# ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

## CHEMISTRY

### ALKALOIDS

**Alkaloids, Adsorption of, on Alumina.** H. Thies and S. Zauner. (*Arch. Pharm. Berl.*, 1952, **285**, 191.) A study of the adsorption of the hydrochlorides of quinine and morphine on alumina shows that in general there is no direct adsorption of the base on the alumina, but that the results observed are due to an exchange of H and OH ions on the —AlOH groups, the basic fraction of the alkaloidal salt being set free and, if its concentration exceeds the solubility limit, being precipitated. Basic alumina is an amphoteric adsorbent and takes up H ions from the easily dissociated alkaloidal salt solution with formation of free base. If the salt solution is sufficiently concentrated the whole of the sodium of the adsorbent is exchanged for H ions, the OH ion concentration of the reaction mixture is reduced to such an extent that the alumina is able to give up OH ions in exchange for Cl, and this results in a further precipitation of alkaloid base. Quantitatively this last reaction may closely follow the Freundlich isotherm, although there is no direct adsorption. It follows that an agreement between experimentally observed values and those derived from the adsorption isotherm do not necessarily imply the existence of true adsorption phenomena. G. M.

**Alkaloids, Chromatographic Behaviour of.** H. Böhme and H. Lampe. (*Arch. Pharm. Berl.*, 1952, **285**, 175.) Experiments on the behaviour of a series of alkaloidal salts on an alumina column show that the effects observed depend on ion exchange effects. Owing to the equilibrium $[B.H]^+ + H_2O \rightleftharpoons B + [H_3O]^+$ a solution of the hydrochloride of an alkaloid contains, in addition to alkaloid and chloride ions, free base and hydroxonium ions. If the column contains ion-exchangeable sodium, as is the case with "alkaline" aluminas, the sodium is displaced by the hydroxonium ion, the equilibrium is displaced completely to the right, the base is set free, and the filtrate contains equivalent amounts of sodium and chloride ions. The weaker the alkaloidal base, the more the original state of the equilibrium is displaced to the right, and the high hydroxonium concentration is sufficient to displace calcium from the alumina, while a certain amount of chloride ion is also held. In ethanolic solution the equilibrium is also displaced to the right, and the hydrochlorides even of stronger bases such as quinine and atropine are decomposed by neutral alumina. The effect here is also mainly one of ion exchange. The solubility of the free alkaloidal base is also an important factor. A base such as atropine or codeine, comparatively soluble in water, becomes concentrated in the lower part of the column and prevents the equilibrium from being displaced completely to the right, while in ethanol the strength of the base is reduced and the salt is more completely split up. G. M.

**Novacine (*N*-Methyl-*sec.*-*pseudo*brucine), an Alkaloid from *Strychos nux-vomica*, L.** W. F. Martin, H. R. Bentley, J. A. Henry and F. S. Spring. (*J. chem. Soc.*, 1952, 3603.) From residues obtained during the purification of crude brucine sulphate from *Strychnos nux-vomica* seeds, a new alkaloid was isolated for which the name novacine is proposed. Novacine occurs together

with vomicine in a fraction separated from strychnine and brucine by taking advantage of the solubility of the hydrochlorides of the latter two alkaloids in chloroform. Novacine and vomicine were separated as their hydrogen tartrates which have markedly different solubilities in water. Analysis of novacine and several of its crystalline derivatives established the formula $C_{24}H_{28}O_5N_2$, and it was identified as *N*-methyl-*sec.*-*pseudo*brucine previously obtained by Leuchs and Tessmar (*Ber. dtsch chem. Ges.*, 1939, **72**, 965) by the action of methyl iodide on *pseudo*brucine. A. H. B.

## ANALYTICAL

**Alkaloids, Determination of Small Quantities of.** W. Poethke and H. Trabert. (*Pharm. Zentralh.*, 1952, **91**, 284.) As a preliminary measure towards the development of a method of determination of a few mg. of alkaloid with a fair degree of accuracy, experiments were carried out with 8-hydroxyquinoline, and it was found that amounts between 1 and 30 mg. could be satisfactorily estimated. The method used consists of precipitation with potassium bismuth iodide and determination of the iodine content of the precipitate by titration with iodate in presence of cyanide. It is proposed to investigate the extension of this process to alkaloids themselves. G. M.

**Analgesics, Determination of.** H. Vogt and I. Heeman. (*Pharm. Zentralh.*, 1952, 91, 311.) Two methods, involving precipitation with Reinecke salt, are proposed for the determination of certain modern analgesics. *Titrimetric determination*: About 20 mg. of the compound in 5 to 10 ml. of 1 per cent. sulphuric acid is precipitated with 10 ml. of freshly prepared 1 per cent. solution of Reinecke salt. After cooling for 30 minutes in ice, the precipitate is filtered off and washed with ice water. It is then dissolved in 3 ml. of acetone, diluted with 40 ml. of water, and treated with 1 ml. of Fehling's alkaline tartrate solution. After refluxing for 10 minutes and cooling, the mixture is treated with 20 ml. of 25 per cent. nitric acid and 5 ml. of 0·1N silver nitrate solution. Excess of silver is then titrated back with thiocyanate. 1 ml. of 0·1N silver nitrate is equivalent to 7·09 mg. of pethidine, 8·64 mg. of *dl*-methadone or 11·08 mg. of methorphinan. *Colorimetric determination*: Precipitation of the compound is carried out as above, the precipitate is dissolved in acetone and the absorpton is determined using filter S53. G. M.

**Azulene in Chamomile, Determination of.** R. Fischer and H. Resch. (*Pharm. Zentralh.*, 1952, **91**, 265.) 10 to 20 g. of whole drug is distilled in an essential oil determination apparatus with 400 ml. of saturated salt solution, and the oil is collected in the usual way. If an aqueous preparation of chamomile is to be examined, this is distilled similarly after saturation with salt. The oil obtained is dissolved in xylene to 6 ml., and the absorption of the solution is determined, using a filter with a maximum absorption at 560 mμ. The azulene content of the drug, in mg. per cent., is given by the expression $\frac{E_{1\,\text{cm.}} \times 349{\cdot}85}{\text{wt. of drug taken.}}$ G. M.

**Cinnamon Oil Analysed by the Salicylaldehyde Reaction.** S. Collett (*Mfg. Chem.*, 1952, **23**, 411.) As a continuation of the work described in *Mfg. Chem.*, 1952, **23**, 96 the author has applied the salicylaldehyde reaction to the determination of cinnamic aldehyde in cinnamon oil and cinnamon bark. When the oil was assayed by the method previously described the figures obtained were

considerably higher than those found by the B.P. method or by gravimetric assay using 2:4-dinitrophenylhydrazine. This was thought to be due to the presence of eugenol in the oil. After removal of the eugenol figures were obtained which were in close agreement with those of the gravimetric method but lower than those of the B.P. method. The bark was assayed by ether extraction of an aqueous distillate and treatment of the ethereal solution by the modified method. In the assays the standard of reference was a pure sample of cinnamic aldehyde from which a standard curve was prepared, the absorption being determined in an E.E.L. photoelectric colorimeter using a No. 624 filter. G. R. A. S.

**Essential Oils, Determination of, in Ethanolic Solution.** H. Kaiser and W. Lang. (*Öst. Apothekerztg*, 1952, **6**, 536.) Small quantities of essential oils in ethanolic solution cannot be determined by distillation processes, since the oil forms a ternary azeotropic mixture with the ethanol and water. Shaking out with pentane is also unsatisfactory, on account of the solubility relations, but by the addition of ammonium sulphate this process can be operated with good results. About 20 g. of a preparation is diluted with water to 100 ml. and distilled. The first 50 ml. of the distillate is collected in a separating funnel, treated with 100 ml. of saturated ammonium sulphate solution, and shaken out 3 times with 25 ml. quantities of pentane, the pentane being poured off carefully from the top of the separator. The combined pentane extracts are allowed to stand for a few hours and transferred to a tared flask, taking care that no trace of the aqueous solution is transferred with it. After the removal of the pentane at 40° C. the residue is weighed. In the case of solutions of essential oils in spirit, the distillation may be omitted. The method may be applied to tinctures such as those of cinnamon and valerian, and to cosmetic preparations.
G. M.

**Morphine in Poppy Heads and Opium, Colorimetric Determination of.** C. F. Moorhoff. (*Pharm. Weekbl.*, 1952, **87**, 593.) This method is specially suitable for checking the morphine content of poppy heads and opium in the course of manufacturing operations. A quantity of the material, corresponding to 15 to 40 mg. of morphine, is extracted by one of the usual methods, e.g., in weakly acid aqueous medium. The extract is made strongly alkaline with sodium hydroxide and shaken out 3 times with 25 ml. quantities of benzene, the mixed benzene extracts being washed with 20 ml. of 0·1N sodium hydroxide. The mixed alkaline solution is brought to *p*H 9 by the addition of acid and ammonium chloride, and shaken with chloroform-*iso*propanol, the extract being filtered through anhydrous sodium sulphate and then shaken into water acidified with sulphuric acid. The extract is then adjusted so as to be slightly acid to litmus, and diluted to 100 ml. For the colorimetric determination 15 ml. of the extract is treated with 15 ml. of 0·1N hydrochloric acid, while in another flask is placed 15 ml. of the extract and 17 ml. of the acid. To the first flask is added 2 ml. of 5 per cent. solution of iodic acid. After exactly 120 seconds, the contents of both flasks are treated with 17 ml. of 10 per cent. solution of ammonium carbonate and, 60 seconds later, with 1 ml. of freshly prepared 0·3 per cent. solution of ferric chloride. After 15 to 30 minutes the colour developed is measured against the blank, using a 1 cm. cell and a suitable filter. G. M.

***iso*Nicotinyl Hydrazide, Colorimetric Assay of.** A. Kirschbaum (*Pharm. Acta Helvet.*, 1952, **27**, 229.) To the *iso*nicotinyl hydrazide dissolved in 5 ml. of ethanol add 4 ml. of phosphate buffer, *p*H 7, and shake until the opalescence

due to the precipitation of phosphate disappears. Add 1 ml. of a freshly prepared 1 per cent. solution of picryl chloride in ethanol and allow to stand for 45 minutes at room temperature to obtain the maximum yellow-brown or red-brown colour. Measure the colour, which is stable for several hours, using blue and green filters in the colorimeter, and calculate the quantity of *iso*nicotinyl hydrazide in the sample by reference to a standard curve plotted for the pure product under identical conditions. The greatest precision is obtained with 1 to 10 $\mu$g. of *iso*nicotinyl hydrazide per ml. It is necessary to compensate for the colour of the reagent. The reaction may be carried out by heating to 85° C. for 15 minutes and allowing to stand for a further 5 minutes, providing that the standard curve is made in the same manner. Increasing the quantity of ethanol used causes precipitation of phosphate, but up to 2 ml. of water may be added without precipitation of the reagent. Thus aqueous solutions of the drug may be tested, but if a sample greater than 0·1 to 0·2 ml. is used the quantity of buffer solution should be decreased to compensate for the increased volume of the final solution. Nicotinamide and hydrazine give colours which interfere in the determination. G. B.

**Pethidine, Microchemical Detection of.** R. Opfer-Schaum. (*Öst. Apothekerztg*, 1952, **6**, 543.) A solution of the base in ether is placed on a microscope slide which is raised a little above the heating plate of a micromelting point apparatus at 30° C. to 40° C. Immediately the solvent has evaporated, the residue is surrounded with a glass ring of 5 to 10 mm. height. Another slide, with a hanging drop of water containing excess of undissolved styphnic acid, is placed on top. The apparatus is then heated on the heating table to 75° C. and allowed to cool. Pethidine styphnate crystallises out in characteristic form. Excess of liquid is then sucked off with a piece of hardened filter paper. After drying and mixing the residue, the eutectic melting point (with excess of styphnic acid) is determined under the microscope. This is, for pethidine styphnate, 133° C. G. M.

**Racemic Acid, Separation from *meso*Tartaric, *dextro*Tartaric and Oxalic Acids.** G. Peyronel. (*Ann. Chim. appl. Roma*, 1952, **42**, 373.) The methods usually adopted for separating these acids are based on the varying solubilities of their potassium salts and are very inaccurate. Calcium *meso*- and *dextro*-tartrates form soluble complexes with boric acid, whereas calcium racemate is completely precipitated, as is calcium oxalate. For accurate results the details of carrying out the process should vary with the proportions of the different acids present, for which reference should be made to the original paper, but about 0·7 g. of the potassium salts dissolved in about 130 ml. of water, with the addition of 3 per cent. of boric acid and 0·5 g. of calcium phosphate gives fairly complete precipitation of the racemate on standing for 48 hours. The author gives details of a method of separating the calcium racemate with a minimum of washing, and determining the acids in the precipitate and in the solution by oxidation with 0·5N chromate. Oxalate and racemate can be separated by taking advantage of the fact that on adding calcium acetate to a solution containing boric acid, glycerol and mannite the oxalate will precipitate at once, the precipitation being complete in 15 hours, while the racemate will remain in solution several days unless unduly cooled. H. D.

**Salicylaldehyde Reaction, Essential Oil Analysis with.** S. Collett. (*Mfg. Chem.*, 1952, **23**, 96.) The salicylaldehyde reaction described by Thompson (*J. Soc. Chem. Ind.*, 1946, **65**, 121) has been applied to 35 essential oils and

l floral oil. In each case 0·1 ml. of oil was mixed with 8 ml. of ethanolic potash and the mixture refluxed for one hour. After allowing to cool 15 to 20 ml. of amyl alcohol was added and the mixture transferred to a separator together with 50 to 60 ml. of brine. After shaking, the lower layer was rejected and the solvent layer was washed with a small quantity of brine. The orange coloured amyl alcoholic solution was filtered and diluted if necessary to such a volume that its absorption could be determined in a photoelectric colorimeter. The author concludes that this reaction is of little qualitative use since the majority of the oils examined gave a positive result, but that it might be applied to the quantitative analysis of certain oils. G. R. A. S.

**Scopolamine Solutions, Characterisation of.** F. Weiss. (*Pharm. Zentralh.*, 1952, **91**, 316.) In endeavouring to characterise solutions of scopolamine by extraction of the alkaloid, it was found very difficult to obtain quantitative results for the content of base, or a correct melting point. The method which was ultimately found to be satisfactory for the assay was as follows. About 5 ml. of a 0·1 per cent. solution was treated with sodium bicarbonate and shaken with 3 quantities, each of 1 ml., of chloroform. The chloroformic extracts were evaporated on the water bath in a gentle current of air, and the residue was dissolved in 3 ml. of ethanol (previously neutralised), treated with 5 ml. of 0·01N hydrochloric acid, and titrated back with 0·01N sodium hydroxide, using bromophenol blue as indicator. A correction must be allowed for the value obtained in a blank titration. The picrate of scopolamine melts at 166° C., and the gold chloride compound (containing 2 molecules of gold chloride) at 180° C. In preparing the latter it sometimes happens that the mono compound is obtained, melting at 186° C., but this precipitation is irregular and not readily reproducible. The mono compound forms yellow needles, while the bimolecular one appears as yellow or red feathery forms. The gold content of the precipitate may be determined colorimetrically by dissolving 1 mg. in 50 ml. of water and adding 1 drop of a 0·5 per cent. solution of benzidine in 10 per cent. acetic acid. G. M.

## GLYCOSIDES, FERMENTS AND CARBOHYDRATES

**Glycosides, Use of Ion Exchange Resins with.** M. A. Chambers, L. P. Zill and G. R. Noggle. (*J. Amer. pharm. Ass. Sci. Ed.*, 1952, **41**, 461.) Columns of a strong-base anion exchange resin, Dowex-1 were used, the resin being employed either untreated (chloride form) or after treatment with 0·1M potassium tetraborate (borate form). Solutions of glycosides for experiments on the chloride columns were made with 0·01N ammonium hydroxide to give a reaction similar to that in the borate columns (*p*H 9). Elution was carried out with 0·01N ammonium hydroxide/0·01N ammonium chloride in the chloride columns and 0·001M potassium tetraborate in the borate columns. In the eluted fractions, arbutin was assayed by absorption measurements at 285 mμ, salicin and a saponin from *Quillaia saponaria* by the anthrone method, and digitoxin, gitoxin, methyl β-D-arabinopyranoside and benzyl β-D-arabinopyranoside by the orcinol method. Methyl β-D-arabinopyranoside was easily eluted from borate columns in a manner comparable to sucrose which gives a weakly ionised borate complex. Thus it appears that the pair of *cis*-hydroxyl groups in the pyranose assume positions unfavourable to the formation of a strong borate complex. The corresponding benzyl glycoside is strongly adsorbed and it is suggested that this is due to strong adsorption of the aromatic group by the resin. Neither of these glycosides is strongly adsorbed by the

chloride form. The increased adsorbent power may be due to the presence of borate, or to the absence of the highly polar chloride ion. Arbutin, salicin and saponin were adsorbed on the borate columns and subsequently eluted with potassium tetraborate solution. They were not strongly adsorbed by the chloride form. Digitoxin and gitoxin were not strongly adsorbed by the borate form of the resin. G. B.

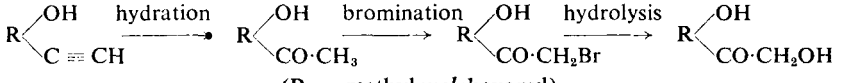
***Strophanthus ambœnsis* E. and Pax, Glycosides of the Seed of.** M. R. Salmon, R. Foppiano and W. G. Bywater. (*J. Amer. chem. Soc.*, 1952, **74**, 4536.) From the seeds of *Strophanthus ambœnis* E. and Pax was obtained 0·69 per cent. of crude glycosides from the ether extract and 4·48 per cent. of crude product from the chloroform extract. The ether-soluble fraction yielded sarveroside and intermedioside (formerly Reichstein's substance 761). The chloroform extract yielded intermedioside and panstroside (formerly Reichstein's substance 762) and a new glycoside which has not previously been found in *Strophanthus* seeds, as well as Reichstein's crystallate 790. This new glycoside melted at 232° to 240° C. and had a rotation of $[\alpha]_D$–25·2° C. It gave a negative result in the Keller-Kiliani test and a positive in the Legal test. The ultra-violet absorption spectrum showed the maximum at 216 to 218 m$\mu$ which is characteristic of the unsaturated lactone ring of the cardiac glycosides. A. H. B.

***Strophanthus schuchardti* Pax, Glycosides of the Seeds of.** R. Foppiano, M. R. Salmon and W. G. Bywater. (*J. Amer. chem. Soc.*, 1952, **74**, 4537.) The seeds of *Strophanthus schuchardti* yielded 1·04 per cent. of crude glycosides from the ether extract and 6·31 per cent. from the chloroform extract. The ether-soluble fraction yielded sarveroside after crystallisation from methanol, and dilution of the methanolic mother liquors with ether yielded intermedioside. From the chloroform-soluble glycosides was obtained a mixture of intermedioside and panstroside by solution in acetone and cooling. The mother liquors from these crystals were chromatographed to yield sarveroside, sarverogenin and panstroside. From 200 g. of seeds was obtained 1·27 g. of sarveroside, 1·09 g. of intermedioside, 780 mg. of sarverogenin and 620 mg. of panstroside.

A. H. B.

## ORGANIC CHEMISTRY

**Cortisone, Simple Analogues of.** J. D. Billimoria. (*Nature, Lond.*, 1952, **170**, 248.) Some methyl-substituted analogues of 1-hydroxyacetyl*cyclo*hexanol have been prepared by the following method. The cyanohydrin was prepared from 2-methyl*cyclo*hexanone and sodium acetylide in liquid ammonia, *cis*- and *trans*-forms being separated, hydrated with dilute sulphuric acid and a mercuric salt and purified as semicarbazones. Bromination, followed by hydrolysis yielded the *cis*- and *trans*-forms of 2-methyl-1-hydroxyacetyl*cyclo*hexanol.




(R = methyl*cyclo*hexanyl)

4-Methyl*cyclo*hexanone gave a mixture of *cis*- and *trans*-4-methyl-1-ethynyl-*cyclo*hexanols from which only a small yield of 1 pure form could be isolated. Starting with 2: 2-dimethyl*cyclo*hexanone, only a small yield of the corresponding 1-hydroxyacetyl*cyclo*hexanol was obtained. In compounds of this type any desired acylation of the primary and tertiary –OH groups may be performed without resort to selective acylation. G. B.

# BIOCHEMISTRY

## GENERAL BIOCHEMISTRY

**Antihistamines, Fungistatic Activity of.** R. B. Mitchell, A. C. Arnold and H. I. Chinn. (*J. Amer. pharm. Ass. Sci. Ed.*, 1952, **41**, 472.) A large number of antihistamines were tested as follows. Sabouraud agar plates were inoculated with the test organisms—*Tricophyton mentagrophytes*, *Tricophyton sp.* (Klein), *Microsporum canis*, *M. gypseum*, *Monosporium apiospermum*, *Phialophora verrucosa*, *Sporotrichum Schenkii* and *Candida albicans*. Filter paper discs impregnated with concentrations of the fungistatic compounds from 0·1 to 0·0005M in ethanol (70 per cent.) were placed on the plates which were incubated at 32° C. and examined for growth after 24 hours for *C. albicans* and after 6 days for other fungi. Fungistatic activity was assessed by the minimum molar concentration for complete and for partial inhibition of growth. Few preparations were active against all the test organisms, *P. verrucosa*, *S. Schenkii* and *C. albicans* being especially resistant. No correlation was established between antihistaminic or anticholinergic and fungistatic properties. Phenothiazine derivatives were among the most active compounds tested, and chlorination generally increased the fungistatic effect. Trihexyphenidyl (artane) containing a *cyclo*hexanyl group was more active than the corresponding benzene derivative. Methaphenilene (diatrin) containing a benzene nucleus was more active than methapyrilene (thenylene), the corresponding pyridine compound. G. B.

**Cortical Hormones, Solubility of.** T. J. Macek, W. H. Baade, A. Bornn and F. A. Bacher. (*Science*, 1952, **116**, 399.) The solubilities of several crystalline derivatives of cortical hormones in distilled water, normal human plasma, a solution of human serum albumin and human synovial fluid are reported. Saturated solutions were prepared by shaking an excess of the crystalline solid with 10 ml. of the test fluid in a centrifuge tube at 25° C. for 1 hour. After centrifuging and filtering, the concentrations of dissolved material in the solutions were determined by ultra-violet spectrophotometry or by the colorimetric method of Mader and Buck (*Analyt. chem.*, 1952, **24**, 666). Solubility data for the following substances are recorded:—cortisone, cortisone acetate, hydrocortisone acetate, hydrocortisone, cortisone tricarballylate, cortisone propionate, cortisone caprylate. The results indicate that hydrocortisone acetate is much less soluble in biological fluids than is cortisone acetate; both steroids are much more soluble than their esters and of comparable solubility in biological fluids. Cortisone tricarballylate shows a very marked increase in solubility in biological fluids as compared with its solubility in water and this is ascribed to salt formation. J. B. S.

**Heparin, Paper Partition Chromatography of Solutions in Water and Plasma.** D. Molho and L. Molho-Lacroix. (*C.R. Acad. Sci., Paris*, 1952, **235**, 522.) Chromatograms were prepared with a mixture of 1 part of *n*-propanol and 1·5 part of water as solvent, the spots due to heparin being observed by the pink-purple colour when the paper was sprayed with a 0·15 per cent. solution of toluidine blue. 5 $\mu$g. of a commercial sample yielded an intense spot, $R_F$ 0·57 and a fainter one $R_F$ 0, containing about 1/25th of the total anticoagulant activity of the sample. The commercial material had an absorption band at 270 m$\mu$, incompatible with the structure of heparin, but the

spot of $R_F$ 0·57 did not exhibit this absorption band. A solution of the commercial heparin in oxalated plasma (5 $\mu$g. in 0·001 ml.) treated as above had $R_F$ 0, but using as solvent a mixture of equal quantities of acetone and water, 2 spots were obtained, $R_F$ 0·67 and 0. Chromatograms of plasma with this solvent yielded spots which stained with ninhydrin $R_F$ 0·67 (albumins) and 0 (globulins). Thus about 4/5ths of the heparin was linked with albumins and the remainder with globulins, without alteration of the $R_F$ values of the proteins. On increasing the concentration of heparin in the plasma and preparing chromatograms, a stain $R_F$ 0·91 due to free heparin, appeared. Heparin combined with albumin had no more anti-thrombin action on fibrinogen than heparin alone, since the plasma co-factor was not present in sufficient quantity.

G. B.

**Hydroxocobalamin, Differentiation from Cyanocobalamin.** J. A. Campbell, J. M. McLaughlan and D. G. Chapman. (*J. Amer. pharm. Ass. Sci. Ed.*, 1952, **41**, 479.) Samples of 10 to 50 $\mu$g, contained in 1 to 2 ml. of solution were mixed with 150 ml. of ascorbic acid, freshly dissolved in 2 ml. of acetate buffer, *p*H 5·0, and heated at 70° C. for 30 minutes. The solutions were assayed microbiologically by a modified U.S.P. method. Under such conditions, pure vitamin $B_{12a}$ and $B_{12b}$ were completely destroyed, pure vitamin $B_{12}$ being unaffected. This was confirmed by measurements of light absorption at 548 m$\mu$. Mixtures were also tested and recovery of the cyanocobalamin (vitamin $B_{12}$) appeared to be unaffected by the amount of hydroxocobalamins ($B_{12a}$ and $B_{12b}$) originally present. In commercial concentrates the $B_{12b}/B_{12}$ ratio was found to vary widely, preparations with a high proportion of $B_{12}$ being apparently more stable. The method was not applicable to liver extracts, since the iron present prevents destruction of the hydroxocobalamin by ascorbic acid. G. B.

**Phosphoric Esters, Paper Chromatography of.** S. Burrows, F. S. M. Grylls and J. S. Harrison. (*Nature, Lond.*, 1952, **170**, 800.) Separation of phosphorylated sugars and adenosine phosphates has been accomplished by paper chromatography, employing an upward migration technique on acid-washed paper. $R_F$ values, although difficult to reproduce, are higher, and running times are shorter with the solvent mixtures used than with the solvent mixtures suggested by other workers. For the detection of phosphate spots on the finished chromatogram the paper is dipped in a reagent prepared from aqueous ammonium molybdate, hydrochloric acid, perchloric acid and A.R. acetone; subsequent heating and treatment with hydrogen sulphide is by the method of Hanes and Isherwood (*Nature, Lond.*, 1949, **164**, 1107). Markham and Smith's photographic method was used for the detection of substances absorbing ultra-violet light. (*Biochem. J.*, 1949, **45**, 294.) Quantitative separation of phosphorus-containing compounds in extracts from baker's yeast have been effected by these methods, a commercial sample of adenosine triphosphate being resolved into six constituents, viz. adenosine diphosphate, adenylic acid, pyrophosphate, orthophosphate, and a trace of an unknown constituent, which absorbs ultra-violet radiation. J. B. S.

**Terramycin and Aureomycin: Effect on Coagulation.** J. W. Parker and L. T. Wright. (*Science*, 1952, **116**, 282.) Experiments to determine the effects on clotting time of the intravenous injection of 100 mg. of aureomycin were conducted on 8 rabbits; similar experiments were conducted with terramycin given in the same dosage. Bleeding and clotting times were also done on 30 patients on terramycin therapy and prothrombin times on 16 patients.

Although there were some individual variations in the clotting times in the rabbits and in the bleeding, clotting and prothrombin times in the patients, there were no significant changes in any of the tests. In the treatment of several hundred patients with both aureomycin and terramycin no increased frequency of embolism has been noticed. It is concluded that neither drug in the recommended dosages produces any significant alteration in the blood coagulation mechanism, and neither drug should be withheld from any patient because of the fear of producing an intravascular clot. S. L. W.

## CHEMOTHERAPY

***S*-Alkyl *iso*Thioureas.** F. N. Fastier and C. S. W. Reid. (*Brit. J. Pharmacol.*, 1952, **7**, 417.) A study of the distribution of certain pharmacological properties amongst *iso*thioureas has shown that according to the length of the *S*- alkyl chain, *iso*thioureas of formula $CH_3(CH_2)_nS{\cdot}C(:NH)NH_2$ either raised or lowered the tone of isolated ileal strips of rabbit and guinea-pig intestine. When the *iso*thiourea decreased tone the intestinal strip became less sensitive to acetylcholine, histamine, nicotine and potassium salts, which increased as the series was ascended to about the *n*-decyl derivative. Lower homologues increased tone when present even in fairly high concentrations, homologues containing 4 to 6 carbon atoms in the side chain had a dual action, while higher homologues had only a depressant effect. Quantitative studies of the anti-acetylcholine and anti-histamine effects on isolated guinea-pig ileum showed that no simple theory of interaction of antagonistic drugs applied. Short-chain *iso*thioureas potentiated the bronchoconstrictor and vasoconstrictor actions of acetylcholine on perfused rabbit lungs, while long chain *iso*thioureas greatly decreased the sensitivity. On perfused blood vessels of the rat *S*-methyl-, *S*-ethyl-, and *S*-*n*-propyl-*iso*thiourea caused vasoconstriction but with higher homologues the action was biphasic. The influence of chemical structure upon the pharmacological activity of aliphatic amines is discussed. G. F. S.

**Anthrapyrimidines as Synthetic Amœbicides.** W. R. Jones, J. K. Landquist and N. Senior. (*Brit. J. Pharmacol.*, 1952, **7**, 486.) Examination of anthrapyrimidine and 81 amino derivatives for amœbicidal activity in rats experimentally infected with *E. histolytica* showed anti-amœbic activity to be narrowly confined to derivatives of 2- or 6-aminoanthrapyrimidine. The therapeutic effect was, however, associated with an undesirable photodynamic action. 6-aminoanthrapyrimidine given orally had an effect in dysentery in cats, but not in monkeys or in man. G. F. S.

**9-Hydroxyalkyl- and Dihydroxyalkyl-aminoalkylaminoacridines as Anthelmintics.** A. R. Surrey, C. M. Suter and J. S. Buck. (*J. Amer. chem. Soc.*, 1952 **74**, 4102.) A series of substituted 9-aminoacridines containing a primary or/and a secondary or tertiary hydroxyl group in the basic side chain was prepared. The route to these compounds consisted of treating the appropriate 9-chloro-acridine with phenol to give the 9-phenoxyacridine followed by treatment with the appropriate primary-secondary diamine. Some of the compounds were found to possess marked anthelmintic activity. Of the compounds tested, 9-(2-hydroxyethylaminoethylamino)-2-methoxyacridine, 6-chloro-9-(3-(2-hydroxyethylamino)-propylamino-2-methoxyacridine and 9-(2-(2:3-dihydroxypropylamino)-ethylamino)-2-methoxyacridine appeared to be the best anthelmintic agents when tested in Swiss mice against the oxyurid worms, *Aspicularis tetraptera* and *Syphacea obvelata*. A. H. B.

**Mepacrine and Trypan Red in Virus Diseases.** E. Weston Hurst, J. M. Peters and P. Melvin. (*Brit. J. Pharmacol.*, 1952, 7, 473.) The results of experiments on the chemotherapeutic effects of mepacrine and trypan red against viruses in mice, rabbits and chickens are reported. Mepacrine beneficially affected, to some extent, infection with Western equine encephalomyelitis, Rift Valley fever, herpes febrilis, lymphocytic choriomeningitis and St. Louis encephalitis, providing treatment was begun either before or shortly after infection. With the last two there was possibly a weak therapeutic effect with a single large dose of mepacrine given late in the infection. Rabies, influenza (neurotropic and otherwise), psittacosis, Russian spring-summer encephalitis, Murray Valley encephalitis, vaccinia, neurovaccinia, poliomyelitis, four mouse encephalomyelitis viruses, grey-lung virus, infectious myxomatosis, Aujeszky's virus, and two avian tumour viruses were at the most only doubtfully affected. Trypan red reduced mortality in herpes febrilis and had a doubtful effect in psittacosis. A number of acridines were tested against Rift Valley fever, but most were inactive. Aminacrine slightly reduced mortality, while 2-methoxy-6-chloro-9-*n*-butylaminoacridine acetate, 6-chloro-9-piperidino-2-methoxyacridine and 2:6-diaminoanthrapyrimidine prolonged the mean period of survival by 50 per cent. or more. G. F. S.

**Curarising Potency, Effect of Chain Length in Three Homologous Series.** H. O. J. Collier. (*Brit. J. Pharmacol.*, 1952, **7**, 392.) An investigation of the influence of chain length on neuromuscular blocking activity in 3 homologous series of polymethylene bis-*iso*quinolinium salts has shown the peak for activity to occur between the nonamethylene and undecamethylene compounds. Curarising potencies were determined intravenously in the rabbit and mouse. Tests for histamine release in man showed the nonamethylene member of the dimethoxy-dimethoxybenzyl series to be a more active histamine liberator than the corresponding decamethylene member.

G. F. S.

# PHARMACY

## NOTES AND FORMULÆ

**α-Cyano-β-(2:4-dichlorophenyl)-acrylic Acid, A New Plant Growth Regulator.** W. B. Ligett, C. N. Wolf, R. E. Hay and D. P. Uhl. (*Science*, 1952, **116**, 393.) The synthesis of α-cyano-β-(2:4-dichlorophenyl)-acrylic acid (I) is reported, together with tests of this new plant growth regulator on tomato and marigold plants. It is obtained by condensation of 2:4-dichlorobenzaldehyde with cyanacetic acid. Preliminary studies indicate that the inhibitory effect of α-cyano-β-(2:4-dichlorophenyl)-acrylic acid is similar to that of maleic hydrazide, both materials being capable of inhibiting the growth of tomato plants without injury. Plants treated with (I) show a decrease in apical dominance, permitting activation of the axillary buds, whereas response to maleic hydrazide is an over-all slow down of growth. In marigolds (I) caused a marked delay in flowering. Preliminary toxicological data in small animals shows that the lethal dose of (I) in rats is between 50 and 250 mg./kg. of body weight, when given orally, whilst that of its diethanolamine salt is between 250 and 500 mg./kg. Effects on tomato plants were evaluated by 4 methods, seed germination, lanolin paste test, single leaf dip test and total spray test. Using a 1 per cent. solution for total spray, death occurred with young plants; a 0·1 per cent. solution caused growth inhibition without injury. J. B. S.

## PHARMACOLOGY AND THERAPEUTICS

**α-Acetylmethadols, Actions and Addiction Liabilities in Man.** H. F. Fraser and H. Isbell. (*J. Pharmacol.*, 1952, **105**, 458.) Observations on some of the actions of *dl*-, *d*- and *l*-α-acetylmethadols in man have shown them all to have addictive properties. Single injections of the *dl*-compound in former morphine addicts produced morphine-like effects which persisted for more than 24 hours. With the *d*-isomer definite morphine-like effects appeared after subcutaneous injection but doses up to 20 mg. had no effect orally. The effects of a subcutaneous or intravenous injection of the *l*-isomer were delayed until 14 hours after administration. They persisted for up to 72 hours afterwards and a danger of a cumulative action therefore exists. Orally the effects appeared earlier but were also of long duration. All three compounds relieved the abstinence syndrome of morphine addiction. G. F. S.

**Barbiturates, Autonomic Ganglion Depressant Properties of.** K. A. Exley. (*Nature, Lond.*, 1952, **170**, 242.) Ganglion-depressant effects were assessed by a method involving periodic stimulation of the pre-ganglionic trunk of the cervical sympathetic and recording the contractions of the nictitating membrane. Amylobarbitone was one quarter as potent as tetraethylammonium bromide. Depressant properties and anæsthetic potencies of some barbiturates relative to amylobarbitone are tabulated.

| Barbiturate (sodium salt) | Mean potency on superior cervical ganglion (A) | Relative anæsthetic potency (B) | Ratio $\frac{A}{B}$ |
|---|---|---|---|
| Amylobarbitone .. | 100·0 | 100·0 | 1·00 |
| Butobarbitone .. .. | 99·1 ± 6·2 | 71·0 | 1·40 |
| *n*-Hexylethylbarbitone .. | 43·4 ± 2·7 | 69·2 | 0·63 |
| Pentobarbitone .. .. | 42·5 ± 1·5 | 163·6 | 0·26 |
| Hexobarbitone .. .. | 31·7 ± 2·9 | 186·2 | 0·17 |
| Barbitone .. .. | 17·1 ± 1·3 | 23·1 | 0·74 |
| Phenobarbitone .. | 14·2 ± 0·6 | 40·3 | 0·35 |
| Thiopentone .. .. | 12·8 ± 1·2 | 450·0 | 0·03 |

G.B.

**Barbituric Acid Derivatives, New, Spasmolytic Action of.** H. Hofmann and E. Phillips. (*Pharm. Zentralh.*, 1952, **91**, 273.) A number of new barbituric acid derivatives were compared for spasmolytic activity. The method used was to determine the minimum dose required to prevent the onset of spasms in rats after the administration of pentamethylenetetrazole. The compounds tested were 5-methyl-5-(*N*-methyl-*N*-propyl)aminobarbituric acid, 5-methyl-5-(*N*-methyl-*N*-*iso*butyl)-aminobarbituric acid, 5-methyl-5-(*N*-methyl-*N*-butyl)-aminobarbituric acid, *N*-*iso*propyl-5-methyl-5-ethylbarbituric acid, *N*-*iso*propyl-5·5-diethylbarbituric acid, and 5-ethyl-5-crotylbarbituric acid. The last-mentioned compound was especially effective compared with phenobarbitone. The aminobarbituric acids also show marked anti-epileptic action. G. M.

**Bis (Quaternary Ammonium Salts) Derived from Laudanosine as Neuromuscular Blocking Agents.** E. P. Taylor. (*J. chem. Soc.*, 1952, 142.) Because it had previously been shown (*J. chem. Soc.*, 1951, 1150) that certain heterocyclic decamethylene bis(quaternary ammonium salts) possess neuromuscular blocking activity of true curare type, a number of bisquaternary salts of laudanosine were prepared. In addition to polymethylene derivatives, compounds containing the $[CH_2]_4{\cdot}O{\cdot}[CH_2]_4$ and the $[CH_2]_5{\cdot}O{\cdot}[CH_2]_5$ chain were prepared. These bis-quaternary laudanosinium salts were found to be powerful neuromuscular

blocking agents, in animals, of true curare type, being antagonised by neostigmine and causing the typical flaccid paralysis in the chick. In rabbits, the two most active compounds were those in which the nonamethylene and the decamethylene chain separate the quaternised laudanosine *N* atoms. Preliminary results with the decamethylene derivative indicate that it possesses approximately half to two-thirds of the curarising activity of (+)-tubocurarine chloride in man, that it is antagonised by neostigmine, and that it appears not to produce undesirable side-effects. A. H. B.

**Chloramphenicol, Anti-acetylcholine Effects of.** L. Donatelli and E. Genazzani. (*Arch. int. pharmacodyn.*, 1952, **90**, 332.) Solutions containing 10 per cent. of chloramphenicol in propylene glycol were tested for anti-acetylcholinic activity on the isolated guinea-pig colon and frog heart, and *in vivo* in the bronchi of the guinea-pig and rabbit blood pressure test. Concentrations of chloramphenicol required to produce anti-acetylcholinic activity were greater than those encountered in the therapeutic use of the antibiotic. The *laevo*-compound showed the greatest, and the *dextro*-compound the least, activity. Control tests were performed on the propylene glycol used as solvent. It is suggested that in the isolated intestine and the bronchi *in situ*, chloramphenicol acts as a light depressor of acetylcholine cellular receptors and as a myolytic, whereas in the frog heart and the blood pressure of the rabbit, the action is a parasympathetic one disturbed by the parallel myolytic action. G. B.

**Chorionic Gonadotrophin, Response of the Male Toad, *Bufo marinus*, to.** J. S. Wannan. (*Med. J. Aust.*, 1952, **2**, 83.) Male specimens of *Bufo marinus*, spermiate when injected with chorionic gonadotrophin. Maximum elimination of spermatozoa occurs after 4 hours with commercially prepared human chorionic gonadotrophin and after 24 hours with pregnancy urine. The toads may be used again after 7 days and are not affected by seasonal variations. The mean median effective dose is 18·3 I.U. with fiducial limits (P = 0·95) 16·9 to 19·8 I.U. and the dose response curve ($\log_{10}$ slope) 3·67 ± 0·30. The pregnancy test with this toad is approximately one-half as sensitive as the Friedman rabbit test. G. F. S.

**Daraprim Resistance in Experimental Malarial Infections.** I. M. Rollo. (*Nature, Lond.*, 1952, **170**, 415.) A highly resistant strain of *Plasmodium berghei* has been produced in white mice in a relatively short time. The technique was to administer to an infected mouse a single dose of the drug when examination of a stained blood film showed 40 to 50 per cent. of the red blood cells to be parasitised; on subsequent relapse after recession of the parasitæmia the mouse was dosed for a second time and on relapse the strain was passaged. After 2 further successive mice had received a dose each in this way the strain was tested in comparison with the normal untreated parent strain, which proved to be more than 20 times less sensitive to the action of the drug. Treatment with one more single dose and 3 drug courses carried out as described by Goodwin (*Nature, Lond.*, 1949, **164**, 1133) resulted in a very high degree of drug resistance. Where, however, the drug is made to act more as a suppressant, as in the technique (described in the communication) for the development of a resistant strain of *P. gallinaceum*, the initial development of resistance is slow and prolonged. Since, in human malaria, the main use of the drug will probably be as a suppressant, the problem of daraprim resistance in the field is unlikely to become a serious disadvantage to its use. S. L. W.

**Disulphiram (Antabuse) in Experimental Animals, Toxicity of.** G. P. Child and M. Crump. (*Acta pharmacol. toxicol.*, 1952, **8**, 305.) Toxicity tests were carried out on mice, rats, rabbits and dogs, 5 animals being used for each dose in determinations of the LD50 and 2 animals for each dose in determining the approximate lethal dose. The disulphiram was usually given orally in water by stomach tube but in chronic toxicity studies it was administered with a small quantity of food. In some tests it was given intraperitoneally or subcutaneously, and in others a fat solvent was used as vehicle in place of water. The signs of toxicity were the same in each kind of animal. The minimal effect was diarrhœa and a small loss in weight; in mice a dose as great as 10 g./kg. produced only this effect. Moderate toxicity was indicated by mucous diarrhœa, anorexia, lethargy and a 15 per cent. weight loss. Severe toxicity was shown by ataxia, hypothermia and flaccid paralysis beginning with the hind legs and ascending until the respiratory muscles were affected, with up to 34 per cent. weight loss and blood in the stools. If the animals did not succumb they recovered completely in 6 to 10 days. With fat solvents instead of water as the vehicle toxicity was markedly increased. In rats disulphiram bezoars were found in the stomach. The single oral doses required to produce moderately severe signs of toxicity were 3·5, 1·0 and 1·0 g./kg. respectively for rats, rabbits and dogs. Tests for chronic toxicity showed that moderately severe signs were produced in rats on a daily dose of 0·5 g./kg. only after 21 days. In rabbits and dogs the corresponding times were 5 and 6 days respectively, death occurring if the drug were administered for 9 and 7 days respectively. Most of the rats, especially those given a suspension in cottonseed oil, had gastric ulceration. Animals which were examined after developing severe toxicity showed a variety of systemic and local effects including generalised visceral hyperæmia, passive congestion of the liver, kidneys, adrenals, spleen, heart and lungs, and demyelinisation of the medulla, cerebrum and spinal cord. Application of a 50 per cent. suspension to the depilated abdominal skin of rabbits caused a slight erythema. Application to the nasal mucosa or conjunctiva rapidly caused inflammation. It is probable that many of the toxic effects of the drug are due to its irritant action but the dose required to produce them is far beyond the amount required to produce ethanol sensitisation in man. H. T. B.

**Gitalin, a Clinical Study of.** M. R. Hejtmancik and G. R. Herrmann. (*Arch. intern. Med.*, 1952, **90**, 224.) Gitalin, a water-soluble amorphous mixture of digitalis glycosides, was used in the initial digitalisation of 49 patients with cardiac decompensation and the maintenance dosage was determined for 131 patients. The efficacy of gitalin in the digitalisation and maintenance of patients in congestive failure was demonstrated. The digitalising dose required varied from 4·5 to 9·0 mg., the average being 6·5 mg. The majority of patients were adequately maintained with 0·5 mg. per day. Toxic effects were uncommon, generally resulting from deliberate increase in dosage, and were similar in type to those occurring with other digitalis preparations. In 22 patients the average minimal maintenance dose was 0·54 mg. and the average minimal toxic dose 0·91 mg. In one case 35 mg. was given in 4½ days without toxicity. Improvement was noted in 15 out of 18 patients with apparently refractory cardiac decompensation when treated with gitalin instead of with other digitalis preparations and in 9 the improvement seemed definitely related to the change to gitalin. In the management of such refractory cases gitalin appears to offer a real advantage. S. L. W.

**Insulin-Zinc Compounds with Prolonged Action.** K. Hallas-Møller, K. Petersen and J. Schlichtkrull. (*Science*, 1952, **116**, 394.) Chemical, biological and clinical experiments are described which were designed to elucidate the interaction between insulin and zinc. Solubility measurements in 0·1M buffer solutions of varying *p*H indicate that insulin in an acetate buffer and in the presence of 2 mg. zinc/1000 U shows a marked extension of the *p*H precipitation zone, so that it becomes insoluble to the same degree as protamine zinc insulin. The authors do not recommend the use of phosphate or citrate buffers, which appear to have a greater affinity for zinc than does the insulin. Experiments with depancreatised dogs indicated that acid solutions of zinc and insulin, and of protamine zinc insulin were not capable of producing sustained effects. Insoluble insulin-zinc compounds gave more prolonged and greater lowering of blood sugar. Precipitation of insulin in crystalline form in the presence of zinc only occurs within a narrow *p*H range (*ca.* 4·7 to 5·7); outside this range the insulin-zinc is amorphous. Amorphous insulin and insulin crystals suspended in zinc-containing media, show a zinc content which depends on both the concentration of the zinc and insulin and also on the *p*H of the medium. Under suitable conditions insulin crystals may then contain up to 2 per cent. of zinc. Crystalline insulin-zinc is insoluble in water at the neutral point and retains its excessive zinc content; suspended in phosphate buffer it dissolves since the zinc becomes precipitated as zinc phosphate. Suspensions of these crystals show a prolonged action in depancreatised dogs, ensuring a low fasting blood sugar. These results are confirmed in clinical experiments in human diabetics. Further experiment shows that it is not a necessary condition for obtaining a prolonged effect that the crystals should possess an increased zinc content before injection, though the effect is completely neutralised in the presence of phosphate ions. The size of insulin crystals used in biological experiments is also important, preparations from larger crystals having a somewhat more protracted action than those from smaller crystals. J. B. S.

**Laudolissin—a Long-acting Curarising Agent.** H. O. J. Collier and B. Macauley. (*Brit. J. Pharmacol.*, 1952, **7**, 398.) Laudolissin, decamethylene-bis [1:2:3:4-tetrahydro-6:7-dimethoxy-1-(3′:4′-dimethoxybenzyl-2-methyl-*iso*quinolinium salts] (Compound 20), has been shown to be a true curarising drug more potent than *d*-tubocurarine in the cat and rabbit, but less potent in the rat and mouse. Its paralysing action is antagonised by neostigmine and by succinylcholine and is of longer duration than with *d*-tubocurarine in the cat. In blocking autonomic ganglia laudolissin had only one-fourth the potency of *d*-tubocurarine and in cat and man it released less histamine. A related compound, decamethylenebis [1:2:3:4-tetrahydro-6:7:8-trimethoxy-2-methyl*iso*quinolinium iodide] (Compound 15), had a shorter curarising action and in man released much more histamine. G. F. S.

**Laudolissin and Compound 15 as Curarising Agents, Evaluation of.** R. I. Bodman. (*Brit. J. Pharmacol.*, 1952, **7**, 409.) The two curarising drugs, Compound 20 (Laudolissin) and Compound 15, have been investigated in man. Compound 15 was a potent histamine liberator and unsuitable for clinical use. Compound 20 had very similar actions to *d*-tubocurarine. Tested on the hand-grip of conscious volunteers it was half as potent as *d*-tubocurarine and its action, like *d*-tubocurarine, was antagonised by neostigmine. At equiactive dose levels Compound 20 acted a little longer than *d*-tubocurarine. Side effects, histamine release and effects on the central nervous system, were identical with those of *d*-tubocurarine. G. F. S.

**Laudolissin (Compound 20), Clinical Trial of.** R. I. Bodman, H. J. V. Morton and W. D. Wylie. (*Lancet*, 1952, **263**, 517.) This is one of the heterocyclic decamethylene bis quaternary ammonium compounds, possessing muscle-relaxing properties, synthesised by Taylor and Collier (*Nature, Lond.*, 1951, **167**, 692). Compound 20 was substituted for the established relaxants in 186 surgical procedures; 91 of the patients were anæsthetised with nitrous oxide, with or without pethidine, and the remainder with *cyclo*propane, induction being by thiopentone in all cases. A dose of 30 mg. of compound 20 was found to provide the same relaxation as 15 mg. of *d*-tubocurarine, but whereas the latter would have been expected to give adequate abdominal relaxation for 30 minutes the relaxation with compound 20 lasted for 40 minutes or more. Maximum abdominal relaxation was not evident until at least 5 minutes after the injection; the relative action on the abdominal muscles and the diaphragm seemed no different from that of *d*-tubocurarine. "Rectangular respiration" frequently occurred and had the same significance as when occurring with other muscle-relaxants. Relaxation of vocal cords, and hence conditions for intubating, was far less satisfactory than with gallamine triethiodide. A satisfactory method is to use succinylcholine (with or without pethidine), which has a very short action, and to follow it with compound 20 for maintaining surgical relaxation. The action of compound 20 is antagonised by neostigmine, which was used on 35 occasions with satisfactory results. No important undesirable side-effects were noticed in this series of patients. Compound 20 is not miscible with thiopentone, pethidine or succinylcholine. S. L. W.

**Mercumatilin (Cumertilin), Toxicology of.** H. Blumberg, A. Schlesinger and S. M. Gordon. (*J. Pharmacol.*, 1952, **105**, 336.) Mercumatilin, 8-(2′-methoxy, 3′-hydroxymercuri-propyl)-coumarin-3-carboxylic acid-theophylline, is a new mercurial diuretic which differs from other mercurial diuretics in that the mercurated methoxypropyl group is attached directly to a ring carbon atom and has no amide linkage; also the ring structure is coumarin, a heterocycle. When dissolved as the sodium salt and adjusted to a *p*H of about 7·3 it forms a highly stable aqueous solution at a concentration equivalent to 39 mg. Hg/ml. This solution contains 93 mg./ml. of the mercury compound and 50 mg./ml. of theophylline, and has been kept for more than 3 years at room temperature without precipitation of mercury or any sign of deterioration. The acute toxicity of the compound was determined intravenously in mice, rats and rabbits; intramuscularly in rats and rabbits; subcutaneously in mice; and orally in rats. In comparative tests for acute intramuscular toxicity in rats, acute subcutaneous toxicity in mice, and chronic intramuscular toxicity in rabbits, the toxicity of mercumatilin was found to be approximately the same as that of meralluride, and the same as or less than that of mersalyl-theophylline. On subcutaneous injection into shaved mice the local irritation produced was approximately the same as that from meralluride and mersalyl-theophylline and much less than that from mercurophylline. S. L. W.

**Methylene Violet and Other Compounds of the Phenosafranine Series, Antifilarial Action and Toxicity of.** F. Hawking, W. E. Ormerod, J. P. Thurston and W. A. F. Webber. (*Brit. J. Pharmacol.*, 1952, **7**, 494.) An investigation of compounds of the phenosafranine series for antifilarial activity in cotton rats infected with *Litomosoides carinii* showed some of them to kill the adult worms, but not to affect the microfilariæ *in vivo*. There was some action upon microfilariæ *in vitro*, but this was not parallel with the action upon the adult worms *in vivo*. The most active compounds of the series were

sufficient proof that the author's decision to reserve for a separate volume the subject of the therapeutic usage of other antibiotics was a wise one.

Under general considerations the author deals briefly with the antibacterial action of penicillin and its pharmacological and physical properties, and especially with allergic manifestations after penicillin administration and their management. The chapter on the administration of penicillin gives a detailed account of the routes of parenteral injection and of methods of inhalation and topical application, and the many illustrations, tables and graphs in this chapter are an invaluable guide to those who are not familiar with the various possible routes of administration. Five chapters deal with the penicillin-sensitivity of micro-organisms, including bacteria, actinomyces, fungi and protozoa, causing localised or systemic disease in man. The remainder of the volume deals with the treatment of diseases of specific organs: infections of the cardiovascular system, skin and soft tissue, joints and bones, central nervous system, thorax, abdomen, the genito-urinary system, nose, ear and throat, eyes, and infections occurring in obstetrical and gynaecological conditions. The final chapter is devoted to battle casualties, of which the author had wide experience in the last war.

The author has provided a detailed and authoritative account of the mode of administration and action of this first and still most valuable antibiotic in every field of medicine and surgery; it is a volume of interest to the pharmacologist and pharmacist no less than to the clinician. The comprehensive bibliography (over 70 pages) adds greatly to its value as an important reference book for anyone concerned with the therapeutic uses of penicillin. J. UNGAR.

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ABSTRACTS (*continued from page* 210).

**Treburon, Preliminary Studies on.** D. A. Scholz and N. W. Barker. (*Proc. Mayo Clin.*, 1952, **27**, 332). Treburon is the sodium salt of sulphated polygalacturonic acid methyl ester methyl glycoside and has an anticoagulant action similar to that of heparin. The effects of treburon were studied in 15 patients; it was given sublingually to 3 patients and intravenously to 12. A dosage of 500 mg. was given sublingually to 2 patients and of 1000 mg. to a third. Intravenously, 3 patients received 150 mg. and 6 patients 200 mg.; the remaining 3 patients were given varying doses of treburon intravenously followed by protamine sulphate intravenously. The coagulation time of the patients receiving treburon sublingually was unaffected. In those receiving 150 mg. intravenously a significant prolongation of coagulation time had developed within 30 minutes, but at the end of 2 hours coagulation time was returning to normal and at the end of 4 hours had returned to normal. In those receiving 200 mg. intravenously the coagulation time of 3 of the patients at the end of 3 hours was still at least twice the normal coagulation time. 50 mg. of protamine sulphate given to 2 patients after 150 mg. of treburon intravenously returned coagulation to normal within 30 minutes, but the same dose given 30 minutes after an injection of 200 mg. of treburon caused a prompt decrease in coagulation time but did not return it to normal. Serious toxic reactions were not observed in any of the patients. S. L. W.

**Triethylene Melamine for Treatment of Polycythæmia Vera.** N. Rosenthal and R. L. Rosenthal. (*Arch. intern. Med.*, 1952, **90**, 379.) Triethylene melamine has an action resembling that of nitrogen-mustard and is effective when given

(*continued on page* 214).

Colour Index No. 842 (methylene violet RRA), C.I. No. 849, and C.I. 851. An aryl group attached to a quaternary nitrogen atom appeared to be essential for activity. Methylene violet was not unduly toxic when injected into mice, cotton rats, rabbits and monkeys. Toxic effects were concentrated on the liver and kidney. Orally it was poorly absorbed. When injected it was mainly excreted in the urine as an oxidised derivative which had no filaricidal activity. Clinical trials showed methylene violet to have no filaricidal action upon the microfilariæ or adult worms of *Wuchereria bancrofti* or *Acanthocheilonema perstans* in man and possibly *Onchocerca volvulus*. Methylene violet had a toxic action on the finger nails of some patients. G. F. S.

***iso*Nicotinyl Hydrazide, Pharmacology of.** J. F. Reinhard, E. T. Kimura and R. J. Schachter. (*Science*, 1952, **116**, 166.) The acute oral, intraperitoneal and intravenous toxicities were determined in mice, and oral and intraperitoneal toxicities also in rats and guinea-pigs. Toxic signs consisted of spasmodic tremors, salivation, convulsions, terminal tetanic spasm and respiratory arrest. An assessment of the LD50s indicated that the drug had relatively low toxicity in all three species. In addition *iso*nicotinyl hydrazide was injected intravenously into unanæsthetised dogs in large dosage (25 mg./kg.). Except for salivation, the animals appeared normal. Dogs were anæsthetised with pentobarbitone, and blood pressure, respiration and intestinal movements recorded kymographically; none of these functions was affected following the intravenous injection of the drug in single doses of up to 100 mg./kg. or in multiple doses totalling 146 mg./kg. On the isolated guinea-pig ileum and uterus no perceptible change was produced in normal functioning with concentrations as high as 100 $\mu$g./ml. of bath fluid. On the isolated guinea-pig, rat and rabbit heart aqueous solutions of *iso*nicotinyl hydrazide (2·5, 5·0, 10·0 and 100 $\mu$g.) injected into the perfusion system had no effect on the rate and amplitude of ventricular contractions or on the coronary perfusion rate. Experiments on mice indicated that both phenobarbitone and chloral hydrate were effective antidotes, but because of its favourable therapeutic index phenobarbitone was preferred. S. L. W.

**Pyrogen, Bacterial, (Piromen) in Neurological Disorders.** A. A. Bailey, E. D. Rooke and E. A. Rodin. (*Proc. Mayo Clin.*, 1952, **27**, 340). The pyrogen used (piromen) is a sterile, non-protein, non-anaphylactogenic bacterial component, of which the active factor appears to be a complex polysaccharide. It can be given intravenously or subcutaneously and produces a general systemic reaction characterised by activation of the reticulo-endothelial system, stimulation of the adrenal cortex, and, in appropriate doses, elevation of the body temperature. It is a relatively non-toxic agent. The present investigation was conducted on 57 patients suffering from a variety of neurological disorders, including amyotrophic lateral sclerosis, multiple sclerosis, retrobulbar neuritis, arachnoiditis, traumatic neuritis, neuronitis, traumatic paraplegia or the residual effects of poliomyelitis. Dosage varied from 2 to 9 $\mu$g. and treatment continued over 4 to 24 weeks. The results were not dramatic; 8 patients improved (4 out of 22 with multiple sclerosis), 32 were unchanged and 17 became worse. Untoward reactions included mild malaise, headache and backache, nausea or dizziness, 4 to 12 hours after the injection. Epigastric distress occurred in 2 patients with peptic ulcer and in 1 patient an exacerbation of previously mild rheumatoid arthritis developed. S. L. W.

reliability of the book as fully as possible. No errors were noted, and the only omission regarding which one had lately met enquiry was that of prostatic extract. In short, the completeness of this volume is striking, and the recent date of many of the entries point to a good number of additions at the galley-proof stage.

The editorial task was begun in 1949 by Mr. T. C. Denston and continued from 1950 by Dr. Capper. They and their assistants deserve warm praise for their work and, it may be suggested, rather more recognition of their responsibility than is given by the brief reference in the preface.

This book is an essential for both pharmacist and physician, and the best present one could find for a student of either profession.

W. P. K.

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ABSTRACTS (*continued from page* 212).

orally. It has been used in the treatment of leukæmia and various neoplasms and its depressant effect on hæmatopoiesis suggested its trial in polycythæmia vera. 30 patients in whom the disease had continued for from 1 to 20 years were treated. Phlebotomy was withheld for at least a month prior to treatment and until the therapeutic effect of the compound was apparent. Blood studies were made at intervals of 2 to 4 weeks. The dosage was 2·5 to 5 mg. every 1 to 3 days, orally one hour before breakfast, until the total amount reached 15 to 40 mg. A further course was given 2 to 3 months later depending upon the response. The only side effect was an occasional complaint of nausea. 20 patients showed a satisfactory symptomatic and hæmatological response with an average remission of 8 to 9 months following an average course of 30 mg. of the drug. Patients in whom the disease was of shorter duration and whose thrombocyte and white blood cell counts were normal responded better than those with a longer history and elevated blood counts. Further observations are necessary before valid comparisons can be made of the treatment of this disease with triethylene melamine and with radioactive phosphorus.

H. T. B.

**_d_-Tubocurarine Chloride U.S.P. and Dimethyl Ether _d_-Tubocurarine Iodide, Comparative Potency of.** E. E. Swanson, W. R. Gibson and C. E. Powell. (*J. Amer. pharm. Ass. Sci. Ed.*, 1952, **41**, 487.) The following comparative potencies were determined using dimethyl ether of *d*-tubocurarine iodide trihydrate and *d*-tubocurarine chloride pentahydrate.

| Animal | Method | Relative potency dimethyl ether of *d*-tubocurarine iodide / *d*-tubocurarine chloride |
|---|---|---|
| Rabbit .. | Head drop (U.S.P. method) | 9·02 ± 0·33 |
| Rabbit .. | Head drop (Single dose cross-over) | 8·25 ± 0·50 |
| Mouse .. | Sloping screen paralysis | 0·803 ± 0·048 |
| Rat .. | Sloping screen paralysis | 8·04 ± 0·33 |
| Rat .. | Intact gastrocnemius sciatic nerve | 5 |
| Frog .. | Isolated gastrocnemius sciatic nerve | 4 |
| Rat .. | Isolated phrenic nerve-diaphragm | 4 |
| Frog | Isolated rectus abdominis | 0·833 |

Except in the tests in mice and in experiments with the frog rectus abdominis, the dimethyl ether was considerably more potent than *d*-tubocurarine itself.

G. B.