NOTES.

Purification of Colchicine by Chromatography. By J. N. ASHLEY and J. O. HARRIS.

COLCHICINE is normally encountered as a yellow amorphous powder which cannot readily be prepared in a pure crystalline condition. It can be obtained in pale yellow needles by crystallisation from ethyl acetate of the amorphous residue left after removal of chloroform from the addition compound of colchicine with chloroform (Clewer, Green, and Tutin, J., 1915, **107**, 839), but the method is tedious and was unsatisfactory in our hands. It has now been found that pure crystalline colchicine can readily be obtained in good yield by the following procedure : A solution of colchicine (U.S.P.) (5 g.), m. p. 140—144°, in chloroform (50 c.c.) was passed through a column (15 cm. long, 1 cm. diameter) of alumina (B.D.H. chromatographic alumina) previously saturated with benzene, and the column afterwards washed down with chloroform (100 c.c.). After removal of the chloroform, the residual gum was triturated with a little anhydrous ether, an almost colourless residue (4·75 g.) of practically pure colchicine being obtained. This crystallised readily from ethyl acetate in very pale yellow needles, m. p. 155°, $[\alpha]_D^{17°}$ — 120·7° (Found : N, 3·6. Calc. for $C_{22}H_{25}O_6N$: N, 3·5%). Clewer *et al.* (*loc. cit.*) give $[\alpha]_D^{16·5°}$ — 120·3°. Crystallisation from benzene gave very pale yellow prisms, m. p. 140°, which contained 1 mol. of benzene of crystallisation (Found : C, 70·0; H, 6·4; N, 3·1. Calc. for $C_{22}H_{25}O_6N,C_6H_6$: C, 70·4; H, 6·5; N, 2·9%).

Elution of the column with methyl alcohol yielded a small amount of brown amorphous material, which could not be crystallised.

The authors desire to thank Mr. S. Bance, B.Sc., for the semi-microanalyses and the Directors of Messrs. May & Baker Ltd. for permission to publish these results.—THE RESEARCH LABORATORIES, MAY & BAKER LTD., DAGENHAM. [*Received, October 28th,* 1944.]

β-Thymoxyethyldiethylamine. By CHARLES E. DALGLIESH.

THYMOXYETHYLDIETHYLAMINE (β-thymoxytriethylamine, Fourneau 929) is a substance of considerable pharmacological interest, but is not available in this country at the present time. It was first prepared by Einhorn and Rothlauf (*Annalen*, 1911, **382**, 256) by distillation of β-diethylaminoethyl thymyl carbonate in a vacuum, and was claimed to have b. p. 126°/18 mm. However, Einhorn (D.R.-P. 224,160) cited the b. p. as 157—159°/16 mm. Details of other methods of preparation or reliable values for the physical constants do not appear to be available, and I therefore record the following simple procedure.

β-Diethylaminoethanol (59 g.), treated with thionyl chloride (120 g.) by the method of Gough and King (J., 1928, 2426), gave β-chlorotriethylamine hydrochloride. Treatment of an ice-cold aqueous solution with dilute sodium hydroxide, followed by ether extraction and distillation, gave β-chlorotriethylamine (50 g., b. p. 66°/20 mm.). To a solution of thymol (50 g.) in alcohol (100 c.c.) was added a solution of sodium (7·5 g.) in alcohol (100 c.c.). After 15 minutes the solvent was removed by distillation, and the residue dissolved in chloroform (100 c.c.), β-chlorotriethylamine (47 g.) then being added with shaking. The temperature started to rise after 5 minutes, and the mixture was cooled in ice as soon as boiling commenced. The resultant, almost solid, product was diluted with alcohol (150 c.c.) and set aside for 1 hour; the liquid was then filtered, and the solid residue washed with ether. The combined ethereal filtrates were dried (sodium sulphate), subsequent distillation giving the required amine as an almost colourless liquid (72 g., 87% of the theoretical yield), b. p. 180°/18 mm., 114°/0·3 mm. (Found : C, 77·3; H, 10·8; N, 5·55. Calc. for $C_{16}H_{27}ON$: C, 77·1; H, 10·8; N, 5·6%).

The compound readily gives a *picrate*, crystallising from alcohol in yellow needles, m. p. 130—131° (Found : N, 11·8. $C_{16}H_{27}ON,C_6H_3O_7N_3$ requires N, 11·71%), and a *methiodide*, very soluble in alcohol, but precipitated by ether in white needles, m. p. 127—129° (Found : I, 32·1. $C_{17}H_{30}ONI$ requires I, 32·5%).

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Preparation of 1-Aminophthalaz-4-one. By (Miss) E. F. M. Stephenson.

1-Chlorophthalaz-4-one (10 g.), ammonium carbonate (7 g.), and aqueous ammonia (*d* 0·940; 100 ml.) were heated in a stainless steel autoclave (oil-bath at 195—210°) for 21 hours and the product, after evaporation to dryness on the water-bath, was extracted repeatedly with boiling water. The first extractions contained the amine (4·3 g.), which was obtained in long colourless needles, m. p. 271—272° (corr.; decomp.), after several crystallisations from hot water (Found: C, 59·4; H, 4·5; N, 26·0. Calc. for $C_8H_7ON_3$: C, 59·6; H, 4·4; N, 26·1%). The later extractions contained mainly phthalaz-1 : 4-dione (1·8 g.). The amine was readily soluble in 10% sodium hydroxide solution and concentrated hydrochloric acid, very soluble in acetic acid, fairly soluble in alcohol and was converted by potassium nitrite and acetic acid at 0° into phthalaz-1 : 4-dione, identified by m. p. and mixed m. p. The dibenzoyl derivative (benzoyl chloride in pyridine for 5 hours), obtained as an oil after removal of the pyridine and crystallised by treatment with alcohol, had m. p. 252—253° (uncorr.; decomp.) after recrystallisation from trichloroethylene–alcohol (Found: N, 11·5. Calc. for $C_{22}H_{15}O_3N_3$: N, 11·4%).—The University, Melbourne. [*Received, August 29th*, 1944.]

Benzylamine-4-carboxylic Acid. By A. Albert and D. Magrath.

Current interest (*e.g.*, Mitchell, Rees, and Robinson, *Lancet*, 1944, i, 627) in the antibacterial action of homosulphanilamide (marfanil, benzylamine-4-sulphonamide) led to a request for benzylamine-4-carboxylic acid, which is structurally (but not necessarily biologically) related to homosulphanilamide in the same way as *p*-aminobenzoic acid is related to sulphanilamide.

The only recorded preparation of benzylamine-4-carboxylic acid is the lengthy synthesis by Günther (*Ber.*, 1890, **23**, 1060). It was more easily prepared by hydrogenating a mixture of 4-cyanobenzoic acid (23 g.), Raney nickel (about 5 g.), aqueous ammonia (60 ml.; *d* 0·88), and water (300 ml.) at atmospheric temperature and pressure. When the theoretical amount of hydrogen had been absorbed (6 hours), the violet solution was filtered, boiled until ammonia ceased to come off, clarified, and concentrated to small bulk. Yield, 80% (m. p. 342°). After recrystallisation from 18 parts of boiling water, cream-coloured crystals were obtained, m. p. 345° (decomp.) (sealed tube), soluble in about 70 parts of cold water and agreeing with Günther's description.

The 4-cyanobenzoic acid was prepared by a modification of the process of Valby and Lucas (*J. Amer. Chem. Soc.*, 1929, **51**, 2718), the yield being increased from 30% to 80%. Sodium nitrite (18·5 g.) and *p*-aminobenzoic acid (35 g.) were made into a paste with water and slowly stirred into a mixture of concentrated hydrochloric acid (75 ml.) and ice (100 g.). The excess of acid was then neutralised by the cautious addition of sodium hydroxide (7·7 g.) in water, with good cooling. The solution was slowly added to a preparation, made by heating and then cooling to 15°, of hydrated nickel sulphate (100 g.), potassium cyanide (73 g.), and water (600 ml.). After an hour, the mixture was warmed at 80° for ½ hour, cooled, and acidified with hydrochloric acid until no further precipitate formed. The precipitate was dried at 100° and refluxed for 4 hours with a mixture of benzene (1500 ml.) and ethanol (75 ml.) to decompose the co-ordination complex. The residue left after evaporation (m. p. 211°) was sublimed at 3 mm., giving pale cream crystals in 78—84% yield; m. p. 219°.—University of Sydney. [*Received, October 4th*, 1944.]

5-Nitro-4 : 6-diamino-2-methylpyrimidine and a Modified Procedure for the Preparation of Chloropyrimidines. By J. Baddiley and A. Topham.

In the course of investigations on purine synthesis in these laboratories, a sample of 5-nitro-4 : 6-diamino-2-methylpyrimidine was required. Huber and Hölscher (*Ber.*, 1938, **71**, 94) claim to have prepared this compound by the action of alcoholic ammonia on 4 : 6-dichloro-5-nitro-2-methylpyrimidine and report that it is readily soluble in benzene and alcohol and has m. p. 234°. On repeating the experiment described by these authors, we obtained a crystalline product which had no m. p. and was virtually insoluble in both benzene and alcohol. That this product is indeed *5-nitro-4 : 6-diamino-2-methylpyrimidine* follows from its ready reduction to the known 4 : 5 : 6-triamino-2-methylpyrimidine. The nature of the German workers' product is obscure, but its formation may possibly be bound up with the fact that the starting material for its preparation, 4 : 6-dichloro-5-nitro-2-methylpyrimidine, was described by them as having m. p. 37°, whereas the same substance prepared by us had m. p. 54—55°.

Attention is drawn to the preparation of 4 : 6-dichloro-5-nitro-2-methylpyrimidine from the corresponding dihydroxy-compound by heating with phosphoryl chloride and dimethylaniline. In the past, preparation of chloropyrimidines from hydroxypyrimidines has usually been effected by heating with phosphorus pentachloride, phosphoryl chloride or a mixture of these two substances, and in many cases it has proved very troublesome. Thus, for example, 2 : 4 : 6-trichloropyrimidine, a valuable intermediate for various purposes, has been obtained by heating barbituric acid with phosphoryl chloride in a continuously rotating sealed tube at 140° (Gabriel, *Ber.*, 1900, **33**, 3666); it may be readily prepared, however, by refluxing a mixture of barbituric acid, phosphoryl chloride, and dimethylaniline for only 5 minutes. This modified procedure, already reported from these laboratories for the preparation of 4 : 6-dichloropyrimidine (J., 1943, 574), has been used successfully for many pyrimidine derivatives and appears to be generally applicable. It is particularly useful in the case of pyrimidines containing nitro- or amino-groups, where the older methods are most frequently troublesome. As an additional example, the preparation of 4-chloro-6-amino-2-methylthiopyrimidine by the new method is also described.

4 : 6-Dichloro-5-nitro-2-methylpyrimidine.—Dimethylaniline (10 c.c.) was added carefully to a mixture of 5-nitro-4 : 6-dihydroxy-2-methylpyrimidine (8 g.) and phosphoryl chloride (40 c.c.), and the reaction completed by heating under reflux for 1 hour. The cooled solution was poured on ice, and the product extracted with ether. The extract, washed with sodium bicarbonate solution, dried over sodium sulphate, and evaporated, left an oil which distilled at 115°/20 mm., the distillate setting to a mass of pale yellow needles (3·7 g.), m. p. 54—55° (Found: C, 29·3; H, 1·6; N, 19·5. Calc. for $C_5H_3O_2N_3Cl_2$: C, 28·9; H, 1·4; N, 20·1%).

5-Nitro-4 : 6-diamino-2-methylpyrimidine.—Methanolic ammonia (25 c.c., saturated at 0°) was added slowly with shaking to an ice-cold solution of 4 : 6-dichloro-5-nitro-2-methylpyrimidine (2 g.) in methanol (25 c.c.). The mixture was allowed to warm to room temperature and after a further 10 mins. the solid which had separated was collected and washed with water. It was purified by dissolution in dilute hydrochloric acid and reprecipitation with ammonia. On heating, it decomposed without melting and it was virtually insoluble in benzene and alcohol (Found: C, 35·8; H, 4·1; N, 40·9. $C_5H_7O_2N_5$ requires C, 35·5; H, 4·1; N, 41·4%). Yield, 82%.

The above nitro-compound (1 g.) was suspended in alcohol (150 c.c.) and reduced with hydrogen at 100°/120 atms. during 3 hours, a Raney nickel catalyst being used. The catalyst was filtered off, and the clear solution evaporated to dryness. The residue sublimed at 100°/10^{-2} mm. in colourless prisms, m. p. 247°, undepressed by authentic 4 : 5 : 6-triamino-2-methylpyrimidine (m. p. 250°). Yield, 90%.

2 : 4 : 6-*Trichloropyrimidine.*—Barbituric acid (52 g.) was added portionwise during 5 minutes to a mixture of dimethylaniline (88·5 c.c.) and phosphoryl chloride (156 c.c.), and the whole refluxed for 5 minutes, cooled, and poured on ice (800 g.). The mixture was extracted with ether, the extract dried and evaporated, and the residual 2 : 4 : 6-trichloropyrimidine purified by distillation at 102°/18 mm. Yield, 46%.

4-*Chloro*-6-*amino*-2-*methylthiopyrimidine.*—6-Amino-4-hydroxy-2-methylthiopyrimidine (120 g.), phosphoryl chloride (450 c.c.), and dimethylaniline (200 c.c.) were refluxed together for 1 hour, the excess of phosphoryl chloride removed in a vacuum, and the residue poured on ice. Excess of aqueous ammonia was added, dimethylaniline removed by extraction with light petroleum (b. p. 60—80°), and the aqueous solution concentrated until solid began to separate. The chloro-compound, recrystallised from water, had m. p. 131°, undepressed by a specimen prepared according to Johnson and Johns (*Amer. Chem. J.*, 1905, **34**, 183). Yield, 65%.

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The Conversion of Acridones into Acridines. By R. A. REED.

THE classical method of bringing about the above conversion by distillation with zinc dust, owing to the volatility of the acridones themselves, never gives good yields of acridine; much acridan is usually produced (cf. Kranzlein, *Ber.*, 1937, **70**, 1785). Clar's modification of the method (*Ber.*, 1939, **72**, 1645) gives no better result.

Better results are obtained by the method used by Kranzlein (*loc. cit.*) to prepare 2 : 3-dimethylacridine, in which the acridone is first reduced to the acridan, this after isolation being oxidised to the required acridine derivative. Ferric chloride appears to be the best oxidising agent for this purpose, although bromine, chromic acid and nitrous acid have all been used by other workers.

The acridone (0·5 g.) was heated with *iso*amyl alcohol (15 ml.) and treated with sodium (1 g.). The mixture was refluxed until the sodium had dissolved and all greenish fluorescence had vanished. The liquid was then steam-distilled to remove amyl alcohol, the cooled residue of acridan collected and dissolved in warm alcohol, and the cooled solution treated dropwise with aqueous ferric chloride until the green colour first given changed to yellow. Excess of ammonia was added to precipitate the ferrous hydroxide with the acridine. After the cold suspension had been filtered by gravity, the damp solid was extracted with boiling methyl alcohol, filtered hot, and the filtrate evaporated to crystallising point.

The following compounds were thus obtained from the corresponding acridones : 1-*methylacridan*, pale yellow needles, m. p. 82—83°, from aqueous methyl alcohol (Found : N, 7·2. $C_{14}H_{13}N$ requires N, 7·2%), and 1-methylacridine, pale yellow needles, m. p. 89° (Graebe and Locher, *Annalen*, 1894, **279**, 279, give m. p. 88°); 2-*methylacridan*, pale yellow leaflets, m. p. 152°, from aqueous alcohol (Found : N, 7·15%), and 2-methylacridine, pale yellow plates, m. p. 122—123°, from aqueous alcohol (Borsche, *Annalen*, 1910, **377**, 118, gives m. p. 125—126°); 3-methylacridan, yellow plates, m. p. 172°, from methyl alcohol (Found : N, 7·2%) (Kahn, *Annalen*, 1894, **279**, 274, gives m. p. 157°), and 3-methylacridine, m. p. 134° (Ullmann, *J. pr. Chem.*, 1889, **36**, 265, gives m. p. 134°); 4-*methylacridan*, pale yellow needles, m. p. 102—103°, from aqueous alcohol (Found : N, 7·2%), and 4-*methylacridine*, yellow needles, m. p. 98—99° (Found : N, 7·0. $C_{14}H_{11}N$ requires N, 7·25%).

Reduction of *N*-methylacridone produced *N*-methylacridan, pale yellow prisms, m. p. 95°, from methyl alcohol (Pictet and Patry, *Ber.*, 1902, **35**, 2536, give m. p. 96°).

5-Methylacridan was prepared by Sastry (J., 1916, **109**, 272) by reduction of 5-methylacridine with sodium amalgam in alcoholic solution and had m. p. 125—126°.

The position of the methyl group in the acridine nucleus makes little difference to the pH range over which the methylacridine changes colour when the solution is viewed under ultra-violet light. The change in all cases is green in acid to blue in alkaline solution and the pH ranges found for these compounds are acridine 4·8—5·8, 1-methylacridine 4·8—5·8, 2-methylacridine 5·2—6·2, 3-methylacridine 5·0—6·0, 4-methylacridine 5·2—6·0.

All nitrogen microanalyses are by Dr. Weiler of Oxford.

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