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SYNTHESIS OF DL-2-AMINO-3,3-DIMETHYLBUTYRO-THIOLACTONE AND BIS(DL-2,2-DIMETHYL-3-AMINO-3-CARBOXYPROPYL) DISULPHIDE

HOMOLOGUES OF PENICILLAMINE AND PENICILLAMINE DISULPHIDE

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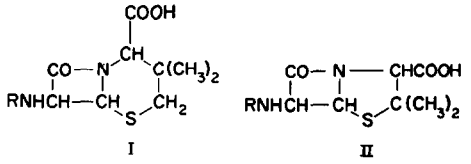
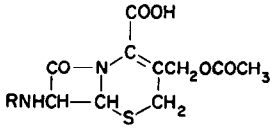
Abstract—For the preparation of these compounds N-acetylpantonine was condensed with benzylmercaptane into N-acetyl-S-benzyl-3,3-dimethylhomocysteine which was hydrolysed to S-benzyl-3,3-dimethylhomocysteine hydrochloride and this was subsequently debenzylated, cyclized and oxidized.

THE total synthesis of penicillins achieved by Sheehan *et al.*[1] led to the preparation of numerous structural analogues and homologues of penicillins. The structural modifications in the penicillin molecule are desirable on account of limited antibacterial activity, their great sensitivity to the enzyme penicillinase and their undesirable side effects. In order to prepare novel penicillins without these disadvantages, the synthesis of therapeutically more valuable antibiotics has been attempted.[2–6]



I

II



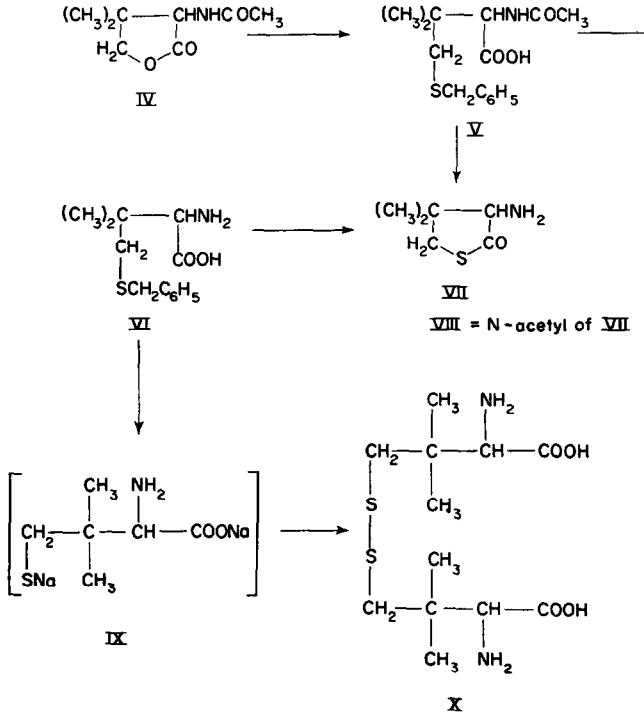
III

It was considered of interest to synthesize homopenicillins containing a fused β-lactam-thiazane ring system (I) in place of the β-lactam-thiazolidine ring system (II)

[1] J. C. Sheehan and K. R. Henery-Logan, *J. Amer. Chem. Soc.* **79,** 1262 (1957); **81,** 3089 (1959).
[2] J. C. Sheehan and P. A. Cruikshank, *J. Amer. Chem. Soc.* **78,** 3683 (1956).
[3] J. C. Sheehan and D. R. Hoff, *J. Amer. Chem. Soc.* **79,** 237 (1957).
[4] W. A. Bolhofer, J. C. Sheehan and E. L. A. Abrams, *J. Amer. Chem. Soc.* **82,** 3437 (1960).
[5] Y. G. Perron, W. F. Minor, C. T. Holdrege, W. J. Gottstein, J. C. Godfrey, L. B. Crast, R. B. Babel and L. C. Cheney, *J. Amer. Chem. Soc.* **82,** 3934 (1960).
[6] H. H. Wasserman, B. Suryanarayma, R. C. Koch and R. L. Tse, *Chem. & Ind.* 1022 (1956).

of the penicillin nucleus, particularly as it has been reported that cephalosporin *C* has a fused *β*-lactam-dihydrothiazine ring system (III).[7–11]

In this paper the first stage in the synthesis of homopenicillins of type I is described. Our attention and efforts were first concentrated upon the preparation of DL-2-amino-3,3-dimethylbutyrothiolactone (VII) as its hydrochloride and bis(DL-2,2-dimethyl-3-amino-3-carboxypropyl) disulphide (X), as key intermediates for the synthesis of homopenicillins with fused four- and six-membered rings. In fact the hydrochloride of VII is the thiolactone form of a new homologue of penicillamine and compound X is



a new homologue of penicillamine disulphide. As far as is known the syntheses of only two homologues of penicillamine, 3-mercaptoleucine and 3-mercaptoisoleucine, have been reported.[12]

N-Acetylpantonine (IV), prepared by the reaction of pantonine hydrochloride with acetic anhydride,[13] was found to react with the sodium benzylmercaptide to yield N-acetyl-S-benzyl-3,3-dimethylhomocysteine (V). By hydrolysis with hydrochloric acid this compound yielded the hydrochloride of VI, which when treated with pyridine afforded S-benzyl-3,3-dimethylhomocysteine (VI). Debenzylation of VI with

[7] E. P. Abraham and G. C. F. Newton, *Biochem. J.* **79,** 377 (1961).
[8] D. C. Hodgkin and E. N. Maslen, *Biochem. J.* **79,** 393 (1961).
[9] C. W. Hale, G. G. F. Newton and E. P. Abraham, *Biochem. J.* **79,** 403 (1961).
[10] B. Loder, G. G. F. Newton and E. P. Abraham, *Biochem. J.* **79,** 408 (1961).
[11] E. P. Abraham and G. G. F. Newton, *Endeavour* **20,** 92 (1961).
[12] H. T. Clark and J. R. Johnson *The Chemistry of Penicillin* (Edited by R. Robinson), Princeton University Press (1949).
[13] F. W. Holly, R. A. Barnes, F. R. Koniuszy and K. Folkers, *J. Amer. Chem. Soc.* **70,** 3088 (1948)

sodium in liquid ammonia in the usual manner[14] resulted in the formation of the sodium salt of 3,3-dimethylhomocysteine (IX), which by acidification with hydrochloric acid yielded the hydrochloride of homopenicillamine thiolactone (VII). Attempts to isolate 3,3-dimethylhomocysteine from its sodium salt were unsuccessful as only the oxidized form of this compound, 3,3-dimethylhomocystine (X) was obtained. The S-benzyl-N-acetyl amino acid V was debenzylated with sodium in liquid ammonia and subsequently treated with hydrochloric acid to give N-acetyl homopenicillamine thiolactone (VIII). The latter compound was also obtained by acetylation of VII with acetic anhydride in pyridine.

EXPERIMENTAL

N-*Acetyl*-S-*benzyl*-3,3-*dimethylhomocysteine* (V)

To 50 ml absolute methanol 2·3 g (0·1 mole) sodium was added until reaction was complete, then 12·4 g (0·1 mole) benzylmercaptane was added and excess of methanol removed *in vacuo*. To the solid sodium benzylmercaptide 100 ml dimethylformamide and 17·1 g (0·1 mole) N-acetylpantonine were added.[13] The mixture was heated in an oil bath at 130–150° for 4 hr and then kept at room temp overnight. The solvent was removed *in vacuo* and the residual reddish oily mass dissolved in 60 ml water. This solution was extracted with 20 ml ether and the ethereal layer discarded. The aqueous layer was acidified with 28 ml hydrochloric acid (1:1) and the solidified oil removed by filtration, washed with water and dried in a vacuum desiccator, yield 23·7 g (80%), m.p. 132–133°. A sample was recrystallized from ethanol for analysis, m.p. 134·5–135·5. (Found: C, 60·88; H, 7·20; N, 4·97 $C_{15}H_{21}O_3NS$ requires: C, 61·00; H, 7·17; N, 4·74%).

S-*Benzyl*-3,3-*dimethylhomocysteine hydrochloride*

A mixture of 29·5 g (0·1 mole) N-acetyl-S-benzyl-3,3-dimethylhomocysteine, 295 ml conc hydrochloric acid and 295 ml water was heated under reflux for 16 hr, treated with charcoal and filtered. After chilling the colourless crystals were dried in a vacuum desiccator yielding 20 g (69%), m.p. 153–155°. A second crop weighing 7·1 g (24%) and m.p. 152–154° was obtained by evaporation of the mother liquor. Recrystallization from hydrochloric acid (1:1) raised the m.p. to 154–156°, (Found: ·C, 53·75; H, 6·75; N, 5·11. $C_{13}H_{20}ClO_2NS$ requires: C, 53·87; H, 6·95; N, 4·83%).

To a solution of 7·1 g of the amino acid hydrochloride in 12 ml absolute ethanol 8 ml pyridine was added. After cooling in the refrigerator overnight, the product were filtered and dried, yielding free amino acid VI 3·2 g (51%), m.p. 204–208°. Recrystallization from dimethylformamide gave colourless crystals, m.p. 208–210°. (Found: C, 61·96; H, 7·64; $C_{13}H_{19}O_2NS$ requires: C, 61·64; H, 7·56%),

DL-2-*Amino*-3,3-*dimethylbutyrothiolactone hydrochloride*

Following the procedure described by Riegel and du Vigneaud[15] for the preparation of homocysteine thiolactone hydrochloride, S-benzyl-3,3-dimethylhomocysteine hydrochloride,m.p. 154–156° (6·67 g, 0·023 mole) was dissolved in approximately 150 ml liquid ammonia. This solution was stirred while 1·1 g sodium was added in small portions and sufficient quantity to ensure persistance of the blue colour for at least 10 min. The excess sodium was decomposed by addition of a few crystals of ammonium chloride. The cooling bath was removed and the ammonia allowed to evaporate, and the flask was then evacuated. To the residual sodium salt 60 ml hydrochloric acid (1:1) was added and the mixture heated on a water bath 1 hr. The solution was extracted with 20 ml ether, the ethereal extract discarded and the solution concentrated *in vacuo*. To the residue 25 ml conc hydrochloric acid was added and the solution again evaporated. The dry residue was extracted 3 times with 20 ml absolute ethanol. To separate the sodium chloride the ethanolic solution of thiolactone hydrochloride was evaporated to dryness and then repeatedly extracted twice with 20 ml absolute ethanol. To the ethanolic solution 10 ml dry ether was added and the solution kept at room temp overnight and then in a refrigerator for 2 days, yielding 2·1 g (50%), m.p. 190–193° (dec.). A sample was recrystallized from ethanol–ether for analysis, m.p. 205–208°. (Found: C, 39·44; H, 6·64; N,

[14] R. S. Sifferd and V. du Vigneaud, *J. Biol. Chem.* **108,** 757 (1935).
[15] B. Riegel and V. du Vigneaud, *J. Biol. Chem.* **112,** 149 (1935).

7·44. $C_6H_{12}ClNOS$ requires: C, 39·66; H, 6·65; N, 7·71%). The sodium nitroprusside test was negative.

2-Acetamido-3,3-dimethylbutyrothiolactone (VIII)

(a) *By debenzylation.* N-Acetyl-S-benzyl-3,3-dimethylhomocysteine (4·9 g, 0·0166 mole) was treated in liquid ammonia with sodium (0·92 g) as described previously. After evaporation of the ammonia 40 ml hydrochloric acid (1:1) was added and the mixture heated on a water bath for 1 hr and then kept overnight at room temp yielding 2·0 g of almost colourless needles (64%) m.p. 165–169°. The filtrate yielded a second crop weighing 0·6 g (19%), m.p. 168–170°. Recrystallization from aqueous ethanol raised the m.p. to 170°. (Found: C, 51·14; H, 6·71; N, 7·87. $C_6H_{13}NO_2S$ requires: C, 51·14; H, 7·00; N, 7·48%). UV Spectrum in 95% ethanol has a peak at λ_{max} 236 (ε_{max} 195).[16]

(b) *By acetylation.* To a mixture of 5 ml pyridine and 1·5 ml acetic anhydride, 0·9 g hydrochloric of VII was added and kept at 60° for 15 min. The solvent was removed under red. press., and the residue recrystallized from aqueous ethanol identified as N-acetyl derivative (VIII) by comparison of m.p. (170°). On admixture with a sample obtained as under (a) no depression of m.p. was observed.

Bis (DL-2,2-*dimethyl*-3-*amino*-3-*carboxypropyl*) *disulphide* (X)

The sodium salt of 3,3-dimethylhomocysteine (IX), prepared by debenzylation of VI (2·9 g, 0·01 mole) with sodium in liquid ammonia, as described previously, was dissolved in 50 ml water and extracted with 20 ml ether. The aqueous solution was neutralized with acetic acid to a pH 8–8·5, 3 drops of a 1% solution ferric chloride added and then oxidized for 6 hr by aeration. The precipitate of X was filtered off and dried. A second crop was obtained by acidification of the filtrate. The yield was 1·1 g (68%), m.p. 243–245° (dec.). The product was purified by recrystallization from water, m.p. 262–263° (dec.). (Found: C, 44·20; H, 7·71; N, 8·86. $C_{12}H_{24}O_4N_2S_2$ requires: C, 44·42; H, 7·45; N, 8·86%). After heating for some time on the water bath X gave a blue colour with ninhydrine.

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[16] R. Benesh and R. E. Benesh, *J. Am. Chem. Soc.*, **78**, 1597 (1956).