ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

***Punica granatum* L. Investigation of the Alkaloids of, by Partition Chromatography.** J. P. Wibaut, H. C. Beyerman and P. H. Enthoven. (*Rec. Trav. chim. Pays-Bas*, 1954, **73**, 102.) The analysis of two samples of commercial "pelletierine sulphate", and of an extract made of pomegranate bark, by means of partition chromatography on paper are described. The sulphates were converted to hydrochlorides and distributed on filter paper between water-*n*-butanol-hydrochloric acid mixtures. After air-drying of the chromatograms, the spots were developed with Dragendorff's reagent. Four (or five) spots were found, three of which had R_F values identical with those of synthetic pseudopelletierine, *dl-iso*pelletierine and *dl*-methyl*iso*pelletierine. It seems highly probably that extracts of *Punica granatum* L. contain one or two other alkaloids.

A. H. B.

ANALYTICAL

Allyl- and Thio-barbiturates, Determination of. R. L. Herd. (*J. Ass. off. agric. Chem. Wash.*, 1954, **37**, 209.) A rapid and convenient method for the determination and identification of some alkenyl barbiturates, either individually or in mixtures is given. When one constituent contains an allyl or *cyclo*pentenyl radical, either of these components can be determined quantitatively by bromination and the other calculated by difference. In addition the solubility of the bromo-derivative is such that it can be separated, purified by recrystallisation, and identified by the melting point. Tables of quantitative results and melting points of the bromoderivates are given. Thiobarbiturates can also be determined by a similar procedure the sulphur being oxidised to sulphate with standard bromine solution. Preliminary investigation demonstrated that the addition of free bromine to the allyl and *cyclo*pentenyl radicals was such as to permit direct titration of these barbiturates. Each of these radicals added two atoms of bromine; the thio-group in barbiturates reacted with eight.

R. E. S.

Barbituric Acids, Identification of, by X-ray Spectroscopy. R. Heiz and B. Jerslev. (*Dansk Tidsskr. Farm.*, 1954, **28**, 11.) X-ray spectra of 5:5-ethylallylbarbituric acids and diallylbarbituric acid are very similar, indicating a close relation in the crystal structure of the two subtances, and the two components form solid solutions with one another. These can be identified readily by X-ray analysis. Mechanical mixtures are more difficult to identify, but it is possible to detect 20 per cent. of one component in presence of the other. G. M.

Citric Acid, Polarographic Determination of. P. J. Elving and R. E. van Atta. (*Analyt. Chem.*, 1954, **26**, 295.) A method is given, based on the conversion of citric acid to pentabromoacetone, which substitutes a direct polarographic measurement for the subsequent petroleum ether extraction, oxidation-reduction treatment, and final titration procedure. The citric acid is essentially quantitatively converted to pentabromoacetone by the procedure of

Hargreaves, Abrahams, and Vickery (*Analyt. Chem.*, 1951, **23**, 467). In the final method a solution containing from 1 to 5 mg. of citric acid is converted to pentabromoacetone according to the procedure prescribed; the polarogram is recorded from − 0·9 to − 1·6 volts against the saturated calomel electrode and the height of the first (pentabromoacetone) wave is obtained, applying the graphical construction described. From the wave height, the amount of citric acid can be obtained by reference to a calibration curve previously prepared for known amounts of citric acid. D-*iso*Citric acid can be determined similarly after conversion to citric acid. The three polarographic waves observed for pentabromoacetone are apparently due to dibromoacetic acid and bromoform produced by hydrolysis. A graphical method for the precise evaluation of diffusion currents is presented which corrects for the geometrical effect of the polarographic wave resulting from the presence of manganous ion in the test solutions. The precision of the polarographic method is comparable to that of the older pentabromoacetone method with a considerable saving in the time required. R. E. S.

Dichlorophene, Hexachlorophene, and 2:2′-Thiobis(4:6-Dichlorophenol), Determination of. J. E. Clements and S. H. Newburger. (*J. Ass. off. agric. Chem., Wash.*, 1954, **37**, 190.) A spectrophotometric method has been devised for the determination of dichlorophene, hexachlorophene, and 2:2′-thiobis (4:6-dichlorophenol) in soap or cosmetic preparations. Any one of the three compounds can be separated from most of the interfering substances and can subsequently be identified and determined by ultra-violet spectrophotometry. The determinations are based on absorbancy readings at 260, 288 and 316 mμ for dichlorophene, on readings at 270, 300 and 330 mμ for hexachlorphene, and on readings at 262, 308 and 354 mμ for 2:2′-thiobis (4:6-dichlorophenol). Details of the extraction procedure for soaps, creams and pastes are given together with recovery results which range from 95 to 99 per cent. Other phenolic compounds present will interfere with the determination, although a variable reference technique can also be used. The complete ultra-violet curve of the unknown is plotted to establish the identity of the extracted material. R. E. S.

Papaveretum, Chromatographic Assay of. C-G. Lindblad and A. Ågren. (*Farm. Revy.*, 1954, **53**, 69.) Narcotine, papaverine and codeine may be readily separated from one another by the use of a column of kieselguhr with a suitably buffered aqueous phase. Applied to papaveretum, the details are as follows: 0·4 g. of papaveretum is dissolved in 20 ml. of water with 5·0 ml. of 0·2N sodium hydroxide, and extracted twice with 10 ml. of chloroform + 30 ml. of ether, followed by 10 ml. of chloroform. The non-aqueous extract is filtered, evaporated to 0·5 ml., and treated with 25 ml. of ether. A column (17 mm. diameter) is prepared by mixing 15 g. of kieselguhr (Hyflo Super Cel) with 3·0 ml. of buffer solution (2 parts of 0·5N phosphoric acid plus 3 parts of 0·5N potassium dihydrogen phosphate; *p*H = 2·0 to 2·1) and 150 ml. of ether, and using this mixture to pack the column. The ethereal solution of the mixed alkaloids is then passed through the column, which is then eluted with 200 ml. of water-saturated ether, at 2 ml. per minute, to remove the narcotine. The column is washed with 10 ml. of chloroform, and the papaverine is eluted with 150 ml. of chloroform. Finally the codeine is eluted with 250 ml. of chloroform saturated with ammonia. Narcotine and codeine are estimated colorimetrically by the methods of Wegner, while papaverine may be determined directly, in ethanolic solution, by measuring the extinction at 238 mμ. G. M.

Quaternary Ammonium Compounds, Microdetermination of. J. Fogh, P. O. H. Rasmussen, and K. Skadhauge. (*Analyt. Chem.*, 1954, **26**, 392). A spectrophotometric method for the analysis of cetylpyridinium chloride in concentrations ranging from 0 to 25 μg. per ml. is given based on the ability of bromocresol purple to produce a blue colour with quaternary ammonium compounds. The procedure gave results which were independent of variations in temperature within certain limits and were not influenced by the presence of calcium, magnesium, ferrous, ferric, and cupric ions up to concentrations of about 1 per cent. The quaternary ammonium compound was readily adsorbed on to glass (especially if very scratched) up to 70 per cent. of the initial concentration (1 in 50,000) being lost. By treating tubes, cuvettes, and pipettes with polymetacrylic acid ester, this adsorption can be diminished to a great extent. The concentration of cetylpyridinium chloride in any foamy phase was found to be appreciably higher than in the liquid phase. Standard curves for the microdetermination of other quaternary ammonium compounds could be obtained using the technique described. R. E. S.

GLYCOSIDES, FERMENTS AND CARBOHYDRATES

Keto-Sugars, New Specific Reagent for. R. Johanson. (*Nature, Lond.*, 1953, **172**, 956.) Anthrone can be used as a specific reagent for keto-sugars under mildly acidic conditions, as when acetic acid and ethanol is used as the solvent for anthrone in the presence of phosphoric acid. The reagent is prepared from anthrone (300 mg.), glacial acetic acid (10 ml.), ethanol (20 ml.), phosphoric acid (sp.gr. 1·60 at 20° C.; 3 ml.) and water (1 ml.). Preferably the reagent should be freshly prepared, but it is stable at 0° C. for periods of several weeks. The reagent is sprayed on paper chromatograms and after heating at 108° C. for 5 to 6 minutes, mono-, di- and tri- and poly-saccharides containing keto-hexoses develop a bright yellow colour. Keto-xylose (pentose) gave a bright purple colour and two keto-heptoses gave orange-colours. The colours are stable to light and insoluble in water. The keto-complexes appear brown, and treated aldoses show a light blue fluorescence under ultra-violet light. Both furanose and pyranose keto-sugars give positive reactions with the reagent. Sugar alcohols, inositol, ascorbic acid, α-ketoglutaric acid and uric acid do not react. Urea gives a grey colour. The intensity of the hexose colour appears to be independent of the sugar itself and is directly dependent on the molecular concentration of keto-hexose units. J. B. S.

Sugars, Chromatographic Separation of, with Hydrocellulose. J. D. Geerdes, B. A. Lewis, R. Montgomery, and F. Smith. (*Analyt. Chem.*, 1954, **26**, 264.) Cellulose powder, dissolved in phosphoric acid and precipitated by the addition of water produced a hydrocellulose which was satisfactory for the chromatographic separation of methylated sugars; details of the preparation of this hydrocellulose are given. The increased capacity and improved resolution obtained with the modified chromatographic column using hydrocellulose made it possible to separate methylated sugars without the slow development rates of larger columns. The column was used successfully for the separation of 2:3:4-tri-*O*-methyl-D-xylose, 2:3-di-*O*-methyl-D-xylose, 2-*O*-methyl-D-xylose, 3-*O*-methyl-D-xylose, and D-xylose, obtained by hydrolysis of the methylated hemicellulose from flax straw. The anomeric forms of ethyl-L-rhamnofuranoside were also separated. However, a series of experiments carried out with the free sugars (D-xylose, D-fructose, L-rhamnose, and D-glucose) using 1-butanol-ethanol-water (4: to 1:5) as the developer, showed that hydrocellulose was not superior to cellulose for separating these sugars. R. E. S.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Cortisone and Hydrocortisone in Cerebrospinal Fluid. D. N. Baron and D. Abelson. (*Nature, Lond.*, 1954, **173**, 174.) Cerebrospinal fluid was extracted within 24 hours of withdrawal by a modification of the method of Nelson and Samuels (*J. clin. Endocrinol.*, 1952, **12**, 519), the resulting extract being dissolved in ethanol for a paper chromatographic examination using the benzene-formamide system of Zaffaroni, Burton and Keutmann (*J. biol. Chem.*, 1951, **188**, 763). Identification of compounds on the chromatographs was based on the running properties of unknown compounds compared with standards added to cerebrospinal fluid, on the ultra-violet absorption at 254 mμ, on the reaction with tetrazolium blue, and on the soda fluorescence. Recoveries of cortisone and hydrocortisone added to cerebrospinal fluid exceeded 75 per cent. Examination of seven single samples of cerebrospinal fluid showed in 5 cases doubtful traces of substances exhibiting soda fluorescence; two pooled extracts showed substances provisionally identified as cortisone and hydrocortisone in concentrations of 0·1 to 0·2 μg. and 0·2 to 0·4 μg./100 ml. respectively.

R. E. S.

17-Ketosteroids, Urinary Neutral, Adsorption and Partition Chromatography. E. R. Cook, S. R. Stitch, A. E. E. Hall and M. P. Feldman. (*Analyst*, 1954, **79**, 24.) The fractionation of urinary neutral 17-ketosteroids by adsorption and by partition chromatography is described. For adsorption chromatography the urine was hydrolysed and the steroids estimated by the methods of Callow *et al.* (*J. Endocrinol.*, 1939, **1**, 76; *Biochem. J.*, 1938, **32**, 1312), followed by chromatography according to Pond (*Lancet*, 1951, **261**, 906); the partition chromatographic technique of Jones and Stitch (*Biochem. J.*, 1953, **53**, 679), was used. Detailed results are given for a number of urines when tested by the different methods, the 17-ketosteroids being reported in 7 fractions. The reproducibility of the methods, the influence of the method of hydrolysis, and the constancy of chromatographic pattern were all examined. Despite the influence of the method of hydrolysis of the 17-ketosteroid conjugates upon the chromatographic results, the constancy of the pattern for the urines from some subjects over a period of weeks was shown by each fractionation procedure.

R. E. S.

Sulphonic Acids and Related Compounds as Plant Growth Regulators. H. Veldstra, W. Kruyt, E. J. van der Steen and B. Åberg. (*Rec. Trav. chim. Pays-Bas*, 1954, **73**, 23.) A number of sulphonic acids and related compounds were tested as growth substances in the pea test, Avena straight growth test and flax root test. Indole-3-methanesulphonic acid and 2:3:6-trichlorophenylmethanesulphonic acid were especially active. The anion must be the active form of these compounds because they are completely dissociated at physiological *p*H values. The fact that the anion is active, and that the anionic group can be varied with retention of activity, is interpreted as evidence of a physicochemical type of action depending upon interaction of the anion with a cationic site in the cell.

A. H. B.

BIOCHEMICAL ANALYSIS

Barbiturate Derivatives in Blood, Rapid Method of Identifying by Paper Chromatography. J. T. Wright. (*J. clin. Path.*, 1954, **7**, 61.) Filter paper strips were sprayed with borate buffer solution, *p*H 10·6 and allowed to dry. Barbiturates, in 0·25 per cent. solution in ethanol were applied to the base line 2·5 cm. apart, using a capillary pipette graduated to contain 0·01 ml. Small spots were obtained by applying the pipette to the paper intermittently under an infra-red lamp. Descending chromatograms were run for 4 to 7 hours, using chloroform as the mobile solvent. The papers were dried in air, viewed in ultra-violet radiation, and the spots marked with pencil. Well defined spots were obtained with 10 to 25 μg. of barbiturate. The slow-acting barbituric acid derivatives travelled slowly and the fast-acting ones more rapidly, speed of movement on the paper and of clinical action following the same order except for cyclobarbitone which ran relatively slowly. Under the experimental conditions there was some variation in observed R_F values but at least 13 barbituric acid derivatives could be separated and identified by using a number of known substances as markers. The slower running derivatives were more widely separated by using paper buffered at *p*H 10, or by using *n*-butanol as solvent. Crude ether extracts of blood may be chromatographed successfully if the approximate concentration is known. Alternatively a solution prepared from blood extracts used for ultra-violet spectrophotometry may be used. The identity of the derivatives may be confirmed by eluting the spots with a 0·05 per cent. solution of sodium hydroxide, buffering to *p*H 10, and submitting the solution to ultra-violet spectrophotometry. G. B.

3:5-Diiodotyrosine, Determination of. N. R. Moudgal, L. K. Ramachandran and P. S. Sarma. (*Analyst*, 1954, **79**, 43.) The ability of *o*-diiodophenols to form stable coloured complexes with metal ions was used as the basis of a method for the determination of 3:5-diiodotyrosine, attempts being made to adapt the qualitative colour test to the colorimetric determination of diiodotyrosine in iodoproteins, after initial separation of thyroxine from diiodotyrosine by butanol fractionation. Details of the final experimental method are given together with the results obtained in a study of the effect of sodium chloride, and of added amino-acids on the colour intensity. Replicate analyses of a standard solution (0·6 mg. in 10·45 ml.) gave an average recovery of 97 per cent., the average deviation from the mean being $\pm$ 2·8 per cent. Experiments on 5 mg. of diiodotyrosine in the presence of 100 mg. of iodinated casein gave an average recovery of 83 per cent., the recovery increasing to 99 per cent. as the amount of added diiodotyrosine was decreased to 1·8 mg. R. E. S.

Serum Cholesterol, Determination of. H. H. Brown, A. Zlatkis, B. Zak and A. J. Boyle. (*Analyt. Chem.*, 1954, **26**, 397.) Two methods were examined both based on the precipitation of the cholesterol with digitonin. The collection of cholesterol digitonide on suspended aluminium hydroxide enhanced the rate of reaction between cholesterol and digitonin. The aluminium hydroxide was dissolved in hydrochloric acid the remaining digitonide being examined quantitatively for cholesterol. The alternative method involved the addition of 30 per cent. aluminium chloride to an ethanol-acetone-water mixture of cholesterol and digitonin; after centrifuging, decanting, and washing with acetone the precipitate was analysed as before using the reagent of Zlatkis *et al.* (*J. Lab. clin. Med.*, 1953, **41**, 486). R. E. S.

CHEMOTHERAPY

Acridine Salts, The *in vitro* Antifungal Activity of a Series of. S. M. Viscia and D. C. Brodie. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 52.) A series of salts of 9-aminoacridine was prepared, including the acetate, propionate, butyrate, caprate, undecylate, undecylenate, laurate, lauryl sulphate, oleate, benzoate, salicylate and sorbate. Tests for antifungal activity were carried out by incorporating various dilutions in Sabouraud's agar medium, streaking with *Trichophyton mentagrophytes* and incubating for 7 days at 25° C. Maximum activity occurred with fatty acids containing 10, 11 or 12 carbon atoms in a chain. Comparison with the results of experiments using free fatty acids and their sodium salts showed that the antifungal action of the 9-aminoacridine salts is greater than the sum of the effects due to the anion and cation. The most active compounds were the caprate, undecylate and undecylenate. G. B.

***N*-9-(Xanthenyl) amides, Chemotherapy of, in Experimental Schistosomiasis.** H. W. Bond and G. W. Luttermoser. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 32.) A series of 35 9-xanthenyl amides was prepared by condensation of xanthydrol with amides in acetic acid solution at room temperature. The series included alkyl and aryl carbonamides and sulphonamides. When tested against *Schistosoma mansoni* in mice, none of the substances was as active as lucanthone hydrochloride, but the *n*-heptadecanyl, chloromethyl, *n*-hydroxypropyl and *n*-hydroxybutyl carbonamides and benzylsulphonamide were almost as active. None of the arylcarbonamides showed significant activity. G. B.

PHARMACY

GALENICAL PHARMACY

Crude Drugs, Effects of Surface-active Agents on the Extraction of. E. Brochmann-Hanssen. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 27.) Extracts were prepared by shaking ipecacuanha or cinchona powder with menstruum and filtering. The time of extraction, and type and concentration of surface-active agent were varied and the *p*H, surface tension and alkaloid content of the extract determined. Assays were carried out by the method of the Norwegian Pharmacopœia, 1939 for cinchona and Danish Pharmacopœia, 1948 for ipecacuanha. In the presence of ethomeens (alkyldipolyoxyethylene amines) ordinary assays gave unreliable results and a spectrophotometric method was used. Fairly high concentrations of non-ionic surface-active agents were necessary to increase the efficiency of extraction of cinchona with water, and no appreciable effect was observed when ethanol was used. Extraction with water containing small concentrations of anionic agents such as sodium lauryl sulphate decreased the yield owing to the formation of alkaloidal precipitates. Higher concentrations of sodium lauryl sulphate showed a solubilising effect and an increased yield was obtained. Cationic agents of the quaternary ammonium type, even in low concentrations, increased the yield from cinchona, possibly by freeing the alkaloids from alkaloid-tannin complexes by a mechanism involving ion-exchange. Tertiary amines were less effective. Water alone extracted alkaloids in good yield from ipecacuanha, apparently because of the presence of a saponin which reduced the surface tension of the extracts. G. B.

PHARMACOGNOSY

Solanaceæ, Production of Alkaloids in. K. Jentzsch. (*Sci. Pharm.*, 1953, **21**, 285.) Using the chromatographic method developed by the author (*Sci. Pharm.*, 1952, **20**, 216), the development of alkaloids in solanaceous plants was followed These results may be best expressed in a table. In the case of

	Date	Alkaloid content, per cent.	Main alkaloid	Subsidiary alkaloid
Datura stramonium var *inermis:*				
	June 16	0·17	scopolamine	hyoscyamine
with buds	June 29	0·11	scopolamine	hyoscyamine
flowered	July 30	0·30	hyoscyamine	scopolamine
Datura tatula:				
	June 23	0·14	scopolamine	hyoscyamine
with buds	July 2	1·155	scopolamine	hyoscyamine
flowered	July 23	0·20	hyoscyamine	scopolamine
Datura metel:				
	June 22	0·115	scopolamine	—
	July 6	0·11	scopolamine	—
with buds	July 20	0·25	scopolamine	hyoscyamine
Atropa belladonna:				
small plants	Sept. 10	0·37	hyoscyamine	—
moderate-size plants ..	Sept. 10	0·37	hyoscyamine	—
large plants	Sept. 10	0·31	hyoscyamine	—

D. metel the hyoscyamine represents about one-third of the total alkaloidal content at the commencement of flowering, but this decreases again so that, as shown by previous investigations of the author, only traces are present in the fully developed plant. With *D. stramonium* var *inermis* and *D. tatula* the ratio of scopolamine to hyoscyamine is about 3:1 before flowering. At flowering there is a reversal of this proportion, and in the course of further growth it is continually displaced in favour of hyoscyamine. G. M.

PHARMACOLOGY AND THERAPEUTICS

Adrenaline, Detection of Some Precursors by Paper Chromatography. D. M. Shepherd and G. B. West. (*Nature, Lond.*, 1953, **171**, 1160.) A method is described for the detection of *m*-hydroxyphenylethanolamine, a precursor of noradrenaline, in biological materials. Using paper chromatography with a butanol-acetic acid solvent, the compound shows an intense violet fluorescence under ultra-violet light when the developing agent is a mixture of potassium ferricyanide or dichromate with formaldehyde followed by exposure to heat. As little as 0·5 μg. can be detected. Noradrenaline under similar conditions gives a turquoise fluorescence, and as little as 0·2 μg. can be detected. Adrenaline gives a yellow-green fluorescence with concentrations of 0·4 μg. or more. Very small amounts of noradrenaline can be detected in the presence of much larger quantities of adrenaline. G. F. S.

Anticholinesterase Poisoning: Failure of Respiration in Death by. C. A. de Candole, W. W. Douglas, C. Lovatt Evans, R. Holmes, K. E. V. Spencer, R. W. Torrance and K. M. Wilson. (*Brit. J. Pharmacol.*, 1953, **8**, 466.) The acute toxicity of the anticholinesterase group of drugs is characterised by failure of respiration, but there has been no general agreement on how this is brought about. Failure may occur by collapse of the central respiratory control centres, by bronchospasm, or by neuromuscular paralysis. Each factor was considered in turn. The anticholinesterases used were eserine, di*iso*propyl-phosphorofluoridate (dyflos DFP), diethyl *p*-nitrophenyl phosphate (E600), ethyl

NN-dimethylphosphoramidocyanidate (tabun), *iso*propyl methylphosphonofluoridate (sarin), 3:3-dimethyl-*n*-butyl 2-methylphosphonofluoridate (soman) and tetraethyl pyrophosphate (TEPP). The experiments were conducted on cats, dogs, rabbits, monkeys, sheep, goats, mice, rats and guinea-pigs. Bronchoconstrictor action was observed directly radiographically and indirectly by tidal air measurement under artificial respiration. Severity of bronchospasm varied with species, being slight in rabbit, severe in cats and often insignificant in monkeys at the time of acute respiratory failure. Neuromuscular block by the anticholinesterases was demonstrated in the anæsthetised rabbit under artificial respiration with the chest open. The responses to regular tetanic bursts applied to the cut phrenic nerve were recorded by a phrenograph. Significant neuromuscular block was obtained with doses of sarin sufficient to cause respiratory failure. Further experiments with the chest unopened and electrodes placed on the intact phrenics in the neck showed that, after a toxic dose of sarin (40 μg./kg., i.v.), spontaneous contractions of the diaphragm ceased when neuromuscular block was incomplete. Bronchospasm and neuromuscular paralysis were therefore considered insufficient to account entirely for respiratory failure in rabbits. To observe central respiratory paralysis the activity of the root of the right phrenic nerve of the rabbit was recorded electrically before and during respiratory failure with sarin. Comparison with a phrenograph record taken at the same time showed a rapid diminution in the frequency and duration of the impulse bursts concomitant with a decrease in diaphragm contractions, after the injection of 40 μg./kg. of sarin i.v., dyflos (4 mg./kg. i.v.) resembled sarin in this respect, but tabun (0·15 mg./kg. i.v.), E600 (1·5 mg./kg.) and TEPP (300 μg./kg.) showed significant neuromuscular block before central failure occurred. The central action is probably not due to reflex influences from the periphery, since intracisternal injections and injections into the vertebral artery also cause respiratory inhibition, although the doses were so small that no peripheral effects occurred. The fall in blood pressure was also insufficient to cause any depression of the respiratory centre due to decreased blood flow. Central failure of respiration, then, appears to be the predominant factory in the acute toxicity of anticholinesterases in rabbits and monkeys, but in cats the bronchospasm may play an important part. Atropine protects against the central inhibition and the bronchospasm produced by these drugs, and artificial respiration against the neuromuscular paralysis. G. P.

Antitussive Agents, Evaluation of, in the Dog. P. L. Stefko and W. M. Benson. (*J. Pharmacol.*, 1953, **108**, 217.) A method is described for provoking a cough in the conscious dog. A localised area of the tracheal mucosa is stimulated electrically by means of embedded electrodes. After obtaining suitable control responses in each dog, by measuring the voltage and frequency of stimulation necessary to elicit a certain intensity of cough, the compound to be tested is administered and the cough response remeasured 15, 30, 60 and 120 minutes afterwards. The compounds were evaluated by the average percentage inhibition of the cough response. A dose of 1·0 mg./kg. of codeine phosphate injected subcutaneously caused a 42 to 45 per cent. inhibition while 2 mg./kg. caused a 76 per cent. inhibition. Morphine was not so effective, a dose of 1·0 mg./kg. had little effect, 2·0 mg./kg. caused less than 50 per cent. reduction although lethargy was apparent; while 4·0 mg./kg. caused a maximum inhibition of about 50 per cent. but the dogs went to sleep. Codeine phosphate is a more effective antitussive compound than morphine in the dog, and it is suggested that in this respect there is a marked species difference between man and dog. G. F. S.

Ethanol, Metabolism of. E. K. Marshall and W. F. Fritz. (*J. Pharmacol.*, 1953, **109**, 431.) The rate of oxidation of ethanol in the body has been regarded as constant and independent of the concentration present. This paper presents evidence that this is true only for high concentrations in the plasma and at very low concentrations the rate of oxidation is proportional to the amount present. The experiments were conducted in trained female dogs, ethanol being given by a slow continuous intravenous infusion. Ethanol was estimated in the plasma using crystalline ethanol dehydrogenase and diphosphopyridine nucleotide as described by Bücher and Redetzki, the method being modified for very low concentrations. The rate of disappearance of ethanol in low concentrations followed an exponential curve, similar to the behaviour of other drugs, the amount disappearing being proportional to the amount present. With concentrations greater than 10 mg. per cent. the ethanol concentrations are fitted best by a straight line but there are wide divergences of the individual points. This is due to the rate of oxidation of ethanol in the blood not being constant from hour to hour but varying eratically in the same dog. Similar variations were found in arterial blood, and the average rate of oxidation of normal doses of ethanol also varied in the same dog from day to day. G. F. S.

(*N*-Ethyl, *N*-β-chloroethyl) amino-methylbenzodioxane—the Atropine-like and Adrenergic-blocking Properties of. A. Loubatières and P. Bouyard. (*Arch. int. Pharmacodyn.*, 1953, **95**, 285.) β-chlorination of one of the *N*-ethyl groups in the structure of 883F (prosympal) results in a complete re-orientation of pharmacological properties. The action of the drug now becomes principally atropine-like, only showing adrenergic blocking effects with larger doses. Vagal stimulation is more readily blocked than injected acetylcholine. Conversely injected adrenaline is more easily blocked than is sympathetic stimulation. With small doses the effects of adrenaline and noradrenaline are potentiated. Also, the drug reverses the pressor response to adrenaline in dog more easily than that to noradrenaline. Besides effects on autonomic neuroeffector junctions, the drug has a curare-like action, is an antidiuretic, causes depression of the central nervous system and prolongs barbiturate anæsthesia. It induces hyperglycæmia and hypothermia. It is an antihistamine, being 4 to 5 times less active than promethazine against bronchospasm in guinea-pigs. It causes a reduction in blood pressure in experimentally-induced hypertension, and has a weak anti-emetic action. There is no antagonism of nicotine-induced or leptazol-induced convulsions, nor is the Straub phenomenon in mice affected. The implications of the differences in peripheral autonomic blockade between the drug, 883F, 933F and their congeners are discussed. G. P.

Hayatin Methiodide—a New Curariform Drug. S. N. Pradhan and N. N. De. (*Brit. J. Pharmacol.*, 1953, **8**, 399.) Hayatin, an alkaloid obtained from the root of *Cissampelos pareira*, Linn., shows strong muscle relaxant properties when isolated as the methiodide. Compared with *d*-tubocurarine chloride, hayatin methiodide has 1·14 times greater curariform activity on the sciatic nerve-gastrocnemius muscle preparation of the dog and cat, 2·05 times greater activity in mice (inclined screen test), and is 2·13 times as active by the rabbit head-drop test. Toxicity tests show it to be 1·7 times as toxic to mice, and 2·15 as toxic to rabbits as *d*-tubocurarine chloride. Duration of curariform activity is similar to that of *d*-tubocurarine chloride, which it also resembles in that it is antagonised by neostigmine and, on the gastrocnemius muscle, by previous tetanisation of the sciatic nerve. The drug does not cause a contracture

of the frog rectus abdominis muscle, but antagonises that produced by acetylcholine. Also the tibialis muscle of dog is less sensitive to the drug than is the gastrocnemius and mouse and rabbit show greater sensitivity than do cat and dog. By these characteristics the drug can be grouped along with *d*-tubocurarine chloride as a pachycurare agent. G. P.

Hydrocortisone (Compound F) Acetate Ointment in Eczema of Infants and Children. L. R. McCorriston. (*Canad. med. Ass. J.*, 1954, **70**, 59.) Very small concentrations of hydrocortisone in suitable ointment bases have been found remarkably effective in clearing up the skins of infants and children with eczema and maintaining this improvement. Cortisone itself is ineffective. Hydrocortisone was incorporated in concentrations of 1 per cent. and 2½ per cent. in 4 different ointment bases formulated from (*a*) carbowax, (*b*) soft paraffin, (*c*) a jelly and (*d*) a cetyl-alcohol lauryl-sulphate paraffin mixture. The jelly base was too drying. The children were those with dermatoses of long duration and greater severity. The 2½ per cent. concentration was used initially when the eruptions and itching were severe, and this was followed later with the 1 per cent. concentration or when the effects were less severe. Improvement occurred within 24 to 48 hours and was maintained with therapy, and in most cases after cessation of treatment, for considerable periods of time. In 60 per cent. of the patients there have been no recurrences over a period of 8 months. There appear to be no contra-indications to its use, percutaneous absorption is too small for systemic effects and there have been no cases of allergic hypersensitivity so far. G. F. S.

Isoniazid, Metabolic Fate of. H. B. Hughes. (*J. Pharmacol.*, 1953, **109**, 444). Monkeys given isoniazid excrete substantial quantities of a substance soluble in a 4:1 mixture of ethylene dichloride and *iso*amyl alcohol, showing a strong absorption band at 265 mμ, which on acid hydrolysis yields a compound which couples with *p*-dimethylaminobenzaldehyde. This compound, which was the main isoniazid-like material to be excreted, has been isolated and identified as a metabolite of isoniazid, 1-*iso*nicotinyl-2-acetylhydrazine. More than 50 per cent. of the isoniazid administered was excreted. The metabolite compound was also found in the urine of one patient to the extent of 91 per cent. of the isoniazid-like material excreted. G. F. S.

Makrotomine, Pharmacology of. I. M. Shapirov. (*Farmakologiya i Toksikologiya*, 1953, **16**, No. 2, 19.) A pharmacological study was carried out on the alkaloid makrotomine, recently isolated from the Transcaucasian plant, *Makrotomia echioides* (*Boraginaceæ*). It had similar parasympatholytic properties to trachelantamine, to which it is closely related chemically, but its activity was much lower. Instillation of a 10 per cent. solution into the conjunctival sac of cats and dogs produced no change in the diameter of the pupil. The minimum dose required to reduce the effect of excitation of the vagus nerve in cats was 1 to 3 mg./kg., and to suppress the effect completely a dose of 3 to 5 mg./kg. was required; the corresponding figures for trachelantamine are 0·05 to 0·10 mg./kg. and 0·3 to 0·5 mg./kg. The LD50 of makrotomine given intraveneously to white mice was 148·4 mg./kg., which compares with 139·1 mg./kg. for trachelantamine. E. H.

Mepiperphenidol, a Visceral Anticholinergic Agent. E. C. McManus, J. M. Bochey and K. H. Beyer. (*J. Pharmacol.*, 1953, **108**, 364.) This paper reports some of the pharmacological properties of mepiperphenidol (darstine), a new visceral anticholinergic agent. On the isolated rabbit ileum,

mepiperphenidol inhibited the normal movements and antagonised acetylcholine stimulation. It had very little activity in antagonising histamine. In dogs with Thiry loops, mepiperphenidol was as active as methantheline in inhibiting the rhythmic contractions and tonus of the ileum. A dose of 15 μg./kg. intravenously inhibited the stimulating action of methacholine. Orally, mepiperphenidol showed a greater activity and a more prolonged action than methantheline in antagonising methacholine. There was a significant delay in the emptying time of the stomach of dogs given mepiperphenidol after a barium meal. Studies of gastric secretion in anæsthetised dogs showed both mepiperphenidol and methantheline to reduce the volume of gastric secretion after stimulation with 5-ethyl-5-(1 : 3-dimethyl-1-butenyl)-barbituric acid, a vagal stimulant of gastric secretion, and to decrease gastric acidity. Tests on salivary secretion in the anæsthetised dog during stimulation with methacholine showed mepiphenidol to have far less antisialogogic activity than methantheline. In blocking the superior cervical ganglion mepiperphenidol was as active as tetraethylammonium chloride. On the cardiovascular system, mepiperphenidol inhibited cholinergic mediation significantly less than methantheline and there was also less inhibition of the bladder tonus after stimulation with methacholine.

G. F. S.

Mepiperphenidol, Effect of, on Gastric Secretion in Dogs. J. D. McCarthy, S. O. Evans, H. Ragins and L. R. Dragstedt. (*J. Pharmacol.*, 1953, **108**, 246.) Mepiperphenidol (5-methyl-4-phenyl-1-(1-piperidyl)-3-hexanol methobromide, darstine), a new quaternary ammonium compound, increases the gastric emptying time and decreases colon motility in the dog. It also antagonises the stimulatory actions of methacholine and vagal stimulation on gastric motility and secretion in experimental animals. This paper describes its actions on gastric secretion in dogs with various types of gastric pouches. In the fasting dog an oral dose of 50 mg. of mepiperphenidol, after a delay of 1 hour, depressed acid gastric secretion for 4 to 8 hours. Vagal innervation of the pouch was not necessary for the drug to have an effect, and it also antagonised the gastric secretory stimulating effect of histamine and insulin-produced hypoglycæmia.

G. F. S.

Nalorphine, Respiratory Depressant Action of, in the Normal Subject and in the Patient with Respiratory Acidosis Secondary to Pulmonary Emphysema. S. M. Tenney and J. C. Mithoefer. (*New Eng. J. Med.*, 1953, **249**, 886.) Nalorphine causes respiratory depression in the normal subject and in the patient with respiratory acidosis secondary to chronic pulmonary disease. By measurement of the alveolar ventilation ratios first in air and then in oxygen with 2·8 per cent. and 4·3 per cent. carbon dioxide added, it was found that the sensitivity of the respiratory centre to carbon dioxide was decreased by 50 per cent. in normal subjects and by 30 per cent. in patients with respiratory acidosis, after administration of nalorphine intravenously. In all patients with respiratory acidosis periodic breathing occurred after nalorphine. In these patients even in absence of nalorphine there was a decreased sensitivity to elevations in inspired carbon dioxide, compared with the normal subjects. To take this into account respiratory depression with carbon dioxide was induced in dogs under pentobarbitone anæsthesia by allowing them to rebreathe 100 per cent. oxygen from a closed circuit spirometer. When carbon dioxide accumulation was great enough to cause the respiratory minute volume to fall to half its peak value nalorphine had no effect on either tidal volume or rate. The conclusions drawn were that nalorphine did not benefit respiratory acidosis

unrelated to drug intoxication, nor did the results support the suggestion that the primary mode of action of nalorphine was that of a central nervous system stimulant, especially of the respiratory centre. G. P.

Oral Analgesics (Morphine, Codeine, Acetysalicylic Acid) and the Problem of Placebo "Reactors". H. K. Beecher, A. S. Keats, F. Mosteller and L. Lasagna. (*J. Pharmacol.*, 1953, **109**, 393.) The analgesic action of acetylsalicylic acid 300 and 600 mg., codeine phosphate 60 mg., morphine sulphate 10 mg. and *N*-(2-(2-pyridyl)-ethyl)-phthalimide 200 mg. by the oral route has been evaluated in patients with postoperative pain. Comparisons were made with lactose placebos and the criterion of response was the patients statements about pain. The high dose of acetylsalicylic acid was effective, whereas morphine, codeine and the phthalimide compound were ineffective in the doses used, being indistinguishable from the placebos. There was a high incidence of vomiting with the phthalimide compound. Some 35 per cent. of the patients reacted to the placebo and in these placebo "reactors" there was no difference in per cent. relief by the various drugs. With the placebo non-reactors greater relief was obtained with aspirin than with codeine and morphine. It is suggested that the ineffectiveness of morphine by mouth is due to slow absorption.

G. F. S.

Phenothiazine Derivatives in the Treatment of Parkinsonism. D. E. Hutcheon. (*J. Pharmacol.*, 1953, **108**, 340.) A study has been made of the relative potencies of diethazine, promethazine and ethopropazine (parsidol) in several pharmacological tests. All showed local anæsthetic activity when injected intradermally into guinea-pigs. Comparisons of the local anæsthetic activity (*a*) with the intravenous toxicities in mice (*b*) gave the following ratios (*b*/*a*):—procaine 1·0; diethazine 4·4; promethazine 2·3 and ethopropazine 8·3. Ethopropazine, which had 5 times the local anæsthetic activity of procaine, was only 50 per cent. more toxic than procaine, and showed only 1 per cent. of the activity of atropine in inhibiting salivary secretion in the dog when stimulated with carbachol. All three phenothiazine derivatives, like atropine, reduced the stimulant action of acetylcholine on the guinea-pig ileum, ethopropazine being 28 per cent., promethazine 19 per cent. and diethazine 4 per cent. as active as atropine. On the isolated driven auricles, ethopropazine, the most active compound, showed 78 per cent. of the activity of quinidine. Diethazine, like promethazine, did not inhibit the stimulant action of histamine on the secretion of gastric juice in the anæsthetised cat. G. F. S.

Poliomyelitis, Immunization Against. T. E. Boyd. (*Bact. Rev.*, 1953, **17**, 339 Supplement.) This is an extensive review on immunization against poliomyelitis in animals and human subjects. Recent advances in knowledge and techniques have made it possible to confer a high degree of immunity against paralytic poliomyelitis in animals. With passive immunisation protection is of brief duration, but with active immunisation it lasts for a substantial period of time. Previous studies on immunisation have been largely vitiated through sources of error, due to lack of quantitative measures for assaying virus and antiserum and through ignorance of immunological diversity among poliomyelitis viruses and the use of inappropriate animal species and routes of innoculation for testing resistance to infection. Virus, antisera and vaccines can now be assayed and the dosages given to test animals can thereby be controlled. Passive immunity has now been achieved in man by means of the gamma globulin

(ABSTRACTS *continued on p.* 429).

The plentiful supply of structural formulæ throughout the book is to be commended, but it is unfortunate that the conventional methods of writing aromatic structures using alternating single and double bonds has not been adopted consistently throughout the book, sometimes different methods of representing aromatic structures being used even on the same page.

The introduction and Part I of the book cover general topics, including structural biochemistry, mechanism of action of drugs, physico-chemical aspects and modification of drugs by living organisms. Part II is devoted to a wide range of brief surveys of specific topics. Despite the confinement of some of the topics to small compass, the clear and concise style of the presentation, and the plentiful supply of leading references, make the book a storehouse of information of value to chemists, biologists, pharmacologists and pharmacists, and to all those even remotely connected with the investigation of compounds with possible actions upon living tissue. A. H. BECKETT.

(ABSTRACTS *continued from p.* 427).

fraction, prepared from immune blood, which confers significant protection for 5 weeks. Active immunisation in man has been shown to result in the appearance of circulating antibody at levels exceeding the minimum required for protection, but further work is required to determine whether active immunisation effectively protects against paralytic poliomyelitis, how long the protection and antibody persist and whether active immunisation can be accomplished without risk of harmful effects. G. F .S.

Pyridoxine Deficiency, Convulsions in Infants Due to. C. J. Molony and A. H. Parmelee. (*J. Amer. med. Ass.*, 1954, **154**, 405.) During 1952 and early 1953 reports were received from all parts of the United States of the occurrence of epileptiform convulsions in infants, unassociated with any other signs of illness or laboratory findings indicating an ætiological factor. The infants had progressed normally from birth until, at 8 to 16 weeks, the convulsions occurred, usually several times a day. All the infants had been fed on a particular proprietary food and in all cases the convulsions ceased when they were given another product in part or complete substitution. The trouble appears to have been associated with a change from coconut to palm oil as the source of fat in the food, and a change in the method of sterilisation to a procedure which may have destroyed pyridoxine. Pyridoxine deficiency in infants is characterised by apathy, failure to gain in weight, anæmia and convulsions and is believed to have been responsible for the illness reported. H. T. B.

Pyrogens, Testing for. A. Engelund and P. Terp. (*Arch. Pharm. Chemi.* 1954, **61**, 42.) Rabbits which are given a pyrogen injection every day acquire a certain degree of tolerance, so that their reaction becomes less. After a rest period of some weeks they again react normally. If, however, injections are given only on alternate days, then there is no decrease in the response. It is desirable that the temperature should be read every half hour, otherwise the maximum may be missed. Quantitatively, the best measure of the action is the difference between the maximum temperature reached and the basal temperature immediately before the injection. The temperature of the injection liquid need not be 37° C. if it is isotonic. Although there is a slight difference in the normal temperatures of free and constrained animals, this is so small (0·2° C.) that it is of no significance. G. M.

(ABSTRACTS *continued on p.* 432).