SYNTHESIS of analogues of biotin is an attractive endeavour and certain investigations were initiated to achieve the same. Circumstances have made it difficult for the author to pursue the scheme of work originally contemplated and so the result of work so far completed is reported. Brown, Safir, Baker, Bernstein and Dorfman obtained 2-keto-4-methyl-2, 3, 4, 6-tetrahydro-1-thieno-(3, 4)-imidazole by a series of reactions, starting from the azlactone of α-benzamido crotonic acid. This reacted with thioglycollic ester to yield, α-benzamido-β-carbethoxy methyl thiobutyrate. Dieckmann cyclisation followed by hydrolysis and treatment with potassium cyanate gave the desired imidazole. It was thought profitable to synthesise the substance mentioned in the title of this paper by an analogous series of reactions:

When a mixture of the azlactone of benzaldehyde and methyl thioglycollate in absolute methanol was treated with a few drops of piperidine, the mercaptan added to the double bond, the azlactone ring opened and the carboxyl group was esterified. This gave in one step 82% yield of methyl-
a-benzamido-β-carbomethoxy phenyl thio-butyrate (II) as a viscous oil. It solidified on titrating with petrol and was crystallised from light petrol (40°–60°) yielding colourless crystals melting at 95–97°. The thioether (II) underwent Dieckmann reaction in the presence of sodium methoxide to give 2-phenyl-3-benzamido-4-keto-thiophane (IV) in 50% yield. The decarboxylation, probably elimination as carbonate, could not be prevented experimentally; which is a circumstantially favourable position when it is desired to introduce a side chain in position five by condensation with appropriate aldehydes. The cyclisation product was soluble in water but could be completely extracted by continuous ether extraction. It crystallised from ethanol, m.p. 236°. That elimination of the ester group had taken place during cyclisation was established by analysis and infra-red data. The ketone gave a 2, 4-dinitrophenyl hydrazone melting at 185°. The 2-phenyl-3-benzamido-4-keto-thiophane (IV) was hydrolysed by a mixture of hydrochloric and phosphoric acids, when the hydrochloride of 2-phenyl-3-amino-4-keto-thiophane (V) was obtained. It crystallised from concentrated hydrochloric acid melting at 94°. The pure hydrochloride dissolved in water was treated with potassium cyanate to afford 2-keto-4-phenyl-2, 3, 4, 6-tetrahydro-1-thieno-(3, 4)-imidazole (VI).
EXPERIMENTAL

*Methyl-a-benzamido-β-carbomethoxy phenyl thio-butyrate (II)*

To the azlactone (12.5 g.) in absolute methanol (100 ml.) was added methyl thioglycollate (5.3 g.) and a few drops of piperidine. The azlactone went into solution slowly and after the mixture was allowed to stand at room temperature for 3 days, was refluxed on the steam-bath for an hour. The excess of methanol was removed under reduced pressure and the residual oil was poured on to ice under vigorous stirring. The pasty mass that separated was taken up in ether, the solution dried over anhydrous magnesium sulphate and the ether removed. The product was repeatedly crystallised from light petrol (40°–60°) and after hard crystals were obtained, purified by further crystallisation from dilute acetic acid. Yield 15 grams (82%), m.p. 95°.

Found: C, 61.9  H, 5.3  N, 3.4
Calculated for C_{28}H_{21}SO_{3}N: C, 62.0  H, 5.4  N, 3.6

*2-Phenyl-3-benzamido-4-keto thiophane (IV)*

The thiobutyrate (4 g.) in dry benzene (100 ml.) was added to sodium methoxide prepared from 0.6 gram of sodium and the mixture allowed to stand overnight. It was then refluxed for 18 hours and then poured on to ice with vigorous stirring. The benzene layer was removed and the aqueous portion extracted with benzene. The aqueous solution was cooled in ice and acidified with acetic acid and then continuously extracted with ether. The ethereal solution was dried over anhydrous magnesium sulphate and the ether removed. The resulting product was crystallised from ethanol yielding 1.5 grams (50% yield) of the pure product of m.p. 236°.

Found: C, 68.6  H, 5.0  N, 4.9  S, 10.1
Calculated for C_{17}H_{15}SNO_{2}: C, 68.7  H, 5.1  N, 4.8  S, 10.8

**Infra-red spectrum data.**—The data confirms the structure assigned to the product (please see curve). The compound absorbed in the region 770 cm.−1 characteristic of −CH_{2}−S−CH_{2}−grouping. The absorptions in the regions 1683 cm.−1, 1633 cm.−1, 1683 cm.−1, and 3224 cm.−1 are characteristic of the keto group, the NH−CO−R and the −NH groups. That the compound exists in the enolic form is indicated by its absorption in region 3224 cm.−1.

*2-Phenyl-3-amino-4-keto thiophane hydrochloride*

2-Phenyl-3-benzamido-4-keto-thiophane (0.5 g.) was added to a mixture of orthophosphoric acid (1.0 ml.) and water (2.0 ml.) and the mixture
refluxed for an hour. Hydrochloric acid (10 ml.) was then added in two lots and refluxing continued for 5 hours. On cooling the hydrochloride separated out. It was collected and crystallised from concentrated hydrochloric acid. Yield 0·4 gm., m.p. 94°. This product was not analysed but was used immediately for the next step.

2-Keto-4-phenyl-2, 3, 4, 6-tetrahydro-1-thieno-(3, 4)-imidazole (VI)

The hydrochloride (200 mg.) was dissolved in water (3 ml.) and potassium cyanate (200 mg.) added. A clear solution was obtained, which was allowed to stand at room temperature for a day and then evaporated to dryness over a low boiling water-bath. The residue was repeatedly extracted with ethyl acetate, the solvent removed and the residue crystallised from acetone. Yield 50 mg., m.p. 130°.

\[
\begin{align*}
\text{Found:} & \quad C, 60.4 \quad H, 4.5 \quad N, 12.9 \\
\text{Calculated for } C_{11}H_{10}N_2SO & \quad C, 60.5 \quad H, 4.6 \quad N, 12.8
\end{align*}
\]

ACKNOWLEDGEMENT

I take this opportunity to thank Dr. K. N. Menon for suggesting this problem and for guidance and help during its execution. I thank the Government of India for a scholarship, Dr. Gurubakh Singh of the National Physical Laboratory for the Infra-Red Spectrum and Mr. S. Selvavinayakam for analysis.

SUMMARY

The synthesis of 2-Keto-4-phenyl-2, 3, 4, 6-tetrahydro-1-thieno-(3, 4)-imidazole is reported.

REFERENCE