not more than 0·5 ml. of 0·02 N sodium hydroxide for neutralisation to methyl red. Hexylcaine hydrochloride contains not more than 30 p.p.m. of heavy metals and yields not more than 0·05 per cent. of residue on ignition; the loss in weight on drying *in vacuo* over phosphorus pentoxide for 4 hours does not exceed 0·1 per cent. It contains 95 to 105 per cent. of hexylcaine hydrochloride, when assayed spectrophotometrically by measuring the absorption of a 0·001 per cent. w/v solution in 0·1 N hydrochloric acid at 232 mμ. It also contains 11·7 to 12·1 per cent. of chloride, determined by the addition of an excess of silver nitrate and titration with ammonium thiocyanate. Hexylcaine hydrochloride is a soluble local anæsthetic. G. R. K.

Hydrocortisone (Cortef, Hydrocortone). (*New and Nonofficial Remedies, J. Amer. med. Ass.*, 1954, **155**, 442.) Hydrocortisone, 11-hydroxycorticosterone, is a white, odourless powder, m.pt. 215° to 220° C. with decomposition, freely soluble in dioxan and methanol, very slightly soluble in ether and water, and soluble 1 in 50 in ethanol and 1 in 250 in chloroform. When treated in ethanolic solution with a saturated solution of 2:4-dinitrophenylhydrazine in hydrochloric acid, it yields a red precipitate (cortisone acetate and hydrocortisone acetate yield reddish-orange precipitates). It crystallises from ethanol in rectangular crystals (cortisone acetate crystallises in slender rods, and hydrocortisone acetate in triangular prisms). A solution in sulphuric acid is brownish-red by transmitted light and shows a strong yellowish-green fluorescence by reflected light (cortisone gives a yellowish solution without fluorescence). Specific rotation of a 0·5 per cent. w/v solution in methanol, + 160° to + 170°; loss in weight on drying at 105° C. for 4 hours, not more than 1·0 per cent. It contains 95·0 to 105·0 per cent. of hydrocortisone, when assayed spectrophotometrically by measuring the absorption of a 0·001 per cent. w/v solution in methanol at 242 mμ ($E^{1\text{ per cent.}}_{1\text{ cm.}}$, 242 mμ, about 445). G. R. K.

Tetracycline Derivatives, Stability of. N. Å. Diding and N. Sterner. (*Svensk farm. Tidskr.*, 1954, **58**, 745.) A comparative investigation of the stability of tetracycline, oxytetracycline and chlortetracycline was made, using a modified turbidimetric method and an agar plate method for the assays. In horse serum both tetracycline and oxytetracycline suffered no appreciable loss after 24 hours at 37° C. Chlortetracycline lost 60 per cent. of its strength. In buffered solution tetracycline lost only 8 per cent. after 7 days at 20° C., but 68 per cent. at 37° C. Comparative stabilities at *p*H 6 are shown in the table below:—

	Strength (mg./ml.)	Days at 37° C.			
		1	2	3	7
		Percentage activity found			
Tetracycline	1000	85	63	43	29
	10	84	64	58	54
Oxytetracycline	1000	49	58	43	28
	10	53	55	32	<10
Chlortetracycline	1000	34	16	10	<10
	10	35	28	14	<10

Thioglycollic acid had no stabilising effect on tetracycline at *p*H 6·0. G. M.

PHARMACOGNOSY

***Datura innoxia*, Miller, Influence of Various Factors on Alkaloid Production.** H. Flück and A. Nisoli. (*Ann. pharm. franç.*, 1954, **12**, 250.) The experiments reported in this paper were carried out over a period of two years. Four collections were made each season and precautions were taken to ensure that each collection really represented the stage of growth at which it was collected. As a result it was shown that, while the addition of nitrogenous fertilisers increased the alkaloidal content of collections made early in the season, it had no effect on collections made later; in fact the latter showed a higher alkaloidal content when no fertilisers had been used. The authors concluded that these results were due to the effect of fertilisers in hastening floration and fruit setting; after fruit was set the alkaloidal content diminished. Accordingly they removed the flowers and young fruits from certain plants, as they appeared, and found that the deflorated plants continued to make new leafy growth and that the percentage of alkaloids continued to increase. This dual effect resulted in a very large increase of alkaloid production per acre. Variation in the spacing of the plants played no part in alkaloid production. The proportion of hyoscine to hyoscyamine was not significantly altered in any of the samples treated as described in the paper. J. W. F.

Ergot, Culture of, on Tetraploid Rye. J. Deufel. (*Arch. Pharm. Berl.*, 1954, **287**, 329.) A comparison of the yields of ergot obtained from diploid and from tetraploid rye, grown side by side, showed important differences. These results are summarised in the table below.

Type of rye	No. of ears per sq. m.	Weight in g./m.²		No of sclerotia/m.²	
		Primary	Secondary	Primary	Secondary
2*n*	258	4·2	4·0	52·5	53·3
4*n*	258	11·4	17·5	57·0	86·5

With the tetraploid rye the secondary infection was thus considerably increased, while the size of the individual ergots was also much greater. There was little difference in alkaloidal content; the 2*n* plant gave 0·25 per cent., and the 4*n* 0·28 per cent. Thus the yield of alkaloids per square metre was increased by approximately 3 times. Actually, the 4*n* ergot, with a mean length of 20 to 40 mm. and mean diameter of 4 to 8 mm., was too large to comply with the requirements of the German Pharmacopœia. G. M.

Isoniazid, Effect of, on Higher Plants. D. J. Wort. (*Science*, 1954, **120**, 72.) The effect of isoniazid on higher plants was investigated by treating bush beans, sugar beets, buckwheat and spring oats with solutions of various strengths in the following ways: spraying the aerial parts of the plant, immersing a leaf for 30 seconds, immersing a leaf after removal of the upper epidermis, and applying the solutions to the soil in which the plants were growing. Solutions containing 0·4 per cent. or more, however applied, stunted the growth of each of the plants. Buckwheat was the most sensitive plant tested and was the only plant to be killed by treatment of abraded leaves with 1·2 or 1·6 per cent solutions. All the plants were killed by watering the soil with a 1·6 per cent. solution. Flowering occurred in all the surviving plants but was delayed 3 to 7 days. There was a considerable drop in photosynthesis and in catalase activity. The effects differ in several respects from those produced by maleic hydrazide. H. T. B.

PHARMACOLOGY AND THERAPEUTICS

Adrenaline, Assay of, using the Hexamethonium-treated Cat. G. F. Somers. (*Analyst*, 1954, **79**, 627.) A suitable alternative to using a spinal cat for the assay of adrenaline, based on its vasopressor action, is a chloralosed cat given hexamethonium. This drug blocks the autonomic ganglia, thus lowering the blood pressure and cutting out compensatory mechanisms, thereby increasing the sensitivity to adrenaline. Using hexamethonium-treated cats and the standard 4-point assay method, an accuracy can be obtained which, although not quite so high as with spinal cats, is of a sufficient standard for most purposes. M. M.

Adrenal Medulla, Analysis of Granules in. N. Hillarp and B. Nilson. (*Acta physiol. scand.*, 1954, **32**, 11.) The specific fraction of the adrenal medulla of the cow, containing the granules in which the sympathomimetic amines are held, is analysed for adrenaline and noradrenaline, total lipids, phospholipids, fatty acids and cholesterol. M. M.

Adrenergic Blocking Drugs, Modification of Traumatic Shock by. E. Levy, W. North and J. Wells. (*J. Pharmacol.*, 1954, **112**, 151.) Traumatic shock in rats is produced by placing them in a rotating drum. Although no rats die during the treatment, most die within 24 hours and the percentage mortality is related to the number of turns of the drum. If the rats are pretreated with adrenergic blocking drugs such as dibenzyline, dihydroergotamine, piperoxane or tolazoline the mortality is significantly reduced but also a significant number die during the period of producing the trauma. If these drugs act by virtue of their adrenergic blocking properties it seems that the sympathetic discharge is a protective mechanism during the trauma but that it initiates other processes which are eventually detrimental to survival. M. M.

Anthrax, Experimental, Cause of Death in. H. Smith, J. Keppie, J. M. Ross and J. L. Stanley. (*Lancet*, 1954, **267**, 474.) Guinea-pigs were infected intradermally with a dose of anthrax spores sufficient to kill all the animals in $3\frac{1}{2}$ days. In the 12 hours preceding death the number of organisms in the blood rose from about $0{\cdot}3 \times 10^6$ to $1{\cdot}0 \times 10^9$ chains per ml. For a few hours after the initial invasion of the blood stream streptomycin injection saved the animals, but when the bacteræmia exceeded about 3×10^6 chains per ml., which occurred about 8 hours before the guinea-pigs would otherwise have died, streptomycin failed to save the animals although it promptly terminated the infection. The observations were therefore made during the final 10 hours when the major physiological changes occur. The blood pressure fell from 84 to 10 per cent. of the normal value between 9 hours to less than $\frac{1}{2}$ hour before death. The bleeding volume was 33 per cent. of normal. There was a reduction of 25 to 40 per cent. in the circulating blood volume, and a 10 to 20 per cent. hæmoconcentration. Plasma-protein nitrogen decreased by 30 per cent. and there was much œdema and hæmorrhage. Rectal temperatures dropped from 99° to 88° F. in the last 6 hours and from 90° to 80° F. in animals treated with streptomycin after the critical point. Plasma inorganic phosphate rose $2\frac{1}{2}$ times and whole blood organic phosphate rose 13 per cent. The plasma *p*H was low; there were reductions in the sodium, carbonate and chloride contents and rises in the potassium, magnesium and calcium. Plasma glucose rose by 20 per cent. in the early stages of the final bacteræmia and fell by 20 per

cent. about 1½ hours before death. Determinations of non-protein nitrogen and of urea showed evidence of acute renal failure. Animals given streptomycin after the critical point developed anuria. Alkaline phosphatase in the plasma determined 1½ hours before death was exceptionally high at 191 units/100 ml. as compared with a normal value of 6·3 units/100 ml. No liver abnormality was found, but high concentrations of alkaline phosphatase in the urine suggested that the kidneys were the source of the enzyme although on histological examination the kidneys showed an over-all reduction. There was considerable tubular damage. A concentrate of the specific lethal factor in the plasma of guinea-pigs dying of anthrax kills mice and guinea-pigs and produces an œdematous lesion in the skin of guinea-pigs. Hyperimmune horse serum prepared in the horse from an avirulent strain of *Bacillus anthracis* neutralises the lethal factor, which does not appear to be connected with the capsule of the organism. It is possible that the protective antigen is a "toxoid" form of the lethal factor. H. T. B.

Chlorpromazine, Action of, on the Circulation. C. A. Foster, E. J. O'Mullane, P. Gaskell and H. C. Churchill-Davidson. (*Lancet*, 1954, **267**, 614.) A study was made of the action on the circulation of chlorpromazine, dimethylaminopropyl-*N*-chlorophenothiazine hydrochloride, which is used to reduce metabolism and guard against the shock syndrome. 10 conscious male volunteers and 12 anæsthetised patients were given an intravenous drip of saline or 5 per cent. dextrose and after at least 30 minutes 5 to 50 mg. of chlorpromazine was addded. Blood pressures and pulse rates were determined before and after the drug was given. Usually the blood pressure fell and the pulse rate rose, but the extent of the changes was variable and unpredictable. Doses as small as 5 to 10 mg. reduced the blood pressure by as much as 25 per cent. in patients over 60. The hypotension passed off in 4 to 6 hours and had no ill effects. A feeling of lethargy occurred for 6 to 8 hours after administration and there was bilateral ptosis and meiosis but the face was still capable of sweating. In the conscious patients the blood flow in the hand, forearm and calf was measured by venous-occlusion plethysmography, being expressed as ml./100 ml. of limb/minute. The resistance was determined as the ratio of the mean blood pressure to the blood flow. With a dose of 25 mg. of chlorpromazine the average blood flow in the hand increased from 5·9 ml. to 22·9 ml.; increases of 72 per cent. occurred in the forearm and calves. There were large decreases in the resistance. Determinations of the blood flow in the hand when the drug was infused into the brachial artery showed that there was a local vasodilator action on the blood vessels of the hand but the effect when the chlorpromazine was present in the general circulation was much greater, showing that in addition to the peripheral action there is a central inhibitory action on vasomotor tone. A rise in blood flow in the hand was produced by intravenous doses of 25 to 50 mg. after blocking the brachial plexus on one side, thus producing complete muscular paralysis on that side and releasing all vasoconstrictor tone, suggesting that the local action is in part due to direct action on the arterial muscle. In anæsthetised patients the intravenous administration diminished the pressor action of noradrenaline and prevented the occurrence of bradycardia. No definite evidence was obtained that chlorpromazine blocked the action of noradrenaline on the vessels of the hand. Intra-arterial injection of chlorpromazine reduced the vasoconstrictor action of intra-arterial injection of adrenaline, while intravenous injection reversed the action of adrenaline. Noradrenaline rather than adrenaline is recommended to restore blood pressure in cases of excessive hypotension due to chlorpromazine. H. T. B.

Chlorpromazine, Clinical Studies of its Anti-emetic Properties. J. H. Moyer, B. Kent, R. W. Knight, G. Morris, M. Dizon, S. Rogers and C. Spurr. (*J. Amer. med. Sci.*, 1954, **228**, 174.) In this study the anti-emetic properties of chlorpromazine were evaluated in 306 patients in whom vomiting was a definite therapeutic problem arising from drug administration, from infections or toxicosis, from diseases of the cardiovascular and gastro-intestinal systems, and from a variety of miscellaneous conditions. The drug was given in 10, 25 or 50 mg. doses, either by the oral or intramuscular route, the dose being repeated at varying intervals as frequently as necessary in order to control the symptoms. The initial dose was usually given intramuscularly, and subsequent doses orally. The results of the treatment were as follows: Excellent (vomiting stopped and nausea completely relieved) 215; good (vomiting stopped but slight nausea remaining) 57; fair (vomiting stopped but nausea continued) 20; failure 14. The chief side-reactions were sedation (144), dizziness (73), dryness of mouth (57), tachycardia (42), hypotension (38). In order to avoid dizziness and orthostatic hypotension, the initial dose or two should probably be administered to the patient in a reclining position. The sedative and analgesic properties of barbiturates and opiates were markedly enhanced in those patients who previously had received chlorpromazine. Patients with renal and hepatic failure appeared to experience greater sedation from chlorpromazine. During the course of these studies 10 patients were treated for intractable hiccough. The hiccough was arrested within 20 minutes after intramuscular injection of 25 mg. of chlorpromazine in 6, after the second dose in an additional 2 patients, and in two patients the drug was ineffective. S. L. W.

Chlorpromazine in the Treatment of Mental Syndromes. H. Azima and W. Ogle. (*Canad. med. Ass. J.*, 1954, **71**, 116.) 100 unselected patients with mental syndromes (neuroses, schizophrenia and manic depressive psychoses) were treated with an average dose of 400 mg. of chlorpromazine daily for an average period of 3 weeks. In 75 per cent. with neurotic anxiety states there was moderate to marked improvement; in 70 per cent. of cases the anxiety state returned shortly after the sudden interruption of chlorpromazine. No favourable response was noted in cases of obsessive-compulsive and mixed border-line psychoneuroses. Favourable results were seen in cases of drug addiction (4). In all non-excited schizophrenics no particular effect was observed. In all excited, impulsive, tense and anxious schizophrenics a moderate reduction of these symptoms appeared, associated with better behaviour. Out of 5 cases of mania, 3 recovered completely but 2 remained partially refractory. In 5 cases of agitated depression and 3 of anxious and tense depression moderate improvement was noted, though the symptoms returned after cessation of the drug. Toxic effects occurred in 17 patients; there were 5 cases of maculo-papular rash, 4 of Parkinson-like syndrome and 8 of toxic hepatitis. Chlorpromazine is a useful therapeutic tool in the management of some mental disorders, especially in excited states and for the relief of anxiety and tension. S. L. W.

Curare Agents, Quaternary Salts of 2:4:6-(Dialkylaminoalkoxy)-1:3:5-Triazines and 2:4-(Dialkylaminoalkoxy) Quinazolines as. J. R. Hohmann and J. W. Jones. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 453.) 2:4-(Dialkylaminoalkoxy)quinazolines were obtained by reaction of the corresponding sodium aminoalkoxide with 2:4-dichloroquinazoline in benzene solution. Quaternization of the side-chain amino groups was accomplished by heating under a reflux condenser with a solution of methyl iodide in dehydrated

ethanol. 2:4:6-(Dialkylaminoalkoxy) 1:3:5-triazines were prepared by reaction of the required sodium aminoalkoxide with cyanuric chloride in benzene solution. Quaternary salts were obtained by reaction with ethyl or methyl iodide. When tested in chicks, the quaternary salts caused the flaccid paralysis associated with a pachycurare type of blocking action. The most powerful curarising agent in these series was 2:4:6-(β-diethylaminoethoxy) 1:3:5-triazine tribenzchloride. This substance was about twice as active as gallamine triethiodide by the mouse sloping screen test and 7 times as active by the rabbit head-drop method. Preliminary toxicity studies in mice are reported for this compound. The relationship of structure to activity in the series is discussed.

G. B.

Dieldrin, Pharmacology of. C. W. Gowdey, A. R. Graham, J. J. Seguin and G. W. Stavraky. (*Canad. J. Biochem. Physiol.*, 1954, **32**, 498.) Dieldrin, hexachloro-epoxy-octahydro-dimethanonaphthalene, is a new chlorinated insecticide closely related to aldrin. Its effects on the central nervous system have been studied in spinal and decerebrate cats and cats anæsthetised with chloralose-urethane. In all experiments it produced convulsions and greatly increased the excitability of the central nervous system to reflex stimulation and to intra-arterial injections of acetylcholine. In chloralosed cats 1·9 to 7·5 mg./kg. produced generalised convulsions but in decerebrate cats larger doses (15 and 28 mg./kg.) were required. Spinal preparations were less sensitive. In two intact rabbits doses of 1·25 to 6·0 mg./kg. produced strychnine-like convulsions. The convulsant effect of dieldrin in chloralosed cats was antagonised by pentobarbitone. An intra-arterial injection of 4 mg./kg. of dieldrin caused a marked augmentation of the knee jerks obtained by tapping the tendons of the two quadriceps muscles with electrical hammers, and also when reflexly stimulating the tibialis anticus muscle electrically through the ipsilateral posterior tibialis nerve. Dieldrin potentiated the action of acetylcholine on the central nervous system, as shown by the effects of close intra-arterial injections of acetylcholine on the quadriceps muscle. The effects were not due to an action of dieldrin on the muscle or motor-end-plate. Dieldrin also augmented the effect of acetylcholine on the cat's blood pressure and duodenal motility, and the effects were abolished by vagal section. Dieldrin did not alter the secretory effect or the vasodilatation produced by electrical stimulation of the chorda tympani on the isolated submaxillary gland, nor did it alter the response of the gland to acetylcholine. It was concluded that although dieldrin had a marked parasympathomimetic action, this effect was exerted through stimulation of the central nervous system mechanisms and not peripherally.

G. F. S.

Dimethylkynurenamine, Action of, on Blood Pressure. K. Makino and H. Takahashi. (*Science*, 1954, **120**, 544.) Dimethylkynurenamine has been prepared by the hydrogenation of dimethyl-*o*-nitrobenzoylethylamine in the presence of palladium charcoal. The m.pt. of the hydrochloride was 158 to 160° C., and the compound was recognised on paperchromatograms as a blue fluorescent spot showing with Dragendorff reagent a reddish-orange colour, with *p*-dimethylaminobenzaldehyde in hydrochloric acid an orange colour and with sulphanilic acid a yellow colour. Pharmacological studies showed the compound to have a powerful hypotensive action in anæsthetised rabbits in contrast to the hypertensive action of tryptamine and dimethyltryptamine to which it is closely related chemically.

G. F. S.

Levorphan in Anæsthesia. A. K. Brown. (*Brit. med. J.*, 1954, **2**, 967.) This paper describes the use of levorphan (dromoran) as a premedicant, and as a supplement to nitrous oxide and oxygen anæsthesia when given by continuous intravenous drip. For premedication, after subcutaneous injection, analgesia occurred in 20 minutes; was maximum in 1½ hours; and against very severe pain had a duration of 7 hours. Repeated doses showed a marked cumulative action, for after 4 mg., given in divided doses, analgesia could be maintained with 0·5 mg. every 12 hours. For premedication the standard dose was 2 mg., in some cases combined with 1/100 grain of atropine and others with 1/150 grain of scopolamine. The results of premedication were assessed before anæsthesia and compared with a series of patients given omnopon and scopolamine. Records were made of drowsiness, respiratory depression, nausea and amnesia. Sedation was achieved satisfactorily with levorphan alone in 22/30 cases. There was no difference in sedation to patients receiving omnopon and scopolamine. 23 per cent. of patients receiving levorphan alone were drowsy, which was increased to 57 per cent. with the addition of atropine and scopolamine from which it was concluded that levorphan had a slight hypnotic effect. Only 5 per cent. of the patients showed respiratory depression, which in all cases was mild. Nausea was present in 5 per cent. of the patients, but only severe in one. Levorphan showed no evidence of amnesia. When used as a continuous drip during nitrous oxide and oxygen anæsthesia respiratory depression occurred with adequate analgesia. G. F. S.

Liquorice Preparations in the Adrenalectomised Rat. W. E. Hassan Jr., J. F. Palumbo and F. Elmadjian. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 551.) Liquorice extract and various constituents of liquorice were administered orally to bilaterally adrenalectomised rats, and the results compared with the effect of deoxycortone acetate, injected in the form of an oily solution. Extract of Spanish liquorice, ammoniated glycyrrhizin and monoammonium glycyrrhizinate showed an activity similar to deoxycortone, increasing the retention of sodium and water with increasing dosage, while the potassium output remained substantially unchanged. Glycyrrhetinic acid, however, produced a fall in the K/Na ratio with increasing dosage, the substance increasing the retention of both potassium and sodium, the former to a greater extent than the latter. G. B.

Methylpentynol in Labour. G. Bourne. (*Lancet*, 1954, **267**, 522.) An elixir of methylpentynol was given to 100 patients in labour with a view to determining whether the drug has any detrimental effect on the woman or the child and whether it reduces apprehension. 100 controls, whose labours were conducted along the same lines as those of the treated women, were each given a dose of a mixture containing potassium bromide 30 grains chloral hydrate 30 grains and tincture of opium 15 minims. All cases received analgesics if requested, and gas and air analgesia unless contraindicated. The dose of methylpentynol was 0·5 to 1 g. at intervals of not less than 3 hours. When given early in labour methylpentynol calmed nervous patients and allowed them to relax to an extent previously thought impossible without sedation. An unusual degree of amnesia occurred in some cases. The drug has no analgesic effect. Most patients will sleep or feel like sleeping after a dose of 1 g. but if sleep is required a sedative should be given in addition. Its use with pethidine 100 to 150 mg. when labour is well established often enabled the patient to relax and co-operate well. Gas and air analgesia seemed to be more effective after methylpentynol had been given. The drug was especially effective

in patients admitted in labour. The average blood loss and post-partum hæmorrhage rate were high but they were also high in the controls and more experience is needed. No ill effects were noted in either the mother or the child. It is less helpful in cases which have been in labour for more than 20 hours.

H. T. B.

Nalorphine, Effect of, on the Toxicity of Morphine. C. M. Gruber, Jr. (*J. Pharmacol.*, 1954, **111**, 404.) A study of the antagonism of morphine by nalorphine in mice has shown that for a particular dose of morphine there is an optimum dose of nalorphine. The mice were injected subcutaneously, the dose of nalorphine being given 10 to 15 minutes after the morphine. As the dose of morphine increased the optimum dose of nalorphine decreased, and when the dose of nalorphine exceeded the optimum, toxicity was additive. Given alone, morphine was approximately twice as toxic as nalorphine, but when nalorphine and morphine were given together, in excess of the optimum dose, nalorphine and morphine were equally toxic. Morphine did not antagonise the toxic effects of nalorphine. G. F. S.

Nitrofurantoin in Urinary Infection. H. B. Hasen and T. D. Moore. (*J. Amer. med. Ass.*, 1954, **155**, 1470.) Nitrofurantoin, or *N*-(5-nitro-2-furfurylidene)-1-amino-hydantoin, is a yellow crystalline compound of bitter taste, which darkens on exposure to light or alkali. When administered to man about 40 per cent. is excreted in the urine, the remainder being apparently catabolised by various body tissues into inactive brownish compounds which may tint the urine. It is thought that the nitrofurans act by interfering with the enzymatic metabolism of the bacterial cell and that they retain antibacterial effectiveness in the presence of serum, pus and urine. Nitrofurantoin does not appear to be effective against viruses or fungi, but does appear effective against certain protozoa. Nitrofurantoin was used clinically in the treatment of 100 patients with urinary infections (23 acute cases and 77 chronic). The average period of treatment was 8·6 days in the acute infections and 14·7 days in the chronic infections. The dosage employed was 5 to 7 mg./kg./24 hours, or about 400 to 600 mg./day, given in 4 equal doses with meals and at bedtime with a glass of milk. Of the patients with acute infections, 22 (95·7 per cent.) were benefited, with a clinical and laboratory cure rate of 73·9 per cent. Of the chronic cases, 82 per cent. were benefited, with a clinical and laboratory cure rate of 20·8 per cent. The drug was most efficacious in *Proteus vulgaris* infections, and in refractory urinary infections due to the coli-ærogenes group, *Klebsiella pneumoniæ* and *Streptococcus fæcalis*. There was no evidence of toxicity to the kidney or the bone marrow. The side-effects consisted mainly of nausea in about one-fourth of the patients and vomiting in a few. S. L. W.

Noradrenaline, *N*-Substituted Derivatives of, as Bronchodilators. J. H. Biel, E. G. Schwarz, E. P. Springeler, H. A. Leiser and H. L. Friedman. (*J. Amer. chem. Soc.*, 1954, **76**, 3149.) Many compounds containing the 1-(3 : 4-dihydroxyphenyl)-2-aminoethanol skeleton, $(HO)_2C_6H_3CH(OH)CH(R)$-NHR' where R = H or alkyl and R′ = *n*-alkyl, branched alkyl, hydroxyalkyl, *cyclo*alkyl, *cyclo*alkyl-alkyl, aralkyl, substituted aralkyl and heterocyclic alkyl were prepared as potential bronchodilators. They were prepared by the condensation of chloroacetylcatechol with primary amines and subsequent catalytic reduction to the amino-alcohol. The compounds were screened for their broncholytic effect against histamine induced bronchoconstriction in the excised

(ABSTRACT *continued on page 224.*)