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STEREOSPECIFIC SYNTHESIS OF SOME POLYCYCLIC CIS-β-LACTAMS

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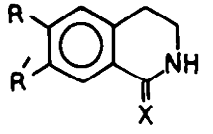
Abstract—Amides **1** on reaction with P_2S_5 in pyridine give thioamides **2** which on treatment with methyl iodide afford the corresponding 1-methylthio-3,4-dihydroisoquinolines **3**. Annelation of these imines with phenoxyacetyl chloride in the presence of triethylamine furnish 6-methylthio-7-phenoxy-2′,3′-dimethoxybenzo[*a*]octem **4a** and 6-methylthio-7-phenoxy-2′,3′-methylenedioxybenzo[*a*]octem **4b** respectively. Desulphurisation of these β-methylthio-β-lactams with Raney nickel yield the novel polycyclic cis-β-lactams **5a** and **5b**.

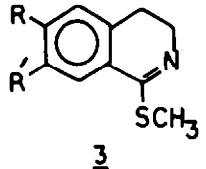
In recent publications[1,2] we have demonstrated the use of glycine for the preparation of some novel monocyclic cis-β-lactams. A low level of antibacterial activity associated with these β-lactams can be attributed to the fact that the β-lactam ring in such compounds is not as fragile as that of penicillins and cephalosporins. Therefore, the preparation of polycyclic β-lactams is essential. Bose and associates[3] demonstrated the use of dihydroisoquinolines for the preparation of a number of β-aryl substituted polycyclic β-lactams which was then successfully extended by us for the synthesis of novel equilenin-type β-lactams.[4] However, annelation of 3,4-dihydroisoquinoline and the like to get the more desired polycyclic cis-β-lactams is not possible.[4] This prompted us to device an alternate route to accomplish the synthesis of polycyclic β-lactams with a cis-stereochemistry. With a similar goal, Perchonock *et al*[5] reported the conversion of monocyclic cis-β-lactam into a polycyclic β-lactam involving an intramolecular Wittig reaction.

Our route for the preparation of such compounds utilises a highly stereospecific reaction involving desulphurisation[6] of the cardinal intermediate polycyclic β-methylthio-β-lactams **4** prepared through the sequence of reactions as depicted (Fig 1). Though this reaction has been used[7] in preparing some monocyclic cis-β-lactams, no successful attempt seems to have been reported in the case of more fragile polycyclic β-lactams. It is just possible that removal of the β-alkylthio group proceeds more smoothly when the β-lactam ring is fused to a carbocyclic system than to a heterocyclic ring.[8] Moreover, desulphurisation occurs more successfully in acetone than in ethanol.

The cyclic amides **1** were prepared through a known procedure[9] and were treated with phosphorus pentasulphide in pyridine[10] to convert them into the thioamides **2** in 50% yield. These thioamides were converted to the corresponding 6,7-dimethoxy-1-methylthio-3,4-dihydroisoquinoline **3a** and 6,7-methylenedioxy-1-methylthio-3,4-dihydroiso-quinoline **3b** after treatment with methyl iodide in



1 X=O
2 X=S



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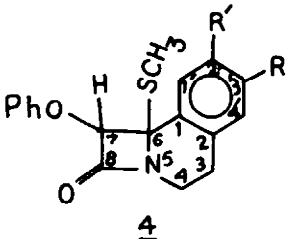

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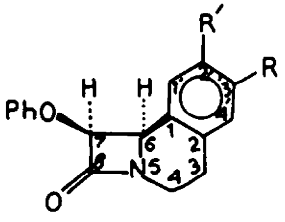

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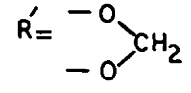
(a) R=R′=OCH$_3$

(b) R R′= 

refluxing dichloromethane followed by basification. PMR spectrum of **3a** showed a typical pattern of ring methylenes as triplet each (J = 7.0 Hz). The, two aromatic protons, as expected, appeared as singlets. Annelation of **3a** with phenoxyacetyl chloride in the presence of triethylamine in dichloromethane resulted into 6-methylthio-7-phenoxy-2′,3′-dimethoxybenzo[*a*]octem[11] **4a** in 65% yield. IR showed a strong absorption band at 1765 cm^{-1} (β-lactam carbonyl). PMR exhibited C_6-SCH_3 signal at δ 2.25 and C_7-H at δ 5.32 as singlets. Similarly 6-methylthio-7-phenoxy-2′,3′-methylenedioxybenzo[*a*]octem **4b** was prepared in 60% yield from the imine **3b**. The PMR spectrum of this compound was also similar to that of β-lactam **4a**. The C_6-SCH_3 signal appeared at δ 2.28 and C_7-H at δ 5.27 as singlets.

Desulphurisation with Raney Michel in acetone converted the β-methylthio-β-lactam **4a** into the polycyclic cis-β-lactam **5a** in 50% yield. The cis orientation of C_6-H and C_7-H in **5a** was confirmed from its PMR spectrum where these two protons appeared as doublets at δ 4.82 and 5.56 with the required cis-coupling (J = 4.5 Hz). Similar treatment on **4b** produced **5b** whose PMR spectrum exhibited signals for C_6-H and C_7-H at δ4.73 and 5.46 as doublets (J = 5.0 Hz, cis).

An interesting observation in the PMR spectra of the β-lactams **4** and **5** is the deshielding effect of $-SCH_3$ group on the chemical shifts of one of the $N-CH_2$-protons. In the methylthio-β-lactams **4** these two protons appear separately and downfield from the benzylic $-CH_2-$. After the removal of the $-SCH_3$ group, i.e. in β-lactams **5** one of the $N-CH_2-$ protons shifts higher field than even the benzylic methylene protons. The same sort of an effect was also seen on the chemical shift of one of the two $-OCH_3$ group protons in going from **4a** to **5a**.

EXPERIMENTAL

Mps are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer Model 337 spectrophotometer with sodium chloride optics. PMR spectra were obtained on Varian EM-390 90 MHz instrument in $CDCl_3$ solution containing tetramethylsilane as an internal standard with chemical shifts (δ) expressed in ppm downfield from TMS. Mass spectra were run on MM-70 70 spectrometer.

6,7-Dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline (**1a**)

A mixture of the urethane, prepared from homoveratryl amine and ethyl chloroformate (8.0 g), $POCl_3$ (60 ml) and a pinch of phosphoruspentaoxide in dry xylene (80 ml) was refluxed during 3 h. The volatile materials were distilled off under reduced pressure. The residue was treated with water and then with conc. HCl. The resulting solution was filtered and the filtrate was made alkaline with 20% NaOH solution. This was then extracted thoroughly with chloroform and the chloroform extract was washed with cold water and then with brine solution and dried (Na_2SO_4). Removal of the solvent afforded the desired product **1a** in 45% yield, m.p. 169–71°C (Lit.[7], m.p. 172°C); IR: 3200 (N–H) and 1650 (amide C=O).

6,7-Methylenedioxy-1-oxo-1,2,3,4-tetrahydroisoquinoline (**1b**)

This compound was prepared similarly by cyclising the urethane, prepared from homopiperonyl amine and ethylchloroformate, in 25% yield; IR 3180 (N–H) and 1660 (amide C=O).

6,7-Dimethoxy-1-thio-1,2,3,4-tetrahydroisoquinoline (**2a**)

A suspension of 6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline (**1a**; 4.0 g) and phosphoruspentasulphide (6.0 g) in pyridine (60 ml) was heated under reflux for ~2.5 h on an oil bath. It was cooled and the contents were poured into crushed ice. Acidification with acetic acid followed by thorough stirring (~30 min) resulted in the separation of a yellow solid which was recovered by filtration. Recrystallisation from a mixture of dichloromethane and n-hexane provided pure **2a** in 54% yield, m.p. 213–14°; IR: 3200 (N–H) and 1240 (C=S).

6,7-Methylenedioxy-1-thio-1,2,3,4-tetrahydroisoquinoline **2b**

The title compound was prepared in the same manner as above from cyclic amide **1b** in 50% yield, m.p. 201–203°C; IR 3330(N–H) and 1260(C=S).

6,7-Dimethoxy-1-methylthio-3,4-dihydroisoquinoline (**3a**)

A solution of 6,7-dimethoxy-1-thio-1,2,3,4-tetrahydroisoquinoline (**2a**; 4.46 g; 0.02 mole), methyl iodide (3.55 g; 0.025 mole) and dichloromethane (200 ml) was refluxed for 2 h on a water bath. Solvent was evaporated and the solid residue was extracted with water (5 × 25 ml). The aqueous medium was basified with dilute NaOH and the precipitated solid was filtered, washed with water and dried under reduced pressure to afford the title compound in 60% yield, m.p. 79–81°C; R_f 0.39 (ether: pet. ether: ethylacetate; 5:5:2); IR 1560 (C=N); PMR 2.46 (s, 3 H; $-SCH_3$); 2.67 (t, 2 H; J = 7.0 Hz; benzylic $-CH_2-$), 3.73 (t, 2 H; J = 7.0 Hz; $-N-CH_2-$), 3.96 (s, 6 H; 2-OCH_3), 6.7 (s, 1 H; aromatic) and 7.23 (s, 1 H; aromatic). (Found: C, 60.59; H, 6.26; N, 5.85. $C_{12}H_{15}NO_2S$ requires C, 60.75; H, 6.37; N, 5.90%).

6,7-Methylenedioxy-1-methylthio-3,4-dihydroisoquinoline **3b**

This compound was prepared in the same manner as above from **2b** in 55% yield, m.p. 120–22°C; R_f = 0.73 (ether: petroleum ether: ethylacetate = 5:5:2); IR: 1550 (C=N). (Found: C, 59.56; H, 4.95; N, 6.17, $C_{11}H_{11}NO_2S$ requires C, 59.72; H, 5.01; N, 6.33%).

6-Methylthio-7-phenoxy-2′,3′-dimethoxybenzo[a]octem (**4a**)

A solution of 6,7-dimethoxy-1-methylthio-3,4-dihydroisoquinoline (**3a**, 2.37 g; 0.01 mole), triethylamine (1.01 g; 0.01 mole) and dichloromethane (150 ml) was stirred at room temperature while a solution of phenoxyacetyl chloride (1.71 g; 0.01 mole) in dichloromethane (50 ml) was added dropwise over a period of 1 h. The reaction mixture was stirred overnight, washed with 20% aq HCl, aq sodium carbonate, water and dried (Na_2SO_4). Removal of the solvent afforded the title compound in 65% yield, m.p. 115–117°C (ethanol); R_f 0.28 (ether: pet. ether: ethylacetate; 5:5:2); IR: 1765 (β-lactam C=O); PMR: 2.25 (s, 3 H; $-SCH_3$), 2.85 (m, 2 H; benzylic $-CH_2-$), 3.3 and 3.95 (m each, 1 H each; $-N-CH_2-$), 3.83 (s, 3 H; $-OCH_3$), 3.9 (s, 3 H; $-OCH_3$), 5.32 (s, 1 H; C_7–H), 6.6 (s, 1 H; aromatic), 6.76 (s, 1 H; aromatic) and 6.9–7.4 (m, 5 H; $-OC_6H_5$); M^+ at *m/e* = 371. (Found: C, 64.60; H, 5.67; N, 3.69. $C_{20}H_{21}NO_4S$ requires C, 64.68; H, 5.70; N, 3.77%).

6-Methylthio-7-phenoxy-2′,3′-methylenedioxybenzo[a]octem (**4b**)

The β-lactam **4b** was prepared by annelating the imine **3b** with phenoxyacetyl chloride in 60% yield, m.p. 99–100°C (ethanol); R_f 0.65 (ether; pet. ether: ethylacetate; 5:5:2); IR: 1770 (β-lactam C=O); PMR; 2.28 (s, 3 H; SCH_3), 2.9 (m, 2 H; benzylic $-CH_2-$) 3.3 and 3.9 (m each, 1 H each; $-N-CH_2-$), 5.27 (s, 1 H; C_7–H), 5.95 (s, 2 H; $-O-CH_2-O-$), 6.6 (s, 1 H; aromatic), 6.8 (s, 1 H; aromatic) and 6.97–7.5 (m, 5 H; $-OC_6H_5$); M^+ at *m/e* = 355. (Found: C, 64.19; H, 4.80; N, 3.81. $C_{19}H_{17}NO_4S$ requires C, 64.22; H, 4.82; N, 3.94%).

7-β-Phenoxy-2′,3′-dimethoxybenzo[a]octem (**5a**)

A solution of 6-methylthio-7-phenoxy-2′,3′-dimethoxybenzo[a]octem (**4a**, 740 mg; 0.002 mole) in

acetone (50 ml) was stirred and heated under reflux during 1.5 h with three half teaspoons full of Raney-nickel catalyst. After heating, the catalyst was filtered and washed with acetone. The acetone was evaporated from the filtrate under vacuum and the residual solid was recrystallised from a mixture of dichloromethane and n-hexane to obtain pure **5a** in 50% yield, m.p. 186–88°C; IR: 1755 (β-lactam C=O); PMR: (2.65 and 4.15 (m each, 1 H each; $-N-CH_2-$), 3.05 (m, 2 H; benzylic $-CH_2-$), 3.43 (s, 3 H; $-OCH_3$), 3.85 (s, 3 H; $-OCH_3$), 4.82 (d, 1 H; J = 4.5 Hz), 5.56 (d, 1 H; J = 4.5 Hz), 6.36 (s, 1 H; aromatic), 6.6 (s, 1 H; aromatic) and 6.9–7.4 (m, 5 H; $-OC_6H_5$); M^+ at *m/e* = 325. (Found: C, 70.05; H, 5.85; N, 4.24. $C_{19}H_{19}NO_4$ requires C, 70.14; H, 5.89; N, 4.31%).

7-β-Phenoxy-2′,3′-methylenedioxybenzo[a]octem (**5b**)

The title compound was made by desulphurisation of 6-methylthio-7-phenoxy-2′,3′-methylenedioxybenzo[a]octem (**4b**) with Raney-Ni in 45% yield, m.p. 128–30°C (ethanol); IR 1775 (β-lactam C=O); PMR 2.55 and 4.05 (m each, 1 H each; $-N-CH_2-$), 3.05 (m, 2 H; benzylic $-CH_2-$), 4.73 (d, 1 H; J = 5.0 Hz), 5.46 (d, 1 H; J = 5.0 Hz), 5.9 (s, 2 H; $-O-CH_2-O-$), 6.5 (s, 1 H; aromatic), 6.6 (s, 1 H; aromatic) and 6.9–7.3 (m, 5 H; $-OC_6H_5$); M^+ at *m/e* = 309. (Found: C, 69.71; H, 4.82; N, 4.38. $C_{18}H_{15}NO_4$ requires C, 69.89; H, 4.89; N, 4.53%).

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