527. *Antibacterial Pteridines. 6 : 7-Dialkyl Derivatives of 2 : 4-Diaminopteridine.**

By N. R. CAMPBELL, J. H. DUNSMUIR, and M. E. H. FITZGERALD.

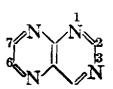
A series of 6 : 7-dialkyl-2 : 4-diaminopteridines * has been prepared; some of them exhibit high antibacterial activity against *Vibrio cholerae*.

DURING an investigation into the possibility of effective chemotherapeutic attack on cholera, we decided that derivatives of 2 : 4-diaminopteridine * were worthy of detailed study. Mallette, Taylor, and Cain (*J. Amer. Chem. Soc.*, 1947, **69**, 1814) have described the preparation of certain 6 : 7-disubstituted derivatives, including the dimethyl compound which has been found by Daniel *et al.* (*J. Biol. Chem.*, 1947, **169**, 689; 1947, **170**, 747) to show antibacterial activity against certain organisms, including *Bacterium coli* and *Staphylococcus aureus*. Although this 6 : 7-dimethyl-2 : 4-diaminopteridine was found not to possess any notable activity against *Vibrio cholerae*, we have now prepared and studied an extensive series of related pteridines with quite promising results.

Pteridines substituted by two identical alkyl groups are made most readily by interaction of tetra-aminopyrimidine, or one of its salts, with the appropriate aliphatic diketone. A suitable salt is the " bisulphite," prepared from 5-nitroso-2 : 4 : 6-triaminopyrimidine by reduction in aqueous suspension with sodium dithionite. This salt, and its method of preparation, have been dealt with by Mallette *et al.* (*loc. cit.*) and we have prepared it by their process, with certain modifications. We are, however, of the opinion that the reduction of nitrosotriaminopyrimidine in this manner is by no means a simple, straightforward reaction; the water-solubility and stability of the product are closely associated with the detailed experimental conditions employed.

Most of the members of this series of pteridines were prepared by reactions in the presence of acetic acid, but in certain cases it was found satisfactory to carry out the reaction in aqueous-alcoholic solution, in the presence of mild alkalis or organic bases.

With the exception of camphorquinone, the α-diketones used were all prepared by oxidation of the corresponding acyloins. The general method used for the preparation of these acyloins was that of Snell and McElvain (*Org. Synth.*, 1943, Coll. Vol. II, p. 114). The solvents employed were boiling ether or benzene at 40°; the former proved quite satisfactory for the shorter-chain members of the series, but when it was used with esters such as hexanoates and octanoates, reaction became retarded and was eventually stopped by the accumulation of insoluble material

* Numbering according to the Ring Index 

on the powdered sodium. Benzene did not share this disadvantage. Only ethyl phenylacetate failed to undergo this reaction; the required acyloin was later prepared by the interaction of benzylmagnesium chloride and acetaldehyde cyanohydrin.

Vibriostatic activities of 6 : 7-*dialkyl*-2 : 4-*diaminopteridines.*

Alkyl groups (at 6 and 7).	α-Diketone from which derived.	Minimal inhibitory dose (μg. per ml.).
H	Glyoxal	>500
Me	Diacetyl	>500
Et	Hexane-3 : 4-dione	40
Pr^n	Octane-4 : 5-dione	80
Pr^i	2 : 5-Dimethylhexane-3 : 4-dione	10
Bu^n	Decane-5 : 6-dione	>500
Bu^i	2 : 7-Dimethyloctane-4 : 5-dione	>500
sec.-Bu	3 : 6-Dimethyloctane-4 : 5-dione	40
n-Amyl	Dodecane-6 : 7-dione	>500
sec.-Amyl	4 : 7-Dimethyldecane-5 : 6-dione	>500
$CHEt_2$	3 : 6-Diethyloctane-4 : 5-dione	>500
n-Hexyl	Tetradecane-7 : 8-dione	>500
n-Heptyl	Octadecane-8 : 9-dione	>500
*cyclo*Hexyl	Di*cyclo*hexyl diketone	>500
*cyclo*Hexylmethyl	1 : 4-Di*cyclo*hexylbutane-2 : 3-dione	>500
Benzyl	1 : 4-Diphenylbutane-2 : 3-dione	>500
	Camphorquinone	80

As has been noted in the literature (particularly see Bouveault and Locquin, *Compt. rend.*, 1905, **140**, 1699), oxidation of acyloins to the α-diketones frequently affords poor yields. A variety of oxidising agents was tried in this work; chromium trioxide proved useful but the most encouraging results were obtained by the use of cupric acetate in diluted acetic acid (cf. Bloch, Lehr, Erlenmeyer, and Vogler, *Helv. Chim. Acta*, 1945, **28**, 1410).

Vibriostatic activities were determined by Dr. H. O. J. Collier, who will report the full biological work elsewhere. The table indicates the comparative activities of members of this series, when tested in a peptone–water medium against an inoculum of 10^3 vibrios (Madras 48210) per ml. at pH 7·2.

These results show a notable degree of specificity. Appreciable vibriostatic activity in the series appears to be restricted to those members which have aliphatic chains two or three carbon atoms in length; the activity is increased by addition of a methyl group on the α-carbon atom and decreased by a methyl group on the β-carbon atom. The effect of the α-methyl group is reversed on replacing it by an ethyl group.

The inactivity of the di*cyclo*hexyl derivative is fully in accordance with these observations and, although the exact relationship of the camphorquinone residue to these pairs of alkyl groups is somewhat complex, we consider the appreciable activity of the pteridine derived from camphorquinone to be quite compatible with the above generalisation.

Experimental.

Preparation of Acyloins and α-Diketones.—Acyloins were prepared from the appropriate esters by the method of Snell and McElvain (*loc. cit.*). Methods used for the oxidation of acyloins to α-diketones were as follows:

(I) Copper sulphate–pyridine, as described by Hartmann and Dickey (*J. Amer. Chem. Soc.*, 1933, **55**, 1228), but with 3 mols. of copper sulphate per mol. of acyloin.

(II) Copper acetate–acetic acid, as described by Bloch *et al.* (*loc. cit.*).

(III) Chromium trioxide, in an equal weight of water, added slowly to a cooled solution of the acyloin in acetic acid.

The following were prepared in the solvent or by the method named in parentheses: 4-*hydroxy*-3 : 6-*dimethyloctan*-5-*one* (ether) (72%), b. p. 95—100°/12 mm., n_D^{20} 1·439 (Found: C, 69·75; H, 11·8. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%), and 3 : 6-*dimethyloctane*-4 : 5-*dione* (II, 62%; III, 46%), b. p. 67—70°/12 mm., n_D^{20} 1·418 (Found: C, 69·7; H, 10·35. $C_{10}H_{18}O_2$ requires C, 70·55; H, 10·65%); 4-*hydroxy*-7-*dimethyldecan*-6-*one* (benzene) (75%), b. p. 110—115°/12 mm., n_D^{20} 1·441 (Found: C, 72·35; H, 11·95. $C_{12}H_{24}O_2$ requires C, 71·95; H, 12·10%), and 4 : 7-*dimethyldecane*-5 : 6-*dione* (III) (40%), b. p. 95—100°/12 mm., n_D^{20} 1·424 (Found: C, 72·85; H, 11·1. $C_{12}H_{22}O_2$ requires C, 72·7; H, 11·2%); 4-*hydroxy*-3 : 6-*diethyloctan*-5-*one* (benzene) (88%), b. p. 112°/12 mm., n_D^{20} 1·443 (Found: C, 71·7; H, 11·8. $C_{12}H_{24}O_2$ requires C, 71·95; H, 12·1%), and 3 : 6-*diethyloctane*-4 : 5-*dione* (II, 70%; III, 60%), b. p. 94—97°/12 mm., n_D^{20} 1·428 (Found: C, 72·75; H, 11·25. $C_{12}H_{22}O_2$ requires C, 72·7; H, 11·2%); 4-*hydroxy*-1 : 4-*dicyclohexylbutan*-3-*one* (ether) (68%), b. p. 117°/0·05 mm., n_D^{20} 1·490 (Found: C, 75·7; H, 11·0. $C_{16}H_{28}O_2$ requires C, 76·15; H, 11·2%), and 1 : 4-*dicyclohexylbutan*-2 : 3-*dione* (III, 60%), b. p. 100°/0·05 mm., m. p. 52° (Found: C, 77·1; H, 10·45. $C_{16}H_{26}O_2$ requires C, 76·75, H, 10·45%).

Preparation of Pteridines.—General method A. A mixture of tetra-aminopyrimidine " bisulphite " (0·01 mol.), the α-diketone (0·01 mol.), acetic acid (60%; 50 ml.), and alcohol (5 ml.) were heated together under reflux for 3 hours. The mixture was poured into water (200 ml.) and neutralised to bromothymol-blue (green). The crude precipitate was recrystallised from alcohol (lower members) or aqueous alcohol (higher members), charcoal being used as required.

General method B. A mixture of tetra-aminopyrimidine " bisulphite " (0·015 mol.), the α-diketone (0·01 mol.), water (50 ml.), alcohol (20 ml.), and the selected base (0·015 mol.) were heated together under reflux for about 1 hour or until diketone could no longer be observed refluxing with the solvent. The mixture was cooled and diluted with an equal volume of water. The crude precipitate was purified as before.

The following pteridines were prepared by the method stated in parentheses : 2 : 4-diaminopteridine (cf. Mallette, Taylor, and Cain, *loc. cit.*) (45%), m. p. 320° (decomp.); 2 : 4-diamino-6 : 7-dimethylpteridine (cf. *idem, ibid.*; also A, 80%) (recrystallised from 0·1N-hydrochloric acid, the resulting hydrochloride being heated with aqueous sodium hydrogen carbonate), m. p. 360°; 2 : 4-*diamino*-6 : 7-*diethylpteridine* (A) (43%) (recrystallised from alcohol), m. p. 268° (Found : C, 54·7; H, 6·4; N, 39·0. $C_{10}H_{14}N_6$ requires C, 55·0; H, 6·5; N, 38·5%); 2 : 4-*diamino*-6 : 7-*di*-n-*propylpteridine* (A) (42%) (recrystallised from alcohol), m. p. 202° (Found : C, 58·6; H, 7·35; N, 33·6. $C_{12}H_{18}N_6$ requires C, 58·5; H, 7·4; N, 34·1%); 2 : 4-*diamino*-6 : 7-*diisopropylpteridine* [A, 50%; B, 90% (sodium hydrogen carbonate)] (recrystallised from alcohol), m. p. 246° (Found : C, 58·4; H, 7·3; N, 34·2%); 2 : 4-*diamino*-6 : 7-*di*-n-*butylpteridine* [A, 40%; B (dimethylamine), 20%] (recrystallised from aqueous alcohol), m. p. 180° (Found : C, 61·0; H, 7·9; N, 30·0. $C_{14}H_{22}N_6$ requires C, 61·3; H, 8·1; N, 30·6%); 2 : 4-*diamino*-6 : 7-*diisobutylpteridine* (A) (30%) (recrystallised from aqueous alcohol, following chromatographic purification from chloroform–alcohol on alumina), m. p. 218° (Found : C, 61·05; H, 7·95; N, 30·8%); 2 : 4-*diamino*-6 : 7-*di*-sec.-*butylpteridine* (A) (21%) (recrystallised from aqueous alcohol, after precipitation by shaking a benzene solution of the crude gummy product with aqueous sodium hydrogen carbonate), m. p. 210° (Found : C, 61·2; H, 7·8; N, 30·8%); 2 : 4-*diamino*-6 : 7-*di*-n-*amylpteridine* (A, 15%; B, 15%) (recrystallised from aqueous alcohol), m. p. 160° (Found : C, 63·3; H, 8·6; N, 27·7. $C_{16}H_{26}N_6$ requires C, 63·5; H, 8·7; N, 27·8%); 2 : 4-*diamino*-6 : 7-*di*-sec.-*amylpteridine* [A, 8%; B (sodium hydrogen carbonate), 14%] (recrystallised from 0·1N-hydrochloric acid, the base being regenerated by treatment with hot aqueous sodium hydrogen carbonate and repeatedly recrystallised from alcohol), m. p. 172° (Found : C, 63·2; H, 8·5; N, 28·4%); 2 : 4-*diamino*-6 : 7-*di*-(1-*ethyl*-n-*propyl*)*pteridine* (A, 15%; B, unsuccessful) (recrystallised from aqueous alcohol), m. p. 181° (Found : C, 63·2; H, 8·7; N, 28·2. $C_{16}H_{26}N_6$ requires C, 63·5; H, 8·7; N, 27·8%); 2 : 4-*diamino*-6 : 7-*di*-n-*hexylpteridine* (A, 25%) (recrystallised from alcohol, after recovery from benzene solution, recrystallisation from 0·1N-hydrochloric acid, and treatment with aqueous sodium hydrogen carbonate), m. p. 140° (Found : C, 64·85; H, 9·2; N, 25·5%. $C_{18}H_{30}N_6$ requires C, 65·45; H, 9·15; N, 25·4%); 2 : 4-*diamino*-6 : 7-*di*-n-*heptylpteridine* (A) (28%) (recrystallised from aqueous alcohol), m. p. 132° (Found : C, 66·6; H, 9·4; N, 23·5. $C_{20}H_{34}N_6$ requires C, 67·0; H, 9·6; N, 23·45%); 2 : 4-*diamino*-6 : 7-*di*cyclo*hexylpteridine* (A) (25%) (recrystallised from alcohol), m. p. 270° (Found : C, 65·8; H, 8·0; N, 26·0. $C_{18}H_{26}N_6$ requires C, 66·25; H, 8·05; N, 25·7%); 2 : 4-*diamino*-6 : 7-*di*(cyclo*hexylmethyl*)*pteridine* [A, 21%; B (dimethylaniline), 22%] (recrystallised from alcohol), m. p. 230° (Found : C, 67·65; H, 8·6; N, 23·7. $C_{20}H_{30}N_6$ requires C, 67·75; H, 8·55; N, 23·7%); 2 : 4-*diamino*-6 : 7-*dibenzylpteridine* (A) (20%) (recrystallised from alcohol), m. p. 258° (decomp.) (Found : C, 70·35; H, 5·05; N, 24·5. $C_{20}H_{18}N_6$ requires C, 70·2; H, 5·3; N, 24·5%).

2 : 4-*Diaminocamphano*(2′ : 3′- or 3′ : 2′-6 : 7)*pteridine.*—A mixture of camphorquinone (6 g.), tetra-aminopyrimidine " bisulphite " (8 g.), hydrochloric acid (4 ml.), alcohol (50 ml.), and water (140 ml.) was boiled under reflux for 4 hours. The mixture was cooled, the pH adjusted to 6, and the separated solid collected, extracted with boiling water, and dried. The *product* (7 g.), recrystallised from alcohol (with charcoal), had m. p. 305° (Found : C, 62·2; H, 6·65; N, 31·2. $C_{14}H_{18}N_6$ requires C, 62·4; H, 6·65; N, 31·1%).

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Organic Chemical Department,
Allen and Hanburys Ltd., Ware, Herts.

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