# ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

## CHEMISTRY

### ANALYTICAL

**Alkaloids, Paper Micro-chromatography of.** R. Munier and M. Macheboeuf. (*Bull. Soc. Chim. biol.* 1950, **32,** 904.) The procedure involves the use of a solvent which is completely miscible with water. An example is given of the application to a mixture of caffeine, theophylline, theobromine, xanthine and trigonelline (all of which have a very small dissociation constant) in a solution containing hydrochloric acid. The quantities of each base were of the order of 20 to 50μg. The chromatographic phase was prepared by mixing 50 ml. of *n*-propanol with 25 ml. of a mixture of 95 volumes of water and 5 volumes of concentrated hydrochloric acid. Movement of the solvent was upwards, and the spots were detected photographically at 270 mμ by the method of Markham and Smith (*Nature,* 1949, **160,** 250.) In order to obtain good localisation it is necessary to pay attention to the water content of the miscible phase. The method may be applied to a mixture of morphine, codeine and thebaine, also to alkaloids of low dissociation constant. In this case the usual method with *n*-butanol does not give satisfactory results because it is impossible to acidify the solution sufficiently with a suitable acid. A mixture containing 3 volumes of water with 3 of acetone gives good results with a mixture of morphine, atropine and scopolamine, but is unsatisfactory for brucine and strychnine, although all these alkaloids have similar dissociation constants. If however the water is replaced by ammonia solution (1·05 per cent.), round spots are obtained with all 5 alkaloids. The authors prefer not to use the term $R_F$, since in the present case the constitution of the stationary phase varies continuously and the speed of displacement of the spots may vary; standard tests should always be run in parallel. G. M.

**Alkaloids, Separation of, by Paper Chromatography.** P. Mesnard and E. Boussemart. (*Bull. Trav. Soc. pharm. Bordeaux,* 1950, **88,** 175.) Application of the paper chromatography method of Macheboeuf and Munier (*this Journal,* 1950, **2,** 716) to a solution containing morphine, scopolamine, sparteine and strychnine did not give a satisfactory separation of the alkaloids, as the $R_F$ values are too close together. By treating the original solution with N sodium hydroxide, sparteine and strychnine are precipitated and morphine and scopolamine remain in solution. Chromatography on paper of the two fractions separately then gives good results. G. M.

**Ampoule glass, Testing of.** L. Domange. (*Ann. pharm franc.,* 1950, **8,** 574.) In testing ampoules for alkalinity and soluble matter, it is undesirable to seal them, on account of the danger of introducing carbon dioxide from the flame, while on subsequent opening there is a possibility of solid matter (especially glass dust from the file scratch) increasing the apparent weight of residue. The method used in the National Laboratory for the Control of Medicaments is as follows. The ampoules, cleaned and cut to a uniform length, are packed into a glass dish containing a layer of solidified paraffin

wax. At opposite sides are placed two tubes, of which the ends, cut to a bevel, rest on the paraffin. The paraffin is melted and allowed to solidify again. The block of ampoules is inverted, and filling is carried out by immersing the tips in water in a vacuum vessel. When filled, the block of ampoules is reversed, covered with a glass dish, and autoclaved. After cooling, it is necessary to remove condensed water which has collected underneath the layer of paraffin: this is done by piercing the wax, inside the two tubes, with a hot wire, and removing the water with filter paper. The block is then inverted and the contents of the ampoules are removed by means of a vacuum. G. M.

**Cocaine and other Local Anæsthetics, Separation of, by Paper Chromatography.** G. Vitte and E. Boussemart. (*Bull. Trav. Soc. pharm. Bordeaux,* 1950, **88,** 181.) For separation of 4 local anæsthetics the method of ascending paper chromatography was used. The solvent was prepared by shaking 50 parts of butanol with 15 of acetic acid and 45 of water; the upper layer is used as a mobile solvent and the lower one for saturating the atmosphere. $R_F$ values are as follows: procaine, 0·69; butelline, 0·90; cocaine, 0·82; orthocaine, 0·82. G. M.

**Diamorphine and Ethylmorphine, Microscopic Distinction between.** G. Denigés. (*Bull. Trav. Soc. pharm. Bordeaux,* 1950, **88,** 165. When a drop of an aqueous solution of diamorphine or ethylmorphine is treated with a small drop of ammonia (excess being avoided), the amorphous base which first separates soon becomes crystalline. In the case of diamorphine radiating groups of hexagonal crystals are formed, whereas with ethylmorphine the crystals are prismatic, the outline being rectilinear. The solid may be examined by placing 1 to 2 mg. on an object glass and adding a drop of water so that the whole dissolves, then adding a drop of ammonia. G. M.

**Progesterone in Oil Solution, Determination of.** H. Cohen and R. W. Bates. (*J. Amer. pharm. Ass. Sci. Ed.,* 1951, **40,** 35.) The following method for the determination of progesterone in ethanolic solutions depends upon the formation of an orange-red crystalline 2:4-dinitrophenylhydrazone of melting-range 272° to 274°C. An ethanolic solution containing 5 to 10 mg./ml. is mixed with sufficient reagent to provide 3 mg. of dinitrophenylhydrazine for each mg. of progesterone, boiled on a water-bath for 1 minute, allowed to stand at room temperature for 1 hour and filtered. The precipitate is washed with a mixture of 1 part of hydrochloric acid and 5 parts of ethanol, and finally with water before drying at 110°C. Each g. of residue is equivalent to 0·466 g. of progesterone. For oily solutions containing 2 to 25 mg./ml., a 1-ml. sample is mixed with 5 to 10 volumes of light petroleum or hexane and treated as above, except that the solution is allowed to stand in a refrigerator instead of at room temperature, and that oil is removed from the precipitate by preliminary washing with light petroleum, before using the ethanolic hydrochloric acid. The dinitrophenylhydrazine reagent, which is stable for 3 months if stored in a refrigerator, is prepared as follows. Shake 0·5 g. of dinitrophenylhydrazine with 5 ml. of hydrochloric acid until the mixture becomes yellow. Add 100 ml. of ethanol (dehydrated), heat until dissolved, add 1 ml. of hydrochloric acid, cool overnight in a refrigerator and filter. G. B.

**Solanaceous Drugs, Rapid Method of Assay of.** S. P. Dijkstra. (*Pharm. Weekbl.* 1951, **86,** 129.) The following is a rapid and simple method

for the determination of alkaloids in belladonna and stramonium: 3 g. of the powdered material is shaken frequently for 1 hour with 30 ml. of water containing 3 drops of 4N sulphuric acid. After filtering through a sintered glass crucible, 13 ml. of the filtrate is shaken vigorously for some minutes with 65 ml. of ether and 4 ml. of 10 per cent. ammonia; 3 g. of tragacanth is added and the mixture is again shaken, and filtered through a 15 cm. diameter paper into a 100-ml. measuring cylinder. The volume of the ethereal solution is noted, and it is transferred to a flask. Ether is removed by distillation, the ether vapour is blown out of the flask, and the residue is again evaporated with a little ether. The residue is dissolved in 2 ml. of ethanol, treated with 10 ml. of water, and titrated with 0·02 N hydrochloric acid, using methyl red-methylene blue indicator. On the basis of an assumed moisture content for the drug of 10 per cent., and extractive content of 2·6 per cent., the 13 ml. of extract taken for the assay is assumed to correspond with 1·254 g. of the drug. G. M.

**Tropine Alkaloids, Colorimetric Estimation of.** F. Durick, J. S. King, Jr., P. A. Ware and G. Cronheim. (*J. Amer. pharm. Ass., Sci. Ed.*, 1950, **39**, 680.) The method depends upon the combination of alkaloids with dyes to form salt-like compounds which are soluble in benzene, the optimum *p*H being 5·5. Mix 5 ml. of buffer solution of *p*H 5·3 with 5 ml. of dye solution (prepared by dissolving 0·2 g. of bromocresol purple in 15 ml. of water and 3·2 ml. of 0·1 N sodium hydroxide and diluting to 250 ml.) and add 10 ml. of the sample, containing 0·1 to 20 mg. of the alkaloid. Extract with two 50-ml. quantities of benzene, remove moisture drops by centrifuging and extract an 80-ml. aliquot with two 10-ml. quantities of 0·05N sodium hydroxide. Dilute the mixed alkaline liquids to 25 ml., filter and measure the transmittancy. Calculate the result by reference to standard curves, which should be prepared with the same batch of dye, and checked frequently, because shifts in sensitivity may occur. Hyoscine gives a much weaker colour than hyoscyamine, atropine or homatropine, probably because the hyoscine-dye compound is less soluble in benzene. The method is applicable to the assay of preparations of belladonna and hyoscyamus, after removal of chlorophyll and other material by the method of the U.S.P. XIII. G. B.

## GLYCOSIDES, FERMENTS AND CARBOHYDRATES

**Saponin Hæmolysis, Course of.** L. Fuchs and J. Koch. (*Sci. Pharm.*, 1950, **18**, 85.) In determining a hæmolytic index, the time for which the saponin is allowed to act is of importance as, while some saponins, especially digitonin, act very rapidly, others (especially primula saponin) are much slower. With the slow hæmolysing saponins especially, the action is delayed by low temperature: a temperature of 15° to 20°C. is to be preferred, and it should not be allowed to drop below 10°C. Further, in determining the hæmolytic index it is advisable to mix the contents of the tubes, not only after 15 minutes, but also after 12, 16 and 20 hours, otherwise the action is retarded by the accumulation of blood corpuscles at the bottom of the tube. In doing this, formation of froth must be avoided. This mixing has no effect with digitonin, the action of which is practically completed before the corpuscles have settled out. Hæmolysis by desoxycholic acid shows no essential difference from that by saponins. G. M.

**Starch and Glycogen, Acid Hydrolysis of.** C. Dumazert. (*Bull. Soc. Chim. biol.* 1950, **32**, 988.) In determining starch and glycogen by estimating the glucose formed on acid hydrolysis, a factor of 0·900 is generally used to convert glucose into the original carbohydrates. By this method there is in fact an error of about −5 per cent. Since this might be due to the uncertainty of ordinary methods of drying with substances of this type, moisture determinations were carried out by the Karl Fischer method. These showed that by drying over phosphorus pentoxide at 85° C. it is possible to reduce the water content to not more than 0·2 per cent. Determinations, by 2 different methods, of the glucose produced on hydrolysis of this dried material showed that the factor for conversion of glucose to starch was 0·948, and for glycogen 0·942. Determination of the carbon content of such dried starch and glycogen showed it to be in agreement with these factors. Thus the formula for these substances appears to be $(C_{12}H_{22}O_{11})_n$, rather than $(C_6H_{10}O_5)_n$, as previously assumed. The equation for the hydrolysis is then: $(C_{12}H_{22}O_{11})_n + n\,H_2O = 2n\,C_6H_{12}O_6$. G. M.

## GUMS AND RESINS

**Euphorbia Resins. Oxidative Degradation of Euphol.** H. K. Krüsi. (*J. chem. Soc.*, 1950, 2864.) Euphyl acetate $C_{32}H_{52}O_2$ treated with *N*-bromosuccinimide in $CCl_4$ gave rise to a mixture of dehydrogenated acetates, m.pt. 105° to 106°C. which gave a brown colour with tetranitromethane. Ultra-violet absorption curves of the mixture showed three maxima: at $\lambda = 232$ mμ ($\log \varepsilon = 3{\cdot}50$), 238·5 mμ ($\log \varepsilon = 3{\cdot}52$) and 247 mμ ($\log \varepsilon = 3{\cdot}33$) which differs from that of the starting material. The values of the three maxima correspond to those of dihydroagnosterol which contains a system of double bonds the partial structure of $C_{19}H_{33}$(-CH:CH.CH:C $Me_2$) (-$CH_2\dot{C}$:$\dot{C}$.$CH_2$-) (>CH.O.Ac) is suggested for the principal product. Chromic acid oxidation of the acetate mixture gave a neutral and an acid product in the ratio of 1:2, both oils. Esterification of the acidic oil with diazomethane gave a methyl-ester, $C_{28}H_{40}O_8$, of a diketo-acetoxy-acid, $C_{19}H_{33}$(-COO Me) (-CO.$\dot{C}$:$\dot{C}$,CO-) (>CHOAc) readily hydrolysed to the corresponding diketo-hydroxy-acid, $C_{19}H_{33}$(-COOH)(-CO).$\dot{C}$:$\dot{C}$.CO(> CHOH). Ease of hydrolysis indicated a primary or secondary carboxyl group.

J. B. S.

**Podophyllotoxin and Picropodophyllin, Reduction of, by Lithium Aluminium Hydride.** Nathan L. Drake and Edward H. Price. (*J. Amer. chem. Soc.*, 1951; **73**, 201.) Podophyllotoxin, one of the constituents of podophyllin resin, and its isomer, picropodophyllin, are of interest because of their effect upon mitosis. Structures have been proposed, but neither compound has been synthesised. The work described was undertaken to prove whether the lactone ring of each of the isomers is essential to biological activity. Both compounds were reduced by lithium aluminium hydride to diastereoisomeric trihydroxy compounds. The formation of these disastereoisomers is evidence that the configuration at carbon-3 of the substituted tetralin nucleus of podophyllotoxin undergoes inversion during conversion of podophyllotoxin to picropodophyllin, by treatment with sodium acetate in aqueous alcohol. The pyrolysis of the benzoate of picropodophyllin gave an improved method of preparation of β-apopicropodophyllin. This substance proved to be resistant to hydrogenation, but treat-

ment with hydrogen and Raney nickel at 60°C. yielded desoxypicropodophyllin which could be reduced with lithium aluminium hydride. The products resulting from the action of lithium aluminium hydride upon podophyllotoxin, picropodophyllin and desoxypicropodophyllin underwent a ready loss of water, in the presence of acidic reagents, to form the corresponding anhydro products. The ultraviolet absorption spectra of a number of compounds related to podophyllotoxin and picropodophyllin were determined. A. H. B.

## ORGANIC CHEMISTRY

**Ethanol from Methanol.** I. Wender, R. A. Friedal and M. Orchin. (*Science*, 1951, **113**, 206.) A new method for the homologation of alcohols is described in which the alcohol is treated with water gas (carbon monoxide and hydrogen) at 180° to 185°C. in the presence of a cobalt catalyst, dicobalt octacarbonyl. The order of reactivity of various alcohols was found to be tertiary > secondary > primary, though methanol was anomalous in that it reacted more rapidly than secondary alcohols. The methanol reaction, described in detail, can be followed by the pressure drop in the reaction vessel and gives rise mainly to ethanol. Other products also isolated from the reaction include methyl formate, methyl acetate, ethyl acetate, methane together with small amounts of *n*-propanol, *n*-butanol, and *n*-propyl acetate. Acetaldehyde, in undetermined amounts, was also identified in the products. The similarity of the reaction with the Fischer-Tropsch reaction is marked, particularly in regard to the high yield of ethanol and low yields of methanol, propanol and higher alcohols, which are obtained in this process. J. B. S.

**Gallic Acid, Esters of, with Higher Primary Alcohols.** G. J. M. van der Kerk, J. H. Verbeek and Miss J. C. F. Cleton. (*Rec. Trav. chim. Pays-Bas*, 1951, **70**, 277.) The esters of gallic acid and higher primary alcohols were prepared in view of their potential value as antioxidants in fats and fat-containing foods. Two methods were used: (a) the reaction of the hitherto unknown galloyl chloride with the appropriate alcohol, (b) the direct esterification of gallic acid with higher alcohols. Galloyl chloride was prepared by heating thoroughly dried gallic acid with a large excess of purified thionyl chloride at 75°C. for 5 hours and stopping the reaction before all the acid had been converted into the acid chloride. Removal of the excess of thionyl chloride under reduced pressure yielded a mixture of galloyl chloride and gallic acid which was heated with excess of higher alcohol at 100°C. for 4 hours to produce the ester. Attempts to prepare pure galloyl chloride failed. An addition compound between galloyl chloride and dioxane was isolated. Method (b) was accomplished by heating gallic acid in xylene or solvent naphtha with an excess of the higher alcohol, using *p*-toluenesulphonic acid as a catalyst in an apparatus allowing continuous removal of the water produced in the reaction and recycling of the solvent. A. H. B.

**2-Mercapto-4-Aminobenzoic Acid, Synthesis of.** C. Van Der Stelt, W. Van Der Lugt and W. Th. Nauta. (*Rec. Trav. chim. Pays-Bas*, 1951, **70**, 285.) The synthesis of 2-mercapto-4-aminobenzoic acid, the sulphur analogue of *p*-aminosalicylic acid is described. 2-Amino-4-nitrobenzoic acid was diazotised and poured into a suspension of cuprous thiocyanate containing potassium thiocyanate to yield 2-thiocyano-4-nitrobenzoic acid. In an attempt to purify the acid *via* the ammonium salt, a disulphide was obtained, apparently by the following reaction:—

$2R.SCN + 2OH' \rightarrow R.S.S.R. + CN' + CNO' + H_2O$. The thiocyano compound and the disulphide were both converted to 2-mercapto-4-aminobenzoic acid by boiling with sodium sulphide solution. This product is colourless, insoluble in cold water and ether, readily soluble in alkalis, dilute mineral acids and organic solvents like methanol, ethanol and actone. On warming in aqueous suspension, it is more stable than *p*-aminosalicylic acid. Diazotisation and warming with alcohol produced diphenyldisulphide-2,2'-dicarboxylic acid. A. H. B.

# BIOCHEMISTRY

## GENERAL BIOCHEMISTRY

**Benzoic Acid, Kinetic Studies on the Metabolism of.** H. G. Bray, W. V. Thorpe and K. White. (*Biochem. J.*, 1951, **48**, 88.) The rates of formation of benzoic acid from various precursors and its conjugation with glycine and glucuronic acid were studied by analysing the individual urine samples of rabbits which had received sodium benzoate, benzamide, toluene, benzyl alcohol and benzaldehyde. The metabolites estimated were ether-soluble acid (in some experiments fractionated into benzoic and hippuric acids) and ester glucuronide. The excretion of hippuric acid by rabbits which had received sodium benzoate took place at a constant rate of 115 to 166 mg./hr. In two experiments in which glycine was administered with the sodium benzoate, the rate of excretion increased to 270 and 480 mg./hr. respectively, supporting the suggestion that the availability of glycine controls the rate of hippuric acid formation. The conjugation of benzoic acid with glucuronic acid follows the kinetics of a first order reaction with a velocity constant of 0·08/hr., and the proportion of benzoic acid excreted in this way depends upon the dose level and whether or not glycine is given simultaneously. The conversion of benzamide, toluene, benzyl alcohol and benzaldehyde to benzoic acid also follow first order reaction kinetics with velocity constants of 0·32, 0·11, 1·00 and 0·33 per hour respectively. The considerable differences in the proportions of benzoic acid conjugated with glycine and glucuronic acid by different species can be accounted for solely in terms of the differences in the rates of formation of hippuric acid.

G. R. K.

**Netropsin, A New Antibiotic Produced by a Streptomyces.** A. C. Finlay, F. A. Hochstein, B. A. Sobin and F. X. Murphy. (*J. Amer. chem. Soc.*, 1951, **73**, 341.) Netropsin, a new antibiotic, was obtained from culture filtrates of a hitherto undescribed actinomycete, *Streptomyces netropsis*, which was isolated from a soil sample. Its toxicity appears to be high for parenteral administration. The free base is unstable, but crystalline salts, namely sulphate, hydrochloride and picrate, were prepared. Analysis of these salts indicate netropsin to be a tetra-acidic base corresponding to the formula $C_{32}H_{48}N_{18}O_4$. Various physical measurements and chemical tests are recorded. Two crystalline products of alkaline hydrolysis of netropsin were isolated. The major product was monobasic and corresponded to the formula $C_{15}H_{20}N_6O_3$, and the other product was also monobasic, probably contained a guanidine moiety, and had empirical formula $C_3H_5N_3O$. The *in vitro* activity of crystalline netropsin hydrochloride against a variety of microorganisms is given. A. H. B.

**Penicillinase, Unit of.** G. B. Levy. (*Nature*, 1950, **166**, 740.) Attempts were made to determine the conditions under which the analysis of penicillinase activity can be made independent of the technique employed in determining the amount of penicillin inactivated; a definition of a unit of potency is proposed which is similar in magnitude to the original unit of McQuarrie *et al.* (*Arch. Biochem.*, 1944, **5**, 307). Essential conditions for controlling the analysis were (1) inactivation of penicillin should be negligible in the absence of enzyme; (2) rate of inactivation should be proportional to the enzyme concentration; (3) rate of inactivation should be independent of the concentration of penicillin. Three unrelated methods, a polarimetric and an iodimetric titration method, and a microbiological method have been developed for the determination of a penicillinase activity; details are given for a determination using the microbiological technique in which essentially identical results were obtained as in the polarimetric and iodimetric procedures. As a result of this work a definition is put forward, namely that a unit of penicillinase effects the inactivation of $10^{-7}$ moles of penicillin (0·356μg., or 59·3 units of sodium benzylpenicillin) per hour at 25°C. at *p*H 7·0. This action takes place in a phosphate buffered solution of a pure alkali salt of benzylpenicillin in sufficient concentration to maintain a zero-order reaction-rate. R. E. S.

**Vitamin A, Absorption Spectrum of.** H. Chatain and M. Debodard. (*C.R. Acad. Sci., Paris*, 1950, **251**, 1102.) The accepted standard for the absorption spectrum of vitamin A is that of Morton. Purer material is now available and the authors have redetermined the spectrum using a pure sample of axerophthol acetate. The results are compared with the figures of Morton and with the International Standard. The maximum absorption $E_{1\text{ cm.}}^{1\text{ per cent.}}$ is slightly greater than that previously accepted: 1544 in ethanol, 1539 in *iso*propanol, and 1513 in cyclohexane. The general form of the curve is rather sharper than that given by Morton. The new figures are closer to those given by the International Standard than to the figures of Morton. G. M.

## BIOCHEMICAL ANALYSIS

**Chloride, Permanent Turbidimetric Standards for Determination of Small Amounts of.** J. Haslam and D. C. M. Squirrel. (*Biochem. J.*, 1951, **48**, 48.) Permanent standards made of cloudy Perspex form a useful basis of comparison for silver chloride, protein and other analytical estimations which depend on the production of finely dispersed precipitates. The preparation involves two stages:—(i) a clear interpolymer is made by heating equal parts of methyl methacrylate and styrene in the presence of benzoyl peroxide under carefully controlled conditions; (ii) a solution of the interpolymer in methyl methacrylate monomer is heated under a reflux condenser for 1 hour, treated with a solution of benzoyl peroxide in methyl methacrylate monomer and again heated. The syrup thus obtained is cooled, transferred to test-tubes and polymerised by heating in an oil-bath at 75°C. until the required degree of turbidity is obtained. The turbidity produced does not vary directly with the concentration of the interpolymer, and the standards must be calibrated against known silver chloride suspensions. After cooling, the test-tubes are broken and the prepared standards cut into suitable lengths and fixed into tightly fitting glass tubes. G. R. K.

**Chloride, Simplified Silver Iodate Method for the Determination of.** E. J. King and D. S. Bain. (*Biochem. J.*, 1951, **48**, 51.) The silver iodate

procedure of Haslewood and King is modified to reduce the number of operations and to allow the use of commercial silver iodate instead of specially prepared material. The method for plasma consists in adding 0·5 ml. of ammoniacal silver iodate solution to 0·2 ml. of plasma, followed by 3·3 ml. of tungstate-phosphoric acid reagent, shaking, filtering, treating 1 ml. of the filtrate with 1 ml. of a 2 per cent. solution of potassium iodide and titrating with 0·005 N sodium thiosulphate, using starch solution as indicator. The ammoniacal silver iodate solution is prepared by adding an equal volume of N sulphuric acid to a stock solution (1·8 per cent. w/v) of silver iodate in N ammonia, centrifuging, and dissolving the precipitate in a volume of 0·3 N ammonia equal to that of the stock solution taken. For determining chloride in simple aqueous solution, the tungstate-phosphoric acid reagent, which consists of a 0·42 per cent. solution of sodium tungstate in 0·15 M phosphoric acid is replaced by 0·15 M phosphoric acid. For whole blood the amount of sodium tungstate in the tungstate-phosphoric acid reagent should be doubled. Results obtained from this, the iodimetric method of Van Slyke and Hiller and the mercurimetric method of Schales and Schales were in good agreement. G. R. K.

**Methanol in Blood in the Presence of Ethanol, Manometric Determination of.** M. F. Mason and R. Solow. (*J. biol. Chem.*, 1950, **187,** 831.) The procedure described is an extension of that previously reported (*Fed. Proc.*, 1949, **8,** 226) and is based on the bichromate-sulphuric acid oxidation of the alcohols in aqueous solution, which may be conducted so that ethanol yields acetic acid, where as methanol is quantitatively converted to carbon dioxide. By performing the oxidation in a closed system, similar to one of those employed in the determination of carbon dioxide from an α-amino carboxy group, the carbon dioxide liberated may be readily transferred to the chamber of a Van Slyke-Neill manometric gas analyser and absorbed by alkali, with subsequent acid decomposition of the carbonate and measurement of the pressure of the $CO_2$ liberated before and after absorption. Blood is prepared for analysis by distilling a tungstate filtrate, the amount of blood required being usually 3 ml., but smaller quantities suffice when high concentrations of methanol are present. Practical details of the procedure are given. Considerable difficulty was experienced at first in attaining good recoveries with blood containing less than 50 mg., per cent. of methanol owing to blank variations but at higher concentrations, blank variations introduced comparatively little error into the calculations. In applying the method in forensic work it was found to be convenient to estimate roughly the amount of methanol present by a qualitative test and in those instances in which the concentrations appeared to be less than about 50 mg. per cent., a larger volume of the tungstate filtrate was distilled. R. E. S.

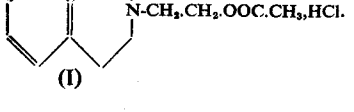
**Thiocyanate in Blood, Determination of.** F. Goldstein. (*J. biol. Chem.*, 1950, **187,** 523.) The method described depends on the spectrophotometric measurement of the colour of resulting ferric thiocyanate, by comparison with a standard curve prepared from blood containing known amounts of thiocyanate. In order to avoid the use of trichloracetic acid which gives low results, ethanol (95 per cent.) was added to the heparinised blood to precipitate the proteins; details of procedure are given based on the use of 1 ml. quantities of heparinised blood. Recovery of added thiocyanate ranged between 97·1 and 101·8 per cent., the mean being 99·6 per cent. Under the conditions given optimum results were obtainable

with concentrations of sodium thiocyanate ranging between 2·5 and 40 mg./100 ml. of blood; for concentrations outside this range 0·5 ml. (or 2 ml.) of blood may be used for analysis, as well as for the preparation of the control and standard. R. E. S.

## CHEMOTHERAPY

**Arsenicals. Relation between Constitution and Action on Cell Division.** Harold King and R. J. Ludford. (*J. chem. Soc.*, 1950, 2086.) Because cacodylic acid has been previously shown to be a mitotic poison, some homologues and other aliphatic arsenicals were synthesised, and their activity on tissue cultures of mouse fibroblasts observed. Two main types of mitotic aberrations were found, dependent on whether the action was primarily on the spindle (" colchicinic effect ") or on the chromosomes. For an investigation of the relation between chemical constitution and mitotic poisoning, attention was directed to the following: (i) methyl-, propyl- butyl-, benzyl-, and 2-phenylethyl-arsonic acids, $R.AsO_3H_2$; (ii) dimethyl-, diethyl- and dibutyl-arsenous acids $R_2AsO(OH)$; and (iii) 3-ethylamino-, 3-propylamino, 3-butylamino, 3-benzylamino, 3-2′-phenylethylamino- and 3-*cyclo*hexylamino-propylarsonic acids, $R.NH.[CH_2]_3.AsO_3H_2$. Those exhibiting a cytological action similar to colchicine are as follows: $Me_2AsO(OH)$, marked activity in dilutions of 1/50,000 to 1/75,000, some activity at 1/100,000; $Et_2AsO(OH)$, not such a good mitotic poison as cacodylic acid, activity in dilutions up to 1/100,000. $B_2AsO(OH)$, inactive within the range of dilutions used; $Me_2As.S.CH_2CH(NH_2)COOH$, better mitotic poison at 1/100,000 than cacodylic acid. The other compounds e.g. $Bu^nAsO(OH)_2C_6H_5CH_2CH_2AsO(OH_2)Ph_2AsO(OH)_2$ etc., acted primarily on the chromosomes. The following *N*-substituted derivatives of 3-aminopropylarsonic acid exhibited varying degrees of mitotic activity in dilutions between 1/10,000 and 1/25,000; *NN*-dimethyl, *N*-methyl, *N*-ethyl, *N*-butyl, *N*-hexyl, *N-cyclo*hexyl, *N*-benzyl, and *N*-2-phenylethyl. The last two were the best mitotic poisons in this group. One tervalent arsenical of this type was tested, 3-(1-phenylethylamino) propylarsine dichloride, and was active at 1/100,000. A. H. B.

**Chemical Constitution and Analgesic Action.** M. B. Slomka and F. W. Schueler. (*J. Amer. pharm. Ass. Sci. Ed.*, 1951, **40**, 47.) A number of compounds were synthesised and tested for analgesic activity in rats and for toxicity in mice. The compounds were analogous to morphine in having sympathomimetic and parasympathomimetic-like moieties, connected, generally, by the same amino nitrogen atom. More than half the compounds tested were active. The compound $C_6H_5.CH(CH_3).CH_2N(CH_3).CH_2.CH_2.OOC.CH_3$, HCl was inactive, although both the α-methyl isomer and the compound $C_6H_5.CH(CH_3).CH_2N(CH_3).CH_2.CH_2.CH_2.OOC.CH_3$, HCl (containing an additional $.CH_2.$ group) were active. The phenylethylamine compounds were less active than the tetrahydro*iso*quinoline compound (I), corresponding to the loss in activity when the piperidine ring of the morphine molecule is ruptured. The fully aromatic quaternary salt corresponding to (I) was inactive. Quaternisation to the methiodidide did not affect the potency of morphine but decreased considerably that of



(I)

diamorphine and codeine. 2-Phenyl-2-acetoxy-1-diethylaminomethyl*cyclo*hexane was active, but the corresponding dimethyl compound was not. A number of phenylacylamine derivative were fund to be inactive. G. B.

**Chemotherapy of Tuberculosis. *N*-4-Diphenylamidines.** L. Bauer and J. Cymerman. (*J. chem. Soc.*, 1950, 1826.) 4-Aminodiphenyl, a lipophilic base possessing a flat surface and of known *in-vitro* tuberculostatic activity on tissue cultures of mouse fibroblasts observed. Two main types factors in relation to activity. A number of *N*-4-diphenylamidines ($C_6N_5.C_6H_4.NH.C$ (=NH).R) possessing high basic strengths and containing a wide range of lipoid solubilising substituents (R) have been prepared. The required compounds were obtained by the method of Oxley and Short (*J. chem. Soc.*, 1946, 147) by condensation of a 4-diphenylylammonium-benzenesulphonic or *p*-toluenesulphonic acid and a series of aliphatic, aromatic, alicyclic and hydroaromatic cyanides. No tuberculostatic activities are recorded for these compounds. J. B. S.

**Thiosemicarbazones and Related Compounds in Tuberculosis.** D. Hamre, J. Bernstein and R. Donovick. (*J. Bact.* 1950, **59,** 675.) *In vivo* mouse tests against *M. tuberculosis* (Ravenal strain) are reported for a wide range of thiosemicarbazones and related compounds. The results, which are classified according to the structure of the compounds under test, are assessed in terms of increased $T_{50}$ ($T_{50}$ = the survival time of 50 per cent. of the animal group under test). *In vivo* activity is found only in para-substituted thiosemicarbazones, the order of activity for various substituent groups being given as: ethysulphonyl = isopropyl > amino = acetylamino = dimethylamino > nitro = sulphamyl = methoxy. Complete evaluation of the significance of these results awaits further experimental data which will relate the maximal acceptable drug level to the chronic toxicity of the drug. Loss of *in vivo* activity results from the following chemical transformations of *p*-acetylaminobenzaldehyde thiosemicarbazone: (1) replacement of sulphur by oxygen (2) by nitrogen (3) formation of alkyl*iso*thiosemicarbazones (4)*N*- alkylation of the terminal amino group or replacement of the terminal amino group by thiomethyl. Differences in the methods of test and assessment from those described by Hoggarth *et al.* (*Brit. J. Pharmacol,* 1949, **4,** 248) are discussed. J. B. S.

# PHARMACY

## NOTES AND FORMULÆ

**Aluminium Methionate, a New Astringent Agent.** J. E. Christian and G. L. Jenkins. (*J. Amer. pharm. Ass., Sci. Ed.*, 1950, **39,** 663.) Aluminium methionate may be prepared by the interaction of calcium methionate and aluminium sulphate in aqueous solution, followed by concentration after removal of the calcium sulphate, and precipitation with ethanol. It is hygroscopic, soluble in water and non-toxic. A 5 per cent. aqueous solution has a *p*H about 3·5. In protein coagulation tests with Hammerstein's casein, aluminium methionate is superior to aluminium chloride, aluminium sulphate, aluminium ethanedisulphonate and other astringent salts. Astringent creams containing aluminium methionate are relatively harmless to cloth, whereas other common astringent agents have been found to weaken cloth considerably. G. B.

**Benzpyrinium Bromide (Stigmonene Bromide).** (*New and Nonofficial Remedies; J. Amer. med. Ass.*, 1951, **145,** 487.) Benzpyrinium bromide is 1-benzyl-3-(dimethylcarbamyloxy) pyridinium bromide, $C_{15}H_{17}O_2N_2Br$. It is a white to slightly yellow, almost odourless, crystalline powder, m.p. 114° to 120°C., very soluble in water and ethanol and almost insoluble in ether; a 1 per cent. aqueous solution has *p*H 4·5 to 5·5. When the residue obtained by evaporating the alkaline solution to dryness is heated at 250°C. for 30 seconds, cooled and dissolved in water, the solution gives a cherry-red colour when cooled in ice and treated with diazobenzenesulphonic acid solution. The picrate obtained by treating an aqueous solution with a saturated aqueous solution of trinitrophenol containing a little sulphuric acid has m.p. 114° to 120°C. Benzpyrinium bromide loses not more than 1 per cent. of its weight when dried at 80°C. for 4 hours; it yields not more than 0·1 per cent. of sulphated ash. A 0·003 per cent. solution exhibits an ultraviolet absorption minimum at about 2420 Å and a maximum at about 2690 Å ($E^{1\text{ per cent.}}_{1\text{ cm.}} = 136 \pm 3$). Benzpyrinium bromide is assayed by distilling an alkaline solution, collecting the distillate in boric acid solution and titrating the liberated dimethylamine with sulphuric acid; it contains 98·5 to 101·5 per cent. of benzpyrinium bromide. It has the same action and uses as neostigmine. G. R. K.

**Metopon Hydrochloride.** (*New and Nonofficial Remedies; J. Amer. med. Ass.*, 1951, **145,** 486.) Metopon hydrochloride, 7-methyldihydromorphinone hydrochloride, $C_{18}H_{21}NO_3$,HCl, is a wide, odourless, crystalline powder; it is very soluble in water, slightly soluble in ethanol, chloroform and ether, and insoluble in benzene. A 1 per cent. aqueous solution has *p*H 5·0 and $[\alpha]_D^{25°C}$, $-97 \pm 5°$. The pale peach colour produced with an alcoholic solution of *m*-dinitrobenzene and sodium hydroxide distinguishes it from dihydromorphinone, which gives a mauve colour. Ammonia yields a precipitate of metopon, m.p., after drying at 105°C. for 1 hour, 240° to 245°C. Metopon hydrochloride loses not more than 0·25 per cent. of its weight when dried at 105°C. for 4 hours and yields not more than 0·1 per cent. of sulphated ash. It contains 87·5 to 91·0 per cent. of metopon and 10·26 to 10·86 per cent. of chloride. It is assayed for metopon by adding sodium bicarbonate to an aqueous solution, extracting with chloroform, dissolving the residue after removal of the chloroform in sulphuric acid and titrating with sodium hydroxide; chloride is estimated by precipitating with silver nitrate in the presence of nitrobenzene and titrating back with ammonium thiocyanate. Metopon hydrochloride is recommended only for the control of pain in a dose of 6 to 9 mg. by mouth. G. R. K.

**Procaine Amide Hydrochloride (Pronestyl Hydrochloride).** (*New and Nonofficial Remedies; J. Amer. med. Ass.*, 1950, **144,** 1465.) Procaine amide hydrochloride is *p*-amino-*N*-(2-diethylaminoethyl) benzamide hydrochloride. It occurs as a white to tan, odourless, crystalline solid, m.p. 165° to 169°C., very soluble in water, soluble in alcohol, slightly soluble in chloroform and very slightly soluble in benzene and ether. When the free base, obtained by extracting an alkaline solution with a mixture of ether and benzene, is treated with benzoyl chloride in pyridine, heated for 30 minutes and poured into sodium hydroxide solution, the organic layer yields crystals of procaine amide benzoate, m.p., after recrystallisation and drying, 180° to 187°C. Procaine amide hydrochloride is distinguished from procaine hydrochloride by measuring the optical density of a 0·0005 per cent. solution spectrophoto-

metrically; procaine amide hydrochloride has a maximum at 2780Å and procaine hydrochloride has a maximum at 2880Å. Procaine amide hydrochloride contains not more than 20 p.p.m. of heavy metals, yields not more than 0·1 per cent. of sulphated ash and loses not more than 0·2 per cent. when dried at 105° for 4 hours. It is assayed by the Kjeldahl method and contains 15·1 to 15·8 per cent. of nitrogen, equivalent to 97·5 to 102·5 per cent. of procaine amide hydrochloride. It is useful for the treatment of ventricular arrhythmias and extrasystoles. It has the advantages over procaine hydrochloride in that its action is more prolonged, it has about one half to two-thirds the toxocity, and it does not produce significant central stimulatory effects. G. R. K.

## PHARMACOGNOSY

**Curaçao Aloe, Anthraquinones Derivatives of, a Chromatographic Study.** T. M. Brody, R. F. Voigt and F. T. Maker. (*J. Amer. pharm. Ass.* Sci. Ed., 1950, **39,** 666.) Free anthraquinones are extracted from Curaçao aloes by heating under reflux with chloroform. Combined anthraquinones are hydrolysed and extracted from the residue by heating under reflux with 25 per cent. sulphuric acid and chloroform. Chromatographic analysis of the diluted chloroform extracts on a mixture of 1 part of magnesia with 3 parts of Celite gives a bright red layer (aloe-emodin), a pink layer (iso-emodin) and a yellow layer (anthranols). A red-brown layer which can be resolved into bright red and pink layers is also obtained. Extracts of aloin, similarly treated, yield similar chromatograms. Socotrine and Cape aloes cannot be analysed successfully on the column described above. A value for the total anthraquinone content of Curaçao aloes, calculated as aloe-amodin, may be obtained from the spectrophotometric absorption of a chloroform solution at 440 mμ. At this wave-length, the extinction coefficients of aloe-emodin and iso-emodin are almost identical. Anthranols have a low absorption at 440 mμ and may be removed from the chloroform solution by discarding the yellow layer of the chromatogram. G. B.

***Hyoscyamus muticus*, Influence of Varying Nitrogen Levels on Hydroponic Growth and Alkaloid Production.** L. J. Schermeister, R. F. Voigt and F. T. Maker. (*J. Amer. pharm. Ass., Sci. Ed.,* 1950, **39,** 669.) *H. muticus* plants were grown in hydroponic jars, using Skok media with concentrations of nitrate varying from 0 to 672 parts per million of nitrogen. Maximum height was reached at 168 p.p.m., maximum leaf size at 336 p.p.m., and optimum green colour of foliage at 252 p.p.m. Plants grown in media with 252 to 672 p.p.m. showed an almost constant maximal amount of branching and yielded the greatest weight of fresh and dried plants. Above 500 p.p.m., plants bloomed one week earlier. Alkaloid production increased up to 252 p.p.m., remaining almost constant for the higher nitrogen levels. The greatest concentration of alkaloid was found in the flowering tops. G. B.

## PHARMACOLOGY AND THERAPEUTICS

**Anti-œstrogens.** A. Lespagnol, J. Schmitt and L. Thiéblot (*Bull. Soc. Chim. biol.* 1950, **32,** 1019.) In view of the creation of antagonistic actions by duplication of a molecule, the authors endeavoured to find if such

an effect could be observed with œstrogenic substances. The compounds tested were as follows: *p*-methoxyphenyl-2-butene-2: *p*-methoxyphenyl-1-propanol-1: *p*-methoxyphenyl-1-propene-1: *p*-hydroxypropiophenone: *p*-methoxypropiophenone: *p*-hydroxyacetophenone: *p*-methoxyphenyl-3-pentene-2: ethyl *p*-methoxymethylcinnamate: *p*-hydroxyphenyl-2-butene-2: *p*-hydroxybenzyl ethyl ketone: *p*-hydroxyphenyl-3-butanone-2: and *p*-hydroxyphenyl-4-hexanone-3. None of these was able to oppose the œstrogenic action of folliculine on castrated rats. G. M.

**Digitalis, Biological Assay of.** A. Lindner. (*Sci. Pharm.*, 1950, **18**, 149.) Exact details are given of the modified Knaffl-Lenz method as recommended by the author for the standardisation of digitalis preparations. In addition to the great advantage of using guinea-pigs, this method gives only a small scattering of results even with only a few animals. The standard deviation of an assay should be less than 6 per cent.: if this is not attained with the use of 5 animals, the number should be increased. In general 5 or 6 animals are sufficient for the assay of a galenical. A comparison of digitalis drugs, derived from other species, with the International standard, is not permissible. G. M.

***Digitalis purpurea* and *D. lanata*, Comparison of Tinctures of.** A. Lindner and J. Römer. (*Arch. int. pharmacodyn.*, 1951, **85**, 306.) In order to compare the action of tinctures of *Digitalis purpurea* and *D. lanata*, 10 times the intravenous lethal dose was given to guinea-pigs perorally over a period of up to 24 hours, and the intravenous dose was then determined. Guinea-pigs are more suitable for this purpose than most test animals, as the drug does not produce sickness. All animals survived 10 times the intravenous lethal dose in the case of *D. lanata*, but died after 12 to 15 hours with *D. purpurea*. With the former, the dose was a minimum 3 to 6 hours after the administration, and then increased, whereas with *D. purpurea* it decreased continually until the animal died. On the whole there is little difference between the two tinctures in the first 6 hours, after which the curves deviate in opposite directions. This is confirmed by electrocardiograph readings. The difference is probably due to the much greater cumulative effect of purpurea glycosides, especially digitoxin. Thus the two tinctures are not therapeutically equivalent, even if they have the same intravenous activity. It would be advisable to administer *D. lanata* tincture several times during the day, while *D. purpurea* tincture should give satisfactory action with a single daily dose. G. M.

**Ethaverine: Coronary Vasodilator Potency compared with Papaverine.** C. V. Winder, R. W. Thomas and O. Kamm. (*J. Pharmacol.*, 1950, **100**, 482.) Ethaverine (also known as diquinol and perparin), the ethyl analogue of papaverine, is 6:7-diethoxy-1-(3:4-diethoxy-benzyl) isoquinoline. It is from twice to 4 times as potent a spasmolytic as papaverine and has been found only half as toxic. It is, on the average, equal to papaverine in peak potency as a coronary vasodilator in the surviving rabbit heart, when injected quickly. Its action is more lasting at suprathreshold dosage so that in total effect over a period it is more effective. In view of its higher tolerated doses it would seem to merit trial in coronary disease. S. L. W.

**Hexamethonium Bromide, Effects on the Stomach.** A. H. Douthwaite and M. G. Thoral. (*Brit. med. J.*, 1951, **1**, 111.) This is an account of a

study of the action of hexamethonium bromide on gastric secretion and motility in 10 patients. 9 were males with clinical and radiological evidence of duodenal ulcer, and 1 was a female without such evidence; all were bed patients and were without symptoms at the time of the test. When given in doses of 100 mg. intramuscularly the drug was found to delay the onset of gastric emptying of a barium meal for periods of up to 30 minutes and completion of emptying until the sixth hour. Gastric peristalsis was diminished but not completely inhibited and there was no change in the shape of the stomach. The small gut, particularly the duodenum and upper jejunum, was shown to be dilated and immobile for periods of up to 6 hours after the drug was given. Gastric secretion, as shown by the gruel test-meal, was only slightly altered by the drug. Possible drawbacks to the therapeutic use of the drug are: the vasomotor side-effects were incapacitating enough to make it unsuitable for ambulant patients; after continued use the drug might lose some of its potency; and the effect on a duodenal ulcer of an artificial duodenal ileus produced by the drug cannot be predicted with certainty. Its potentialities seem to be strongest for bed patients and for use at night.

S. L. W.

**Lysivane and Artane in Parkinsonism.** O. Garai. (*Lancet*, 1951, **260**, 429.) This is a report on 70 patients suffering from all varieties of Parkinsonism—idiopathic, postencephalitic and arteriosclerotic. 51 received artane, 43 lysivane, and 24 both drugs at different times. Improvement was noted in 74·5 per cent. with artane and in 72 per cent. with lysivane. Both drugs were found to control the rigidity better than the tremor, and both reduced the number and duration of oculogyric crises in postencephalitic Parkinsonism. The action of artane is often enhanced by amphetamine sulphate in postencephalitics. The side-effects produced by artane were trivial and much less severe than those seen with lysivane and most of the 24 patients treated with both drugs preferred artane; this was related to its greater efficiency, its lower toxicity and the sense of well-being it produces. Some patients however derived equal benefit from the two drugs and a few were decidedly better on lysivane. Since artane is less likely to produce unpleasant side-effects it is likely to prove the drug of choice for most cases of Parkinsonism.

S. L. W.

**Nitrogen Mustard-like Action of bis(Ethylenimines).** F. S. Philips and J. B. Thiersch. (*J. Pharmacol.*, 1950, **100**, 398.) The pharmacological properties of nitrogen mustards can be attributed to their transformation *in vivo* into quaternary ethylenimonium derivatives. These derivatives are known to alkylate a wide variety of important biochemical radicals and their cytotoxic actions presumably result from condensation with vital constituents of proliferating cells. This paper further elucidates the pharmacological activity of ethylenimine constituents by a comparison of the effects of 2:4:6-tris(ethylenimino)-S-triazine and several tertiary bis(ethylenimo) derivatives with those of a typical nitrogen mustard, bis(2-chloroethyl)-methylamine. The toxicological activity, as studied in mice, rats, cats and dogs was found to be similar, but close structural analogues of the bis(ethylenimines), containing no ethylenimine constituents proved to be relatively inactive agents. Given in doses near the LD50, the bis(ethylenimines) and the nitrogen mustards evoked a similar delayed lethal syndrome and identical alterations in hæmatopoietic organs and intestinal epithelium,

[*Continued on p. 383*

proportional to the relative size of the cortical tissue. This argument does not hold for man, however, where, unlike some lower animals, degeneration of adrenal tissue occurs during the first few months of life.

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REFERENCES:

1. Holton, *J. Physiol.*, 1949, **108**, 525.
2. West, *J. Pharm. Pharmacol.*, 1950, **2**, 732.
3. Burn, Langemann and Parker, *J. Physiol.*, 1951, **113**, 123.
4. Shepherd and West, *J. Physiol.*, 1951, *P.* in the press.
5. Holton, 1951, Personal Communication.
6. Crawford and Outschoorn, *Brit. J. Pharmacol.*, 1951, **6**, 8.

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ABSTRACTS (*continued from page* 381)

though doses of 2:4:6-tris(ethylenimo)-S-triazine elicited fewer signs of acute intoxication than comparable doses of the nitrogen mustard, and it would appear to have certain clinical advantages in the treatment of human lymphomas. The common pharmacological properties of bis(ethylenimines) and nitrogen mustards are considered by the authors to be related to the presence of chemically reactive 3-membered heterocylic constituents, namely, tertiary ethylenimine groups in the former agents and quarternary ethylenimonium groups in the *in vivo* transformation products of the latter agents.

S. L. W.

**Senna; Laxative Activity in Mice of the Various Parts of the Plant.** J. W. Grote and M. Woods. (*J. Amer. pharm. Ass. Sci. Ed.*, 1951, **40**, 52.) *Cassia angustifolia* Vahl can be grown successfully in parts of the southern United States (especially the Imperial Valley of California), but plants are killed rapidly by temperatures below 50°F. Both pods and leaflets are comparable in laxative activity to the Indian or Egyptian-grown drug. The pods are slightly more active than the leaflets. The petioles are 75 per cent., the stems, 50 per cent. and the roots, 55 per cent. as active as the leaflets. Several years' storage causes no marked loss of activity. G. B.

**Streptomycin Salt of Insulin, "Depot" Effect of.** R. D. Barnard and A. N. Saperstein. (*J. Amer. pharm. Ass., Sci. Ed.*, 1951, **40**, 55.) A relatively insoluble insulin-streptomycin compound is precipitated when commercial insulin solution is mixed with a solution of streptomycin sulphate. The streptomycin-insulin is formed in a state of fine dispersion suitable for administration through a 24-gauge hypodermic needle. The blood-sugar curve in a glycogen-depleted diabetic subject receiving 50 units of insulin in the form of the streptomycin salt, is similar to that with protamine or globin insulin. The streptomycin compound and a similar dihydrostreptomycin compound may be of use in patients who show sensitivity to protamine or globin conjugates. G. B.