39. Analogues of Pantothenic Acid

1. Attempted Preparation of Growth Promoters

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In view of the importance of pantothenic acid as a growth factor for certain micro-organisms, it was decided to investigate the specificity of this compound by preparing analogues in which one or more groups were omitted from or introduced into the molecule and testing the effect of such constitutional variations on the biological activity. The present paper deals with the effect of such variations on growth-promoting activity, whilst the following paper describes the preparation of analogues of pantothenic acid which were growth inhibitors. Further details of the biological testing and a fuller discussion of the results will be published by Dr H. McIlwain who carried out the biological work.

A number of analogues of pantothenic acid have already been described in the literature, and Table 1 shows their biological activities expressed as fractions of that of pantothenic acid. The compounds were prepared either by condensing β -alanine with various lactones or by condensing amino-acids other than β -alanine with α -hydroxy- $\beta\beta$ -dimethyl- γ -butyrolactone.

We have now prepared additional analogues of pantothenic acid as shown in Table 2. Of these nos. 16 and 17 differ from pantothenic acid only in the absence of methyl groups, while no. 13 differs only in the absence of the α -hydroxy group. The lactones involved in the preparation of these three analogues have been prepared previously. Nos. 14 and 15 contain one carbon atom more than pantothenic acid; neither of the lactones corresponding to these two compounds has been described before. Homopantoyllactone has now been made by a Reformatsky condensation on the corresponding aldol, and dehydrohomopantoyllactone by a malonic acid condensation on the same compound in presence of acetic acid. Numbers 18 to 21 are analogues formed by condensing the parent lactone (α -hydroxy- $\beta\beta$ -dimethyl- γ -butyrolactone) with amino-acids other than β -alanine.

Table 2 shows the results of growth stimulation tests on these analogues. Nos. 13–17 were tested in the form of their sodium salts, while nos. 18–21 were in the form of their calcium salts. Nos. 13–17 were tested for stimulation of growth on *Proteus morgani*. The maximum activity observed was 10^{-4} of that of pantothenic acid; hence the replacement effect in all five cases was negligible.

The suggestion that certain of the pantothenic acid analogues described in this paper might be of biological interest was made to us by Dr McIlwain, who also suggested a simplified nomenclature, following which we have adopted a system based on the name 'pantoyl' for the α : γ -dihydroxy- β : β -dimethyl- γ -butyryl radicle:

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Table 1. Showing the formulae and biological activities of analogues of pantothenic acid prepared previously

No.	Amino-acid	Lactone	Formula of analogue	Growth stimulation as a fraction of pantothenic acid activity	Reference
1	β -Alanine	α -Hydroxy- $\beta\beta$ -dimethyl- γ -butyrolactone	$\text{CH}_2\text{OH}-\text{C}(\text{CH}_3)_2-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	1	Reichstein [1940]
2	"	α -Hydroxy- γ -valerolactone	$\text{CH}_3-\text{CHOH}-\text{CHOH}-\text{CH}_2-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	0	Mitchell <i>et al.</i> [1940, 1]
3	"	α -Hydroxy- δ -valerolactone	$\text{CH}_2\text{OH}-\text{CH}_2-\text{CH}_2-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	0 +ve?	Reichstein [1940] Subbarow & Rane [1939]
4	"	α -Hydroxy- α -methyl- γ -butyrolactone	$\text{CH}_2\text{OH}-\text{CH}_2-\text{C}(\text{CH}_3)\text{OH}-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	+ve, $<10^{-2}$	Mitchell <i>et al.</i> [1940, 1]
5	"	α -Hydroxy- β -methyl- γ -butyrolactone	$\text{CH}_2\text{OH}-\text{CH}(\text{CH}_3)-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	+ve, $<10^{-2}$	Mitchell <i>et al.</i> [1940, 1]
6	"	α - β -Dihydroxy- γ -butyrolactone	$\text{CH}_2\text{OH}-\text{CHOH}-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	0	Mitchell <i>et al.</i> [1940, 1]
7	"	α -Hydroxy- γ -butyrolactone	$\text{CH}_2\text{OH}-\text{CH}_2-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	0	Mitchell <i>et al.</i> [1940, 1]
8	"	α -Hydroxy- β -methyl- β -hydroxymethyl- γ -butyrolactone	$\text{CH}_2\text{OH}-\text{C}(\text{CH}_3)(\text{CH}_2\text{OH})-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	+ve, c. 1/5	Mitchell <i>et al.</i> [1940, 2]
9	α -Alanine	As 1	$\text{CH}_2\text{OH}-\text{C}(\text{CH}_3)_2-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}(\text{CH}_3)-\text{COOH}$	0	Weinstock [1940]
10	β -Amino-butyric acid	As 1	$\text{CH}_2\text{OH}-\text{C}(\text{CH}_3)_2-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{COOH}$	0	Weinstock [1940]
11	Aspartic acid	As 1	$\text{CH}_2\text{OH}-\text{C}(\text{CH}_3)_2-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}(\text{CH}_2-\text{COOH})-\text{COOH}$	0	Weinstock [1940]
12	Lysine	As 1	$\text{CH}_2\text{OH}-\text{C}(\text{CH}_3)_2-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}((\text{CH}_2)_4\text{NH}_2)-\text{COOH} (?)$	0	Weinstock [1940]

Table 2. Showing the formulae and biological activities of new analogues of pantothenic acid

No.	Amino-acid	Lactone	Formula and derived name of analogue	Growth stimulation as a fraction of pantothenic acid activity	
				<i>Prot. morgani</i>	<i>B. coli</i> <i>Strp.</i>
1	β -Alanine	α -Hydroxy- $\beta\beta$ -dimethyl- γ -butyrolactone	$\text{CH}_2\text{OH}-\text{C}(\text{CH}_3)_2-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	1	
13	"	$\beta\beta$ -Dimethyl- γ -butyrolactone	$\text{CH}_2\text{OH}-\text{C}(\text{CH}_3)_2-\text{CH}_2-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	$<10^{-5}$	
14	"	β -Hydroxy- $\gamma\gamma$ -dimethyl- δ -valerolactone	Deoxypantothenic acid $\text{CH}_2\text{OH}-\text{C}(\text{CH}_3)_2-\text{CHOH}-\text{CH}_2-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	$<10^{-4}$	
15	"	$\Delta\alpha\beta\gamma\gamma$ -Dimethyl- δ -pentenolactone	Homopantothenic acid $\text{CH}_2\text{OH}-\text{C}(\text{CH}_3)_2-\text{CH}=\text{CH}-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	$<10^{-5}$	
16	"	γ -Butyrolactone	Dehydrohomopantothenic acid $\text{CH}_2\text{OH}-\text{CH}_2-\text{CH}_2-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	$<10^{-5}$	
17	"	γ -Valerolactone	<i>bisnor</i> Deoxypantothenic acid $\text{CH}_2-\text{CHOH}-\text{CH}_2-\text{CH}_2-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{COOH}$	$<10^{-5}$	
18	Lysine	As 1	<i>isonor</i> Deoxypantothenic acid $\text{CH}_2\text{OH}-\text{C}(\text{CH}_3)_2-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}((\text{CH}_2)_4\text{NH}_2)\text{COOH} (?)$		
19	Leucine	As 1	$\text{CH}_2\text{OH}-\text{C}(\text{CH}_3)_2-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}(\text{CH}_2-\text{CH}(\text{CH}_3)_2)\text{COOH}$		
20	Valine	As 1	$\text{CH}_2\text{OH}-\text{C}(\text{CH}_3)_2-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}(\text{CH}(\text{CH}_3)_2)\text{COOH}$		
21	Taurine	As 1	$\text{CH}_2\text{OH}-\text{C}(\text{CH}_3)_2-\text{CHOH}-\text{CO}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{SO}_3\text{H}$		

Do not appear to have marked activity

PREPARATION OF THE ANALOGUES

Chemical method

All the methods so far published for the synthesis of pantothenic acid depend on the condensation of α -hydroxy- β -dimethyl- γ -butyrolactone (pantolactone), with β -alanine in the form of its esters or salts. This lactone has already been prepared [Glaser, 1904; Köhn & Neustädter, 1918] from the cyanohydrin of $\alpha\alpha$ -dimethyl- β -hydroxypropaldehyde. The aldol itself was described by Wessely [1900] and a modified method of preparation was given by Stiller *et al.* [1940]. Glaser [1904] prepared the cyanohydrin by condensing the aldol with liquid HCN, whilst Stiller *et al.* [1940] prepared it by treating the bisulphite compound of the aldol with potassium cyanide. An improvement on the original method was described by Reichstein [1940], who used sodium cyanide and calcium chloride instead of liquid HCN, the hydrolysis being effected with alkali. A further simplification was published by Carter & Ney [1941] who used sodium cyanide and calcium chloride but hydrolysed the cyanohydrin by means of the calcium hydroxide produced during the reaction. We have found this simplified method satisfactory.

The condensation with β -alanine was effected originally through the ethyl ester of the amino-acid [Stiller *et al.* 1940], whilst a more direct method involving fusion at 100° of the lactone and β -alanine sodium salt was published about the same time by Williams *et al.* [1940]. A simpler technique was described by Reichstein [1940] who found that condensation took place when the lactone and the methyl ester of β -alanine were refluxed together in absolute methyl alcoholic solution for 1 hr.; on removing the solvent and hydrolysing the residue carefully, a solution of pantothenic acid was obtained which was tested directly.

We adapted this last method to the preparation of the sodium and calcium salts of pantothenic acid and its analogues, and found that complete or nearly complete condensation took place when the calcium or sodium salt of β -alanine, or other amino-acid, was refluxed for 1 hr. with the appropriate lactone in absolute methyl alcohol (dried over barium oxide and freshly redistilled before use) with exclusion of moisture. A practically clear solution was obtained which, after being filtered quickly from traces of insoluble material, was poured into about 6 vol. of absolute ether or acetone with vigorous shaking. This gave a fine white precipitate, which was filtered off and washed with absolute ether. Owing to the extremely hygroscopic nature of the sodium salts of most of the analogues, it was necessary to keep the precipitate covered with ether all the time, finally transferring it to a desiccator over phosphorus pentoxide and removing the ether *in vacuo*; the substance was left as a dry white amorphous powder. Synthetic pantothenic acid prepared by this method was fully active when tested bacteriologically. A similar amorphous product could be obtained by evaporating the alcoholic solution to small bulk and cooling. Substantially the same method was described recently by Parke & Lawson [1941], using ethyl alcohol as solvent.

Crystalline sodium pantothenate was obtained by Reichstein [1940] who found that condensation could be effected by adding one equivalent of sodium methoxide to β -alanine in methyl alcohol, followed by the addition of the lactone to the cooled solution, and keeping the mixture at room temperature for 2 days. Concentration of the solution followed by careful addition of acetone gave the crystalline product.

In the normal way, the efficiency of the condensation of the two components to form pantothenic acid, is tested biologically. (In our experiments with pantothenic acid itself, full activity was observed with the sodium salt, prepared both by the fusion method of Williams and by the refluxing method just described.) In the case of the analogues, however, obviously the biological method could not be used to test complete condensation.

We therefore carried out total N determinations on all the analogues. It is clear that if incomplete condensation had occurred, then the ether precipitation would throw down the analogue together with all the amino-acid sodium salt, but would probably not throw out the unchanged lactone, or at any rate only partially. A high total N may therefore be taken to indicate incomplete condensation. We have taken the total N as a rough indication of the maximum condensation which has taken place. The values in every case indicated over 80 % conversion. In only one case (homopantothenic acid) was a nitrogen value found which was slightly lower than the theoretical, but the difference was practically within the limits of experimental error.

Deoxypantothenic acid (no. 13)

$\beta\beta$ -Dimethylbutyrolactone. The lactone was prepared according to the method of Windaus [1921] by decomposition of the silver salt of $\beta\beta$ -dimethylglutaric acid [Kommpa, 1899]. The yield obtained was lower than that given by Windaus (27 % instead of 40 % at the final stage), 17 g. of silver salt giving 1.5 g. of crude lactone, from which 0.9 g. of pure lactone was obtained after two sublimations. It is a hygroscopic, very volatile, waxy solid; m.p. 57° (lit. 57°). The amide, although crystalline, proved to be too deliquescent to be of use for analysis. (Found: C, 62.5, H, 8.6 %. Calc. for $C_6H_{10}O_2$: C, 63.1; H, 8.8 %.)

Condensation. Freshly resublimed lactone (553 mg.) and 542 mg. of β -alanine sodium salt were dissolved in 4 ml. of absolute methyl alcohol. The solution was refluxed for 2 hr. and worked up as described for the general procedure. Yield, 840 mg. (Found: N, 7.1 %. Calc. for $C_9H_{16}O_4N Na$: N, 6.3 %.) This may be taken to indicate 88 % condensation.

Homopantothenic acid (no. 14)

β -Hydroxy- $\gamma\gamma$ -dimethyl- δ -valerolactone. 50 g. of $\alpha\alpha$ -dimethyl- β -hydroxy-propaldehyde (b.p. 90–92°/121 mm.) were dissolved in 250 ml. of absolute benzene, and a little of the benzene was distilled off in order to remove traces of moisture. Then 63 g. of freshly distilled ethyl bromoacetate and 56 g. of thoroughly dried, granulated zinc were added, the latter having been activated by washing in turn with warm NaOH solution, HCl, water (several times), alcohol and absolute ether. The mixture, contained in a flask fitted with a reflux condenser carrying a $CaCl_2$ tube, was gently warmed for about 15 min. until the reaction set in, and was then cooled until the reaction became less vigorous (about 40 min.); finally it was refluxed for a further 2 hr. It was then cooled, 300 ml. ice and water were added, followed by enough ice-cold 10 % H_2SO_4 to dissolve the precipitate. The solution was extracted thoroughly with ether (10 times) and the extract was dried over sodium sulphate and evaporated, leaving a colourless oil, which appeared to be insoluble in water. This ester was hydrolysed by boiling for 1½ hr. with a solution of 33 g. KOH in 20 ml. of water and 1400 ml. of ethyl alcohol. After adding 1 l. of water, the solution was evaporated to small bulk at a temperature not exceeding 50°, and the residue was extracted three times with ether, which removed any unchanged aldehyde and traces of unsaponified material. The aqueous solution and washings were then acidified with 50 % HCl, and extracted ten times with a large bulk of ether (about 5 l. in all). The solution was dried and the solvent was evaporated, leaving a residue which partially crystallized on standing, giving long needles, m.p. 70–75°.

The main bulk of the residue was distilled *in vacuo*, the fraction boiling below 120° (mainly bromoacetic acid) being discarded. The fraction boiling at 125–130°/13 mm. solidified at once in the receiver. It weighed 19 g., had m.p. 75–77°, and did not decolorize bromine water or $KMnO_4$ solution. A small amount of the distillate was purified by resublimation, m.p. 83–85°. Analytical data were exactly right for the free acid, or for the lactone hydrated with one molecule of water of crystallization, but could not fit either

the expected lactone or a dihydroxylactone with a somewhat similar formula, as shown below:

		C %	H %
Calc. for β -hydroxy- $\gamma\gamma$ -dimethyl- δ -valerolactone	$C_7H_{12}O_3$	58.3	8.4
„ α - β -dihydroxy-dimethyl- δ -valerolactone	$C_7H_{12}O_4$	52.5	7.56
„ $\Delta\alpha$: β - $\gamma\gamma$ -dimethyl- δ -penteno-lactone	$C_7H_{10}O_3$	66.67	8.00
„ $\beta\delta$ -dihydroxy- $\gamma\gamma$ -dimethylvaleric acid	$C_7H_{14}O_4$	51.7	8.7
Found	...	51.53	8.58

An attempt to make the amide by the usual method of passing ammonia into the dry methyl alcoholic solution of the lactone and keeping for 48 hr., yielded, on addition of ether, glistening white platelets, m.p. 124–125°, which contained no N, and analysed approximately correctly for the hydrated lactone. This suggested that the lactone might be obtained in crystalline form from ether. About 3 g. of the lactone were taken up in absolute ether, the solution was evaporated slightly, and light petroleum was added until crystallization set in. The product was obtained in the form of needles (1.9 g.), m.p. 110–112°. On recrystallization from ether-light petroleum, it gave needles (1.1 g.), m.p. 126–127°, and a further recrystallization of these needles from a large bulk of light petroleum (b.p. 40–60°) gave glistening flat plates, m.p. 126–126.5°; the m.p. was unchanged by a further recrystallization. Either plates or needles could be obtained at will by seeding. (Found: C, 51.3; H, 8.59%. Calc. for $C_7H_{14}O_4$: C, 51.7; H, 8.7%.)

A Zerewitinoff determination on this material gave a result in excellent agreement with that calculated for the required lactone. (Active hydrogen found (in pyridine), 0.68%; calc. for required lactone, 0.69%; calc. for free acid, 1.23%.)

Condensation. Freshly distilled lactone (535 mg.) dried over phosphorus pentoxide was dissolved in 4 ml. of freshly redistilled dry methyl alcohol and 416 mg. of β -alanine sodium salt were added. After refluxing for 1 hr., the mixture was worked up in the usual way. Yield, 700 mg. (Found: N, 4.92%. Calc. for $C_{10}H_{18}O_5N$ Na: N, 5.48%.)

Dehydrohomopantothenic acid (15)

$\Delta\alpha$: β - $\gamma\gamma$ -Dimethyl- δ -valerolactone. This was prepared, admixed with another lactone, the nature of which is uncertain and which is still under investigation, by the method described by Michael & Ross [1933]. A mixture of 42 g. of $\alpha\alpha$ -dimethyl- β -hydroxypropaldehyde and 23 g. of malonic acid, 22 g. of acetic anhydride and 12 g. of glacial acetic acid, was refluxed for 40 hr. at about 140°. The solution was then distilled with a column up to 120° to remove acetic anhydride, and the residue was fractionated *in vacuo* at 25 mm. The distillate obtained below 130° was discarded, whilst the fraction boiling between 158 and 165° solidified in the receiver to a wax melting at 102–104°. In order to obtain the lactone pure, this crude product was treated as follows.

The crystalline mass was taken up in ether, and extracted with NaOH solution, and the aqueous solution was acidified with HCl, and ether-extracted. On evaporating the ether, the free acid which remained was lactonized by warming on the water bath for 15 min. with 10% aqueous HCl. The solution was made alkaline with $NaHCO_3$ (in which the lactone was insoluble), and ether-extracted. The product (7 g.) crystallized in the form of needles, m.p. 102–106°, which, under the microscope, could be seen to be of two types, one clusters of fern-like needles, and the other long, thin needles. With homopantolactone it gave a depression of about 20°, and it decolorized $KMnO_4$ in the cold. On recrystallization from light petroleum, characteristic clusters of needles were obtained, m.p. 110–110.5°, which did not decolorize $KMnO_4$, whilst from the mother liquors, after five more recrystallizations, long needles were eventually obtained, which decolorized $KMnO_4$ in the cold, m.p. 115°, unchanged by two further recrystallizations. Analysis agreed fairly well with that for the required lactone. (Found: C, 67.28; H, 8.4%. Calc. for $C_7H_{10}O_2$: C, 66.7; H, 8.00%.)

Condensation. The unsaturated lactone (110 mg.) and 97 mg. of pure dry β -alanine Na salt were dissolved in 1 ml. of methyl alcohol and refluxed for $1\frac{1}{2}$ hr. The mixture was worked up as usual. Yield, 160 mg. (Found: N, 7.30 %. Calc. for $C_{10}H_{16}O_4N Na$: N, 5.9 %. This may be taken to indicate c. 81 % condensation.)

bisnorDeoxypantothenic acid (16)

γ -Butyrolactone. This was prepared by the method described by Windaus [1921] and Fichter [1896] by reduction of succinic anhydride with sodium amalgam, B.P. 203–204°. The phenylhydrazide was prepared by refluxing a solution of 1.2 g. of butyrolactone and 1.62 ml. of redistilled phenylhydrazine in 25 ml. absolute alcohol with exclusion of moisture. After removal of the solvent *in vacuo*, the residue crystallized and was re-crystallized from absolute alcohol-ether. M.P. 94–94.5°. Yield, 1.95 g. (Found: C, 61.90; H, 7.27; N, 14.7 %. Calc. for $C_{10}H_{14}O_2N_2$: C, 61.83; H, 7.21; N, 14.4 %.)

Condensation. 1 g. of freshly distilled lactone and 1.27 g. of β -alanine sodium salt were dissolved in 5 ml. of ethyl alcohol and treated as usual. Yield, 1.6 g. (Found: N, 7.9 %. Calc. for $C_7H_{12}O_4N Na$: N, 7.10 %. This may be taken to indicate c. 90 % condensation.)

isonorDeoxypantothenic acid (17)

γ -Valerolactone. This was prepared in the usual way by reduction of laevulinic acid [Fichter, 1903]. It was distilled at normal pressure immediately before use; B.P. 202–204° sharp. The phenylhydrazide was prepared as described under butyrolactone; 300 mg. gave 400 mg. of a derivative obtained crystalline after one week's standing in ether. M.P. 83–85°. (Found: C, 62.81; H, 7.60 %. Calc. for $C_{11}H_{16}O_2N_2$: C, 63.46; H, 7.69 %.)

Condensation. The lactone (510 mg.) and 566 mg. of β -alanine sodium salt were dissolved in 4 ml. of methyl alcohol and treated as usual. Yield, 700 mg. (Found: N, 7.71 %. Calc. for $C_8H_{14}O_4N Na$: N, 6.63 %. This may be taken to indicate 86 % condensation.)

The analogues with lysine, leucine, valine and taurine were prepared in the form of their calcium salts by a similar method. The calcium salts of the amino-acids were prepared by adding an excess of calcium hydroxide to the aqueous solution of the amino-acids, boiling for 1 min., evaporating to dryness under reduced pressure and removing the last traces of water by two more distillations after the addition of small amounts of absolute alcohol and absolute toluene. In this way, the calcium salt was obtained in the form of a dry white powder which was then condensed with α -hydroxy- $\beta\beta$ -dimethyl- γ -butyrolactone in the usual way.

Note. All melting points are uncorrected. Micro-analyses were carried out by Dr Weiler of Oxford. Our thanks are due to Miss P. Turner-Jones and Miss B. Wilson for assistance in preparing some of the intermediates in this work.

DISCUSSION OF RESULTS

It would already appear highly probable, from the results obtained by other workers on the activity of analogues of pantothenic acid (shown in Table 1) that pantothenic acid would prove to be highly specific as a growth stimulator, for the only analogue so far reported as having appreciable activity is hydroxypantothenic acid (no. 8, Table 1) which differs from pantothenic acid only in having a hydroxymethyl group instead of a methyl group on the β -carbon atom. However, the absence of one or both β -methyl groups appears to lead to complete (no. 7) or very considerable (nos. 5 and 6) loss of activity.

The present results tend to confirm this specificity of constitution. Deoxypantothenic acid (no. 13, Table 2) a compound identical with pantothenic acid except for the absence of the α -hydroxy group, is quite inactive. So also, as would be expected, are nos. 16 and 17 in which the α -OH and the two β -Me groups are absent. It is interesting to note here a point which will be dealt with in more detail in the following paper, namely, that loss of

the α -hydroxy group is not only associated with loss of growth-promoting activity, but also gives rise to the ability to inhibit bacterial growth. In fact, the three compounds, 13, 17 and 16 show increasing inhibitory activities in this order.

Homopantothenic acid, no. 14, differs from pantothenic acid only in having an additional CH_2 group in the straight chain of the lactone part of the molecule. It was therefore quite surprising to find that this compound was only 1/10,000 as active as pantothenic acid. Further, the unsaturated homologous compound was also inactive.

This result is in line with the observation of Weinstock [1940] that homologue no. 10 (Table 1) containing one more CH_2 than pantothenic acid, is inactive, although in this case of course the CH_2 is not in the straight chain.

The analogues with other amino-acids show no interesting replacement effects, whilst the remarkable inhibitory effects of pantoyltaurine (no. 21) will be dealt with in the next paper.

Other analogues are under investigation.

SUMMARY

1. Various new analogues of pantothenic acid have been prepared by condensing β -alanine with five different lactones, and by condensing α -hydroxy- $\beta\beta$ -dimethylbutyrolactone with four different amino-acids.

2. In no instance was the analogue able to replace pantothenic acid as a growth-stimulator when tested on micro-organisms. Loss of the α -hydroxy group and increase in length of the carbon chain are associated with loss of biological activity.

3. Two new lactones have been prepared during the course of this work. They are β -hydroxy- $\gamma\gamma$ -dimethyl- δ -valerolactone and $\Delta\alpha$ - $\beta\gamma$ -dimethyl- δ -valerolactone.

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