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AMIDOALKYLATION OF MERCAPTANS WITH GLYOXYLIC ACID DERIVATIVES

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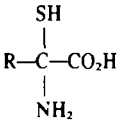
Abstract—The synthesis of α-alkyl mercaptohippuric acid (**3a–d**), N-benzyloxycarbonyl-α-methylthioglycine (**3e**) and their methyl esters (**5a–d**) by the amido-alkylation of mercaptans with α-hydroxyhippuric acid (**2a**), α-hydroxy-N-benzyloxycarbonylglycine (**2b**) and their methoxymethyl ester derivatives **4a** and **4b** is described. Oxidation with *m*-chloroperbenzoic acid afforded the corresponding sulfoxides and sulfones and treatment with N-bromosuccinimide in methanol or chlorine in carbon tetrachloride solution exchanged the sulfur containing side chain for a methoxy or a chloro group respectively. (**4a**, **8**).

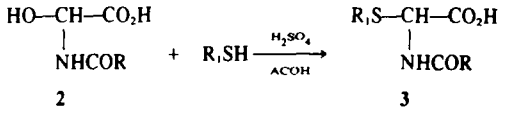
The occurrence of epidithiadioxopiperazine ring system in the antibiotics gliotoxin, sporidesmin and others has initiated a number of approaches to the synthesis of this novel ring system.[1] One approach is the direct introduction of the sulfur function into the dioxpiperazine ring. Since dioxopiperazines are cyclic dimers of amino acids, the epidithiadioxopiperazine can be considered as an oxidized dimer of α-mercaptoaminoacids (**1**) and thus synthesised by first preparing a proper derivative of the sulfur containing amino-acid followed by cyclization to the dioxopiperazinone.[2,3]



1

Only a few derivatives of α-mercapto-α-amino-acids have been described in the literature. These were prepared by the addition of a thiol to oxazolinones[4,5] or from benzylmercaptomalonate by a Curtius rearrangement.[2] In this paper we would like to describe a simple synthesis of N-benzoyl- and N-benzyloxycarbonyl derivatives of α-alkylthioglycines (**3**), and the chemical properties of some of these derivatives.

We have used two procedures, which appear to be quite general, for the amidoalkylation of mercaptans with the glyoxylic acid adducts **2** and **4**. Addition of methyl, isopropyl, butyl and benzylmercaptan to a suspension of α-hydroxyhippuric acid (**2a**) or α - hydroxy - N - benzyloxycarbonylglycine (**2b**) in glacial acetic acid containing concentrated sulfuric acid as catalyst, afforded the expected products in 72–88% yield respectively:



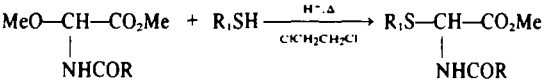
2

3

2a: R = Ph
2b: R = $C_6H_5CH_2O$

3a: R_1 = Me, R = Ph
3b: R_1 = Me_2CH, R = Ph
3c: R_1 = $Me(CH_2)_3$, R = Ph
3d: R_1 = $C_6H_5CH_2$, R = Ph
3e: R_1 = Me, R = $C_6H_5CH_2O$

Refluxing a 1,2-dichloroethane solution of, the non-volatile mercaptans, isopropyl, butyl and benzylmercaptan with the methoxy ester derivatives **4a** and **4b** in the presence of catalytic amount of β-naphthalenesulfonic acid, the methyl esters of the N - acyl - α - alkylmercaptoglycines in 68–92% yield.



4

5

4a: R = Ph
4b: R = $C_6H_5CH_2O$

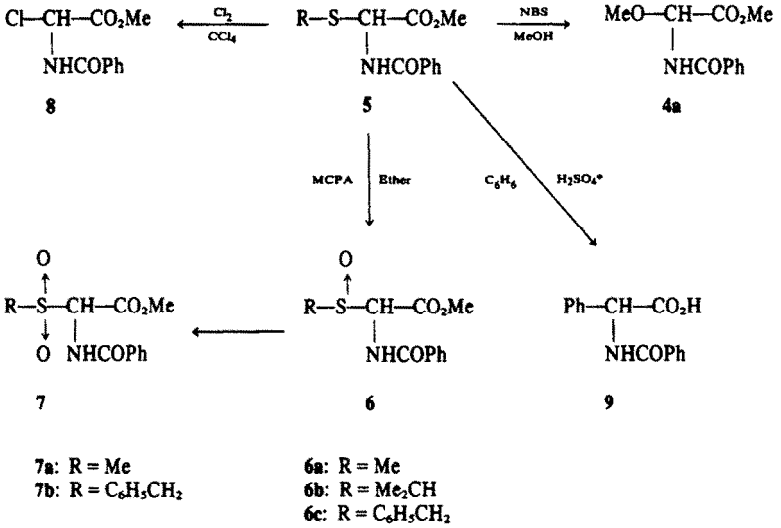
5a: R_1 = Me_2CH, R = Ph
5b: R_1 = $Me(CH_2)_3$, R = Ph
5c: R_1 = $C_6H_5CH_2$, R = Ph
5d: R_1 = $C_6H_5CH_2$, R = $C_6H_5CH_2O$

While the amidoalkylations at C and N atoms are well established, little is known on the amidoalkylation at sulfur.[6,7]

The α-hydroxyhippuric acid (**2a**) and the 2 - hydroxy - N - benzyloxycarbonylglycine (**2b**), used in the reactions, were prepared from glyoxylic acid and benzamide or benzyl carbamate in 72 and 73% yield respectively. Treatment of the hydroxyacids with methanolic sulfuric acid, afforded the methoxy methyl esters **4a** and **4b** in 80 and 92% yield respectively. The acids **3** thus prepared, are crystalline substances, easily purified and characterized. The methyl esters **5** however, are either oils or low melting solids. The hydrolysis of the esters to the corresponding acids or the esterification of the acids to the methyl esters could be conducted smoothly and in high yields.

Oxidation of sulfides of type **5**, using one equivalent of *m*-chloroperbenzoic acid (MCPA) afforded the pure sulfoxide **6** directly by filtration of the mixture. Using three equivalents of the oxidation agent and longer reaction time, afforded the corresponding sulfone **7**. The yields in all were fair to good. Preliminary work showed that the sulfones of type **7** are quite resistant, in the absence of a base, to nucleophilic displacement. Thus, **7b** was recovered unchanged when treated with benzyl mercaptan in refluxing benzene for 18 hr.

Treatment of **5e** (R=Me) with N-bromosuccinimide afforded the methoxy derivative **4a** in high yield. Similarly, treatment of **5c** with chlorine afforded the chloro compound **8**. The latter observation recalls the easy exchange of the sulfur containing side chain by halogen in penicillin chemistry.[8] Reacting α-methylthiohippuric acid (**3a**) with benzene in conc sulphuric acid afforded N - benzoyl - 2 - phenylglycine identical with an authentic sample prepared from phenylglycine and benzoyl chloride. The methylthio group is a good enough leaving group in conc sulfuric acid and thus suggests the use of the α-alkylthio derivatives (**3**) as amidoalkylating agents of aromatic compounds, analogously to similar reactions of α-alkoxy derivatives of acylglycines and related compounds.[9]



7a: R = Me
7b: R = $C_6H_5CH_2$

6a: R = Me
6b: R = Me_2CH
6c: R = $C_6H_5CH_2$

EXPERIMENTAL

General. M.ps are uncorrected. The IR spectra were recorded on Perkin-Elmer 237 spectrophotometer; NMR spectra were obtained on a Varian T-60 spectrometer. Chemical shifts are reported in ppm downfield from TMS. Mass spectra were recorded on Atlas CH4 MAT mass spectrometer.

α-Hydroxyhippuric acid **2a**. Benzamide (24·28 g, 0·2 mol) and glyoxylic acid monohydrate (20·2 g, 0·219 mol) were refluxed for 5 hr in 150 ml acetone. The solution was allowed to cool and crystallization of the product started immediately. Filtration afforded after drying 28·05 g (71·8%) of the colorless product, m.p. 157–159° (resolidified) and 200·5–201·5° (dec) [lit.[5] m.p. 200–202 (from dioxane–$CHCl_3$)]. IR (KBr): 3355, 3320, 1745, 1603, 1567, 1533, 1197, 1110, 1052, 922, 740, 687 cm^{-1}; NMR (DMSO-d_6): δ 9·22 (d, 1H, NH), 8·11–7·80 (m, 2H, arom), 7·73–7·30 (m, 3H, arom), 5·65 (t, 1H, CH).

α - Hydroxy - N - benzyloxycarbonylglycine **2b**. A mixture of benzyl carbamate (30·23 g, 0·2 mol) and glyoxylic acid monohydrate (20·2 g, 0·22 mol) in 200 ml dry ether was stirred overnight. The crystalline product was washed with ether to give 31·0 g (73%) adduct; m.p. 196–198° (dec). IR (KBr): 3327, 1731, 1696, 1532, 1452, 1265, 1246, 1084, 1003, 890, 694 cm^{-1}; NMR (DMSO-d_6): δ 7·4 (s, 5H, arom) 5·28 (t, 1H, CH), 5·12 (s, 2H, OCH_2). (Found: C, 53·42; H, 5·16; N, 6·20. $C_{10}H_{11}NO_5$ requires: C, 53·33; H, 4·92; N, 6·22%).

Methyl α-methoxyhippurate (**4a**). To an ice bath cooled and stirred soln of α-hydroxyhippuric acid (12·7 g, 0·065 mol) in abs MeOH (150 ml), was added conc H_2SO_4 (96%, 2·0 ml). The mixture was stirred for 2 days at room temp and then poured into ice-saturated $NaHCO_3$ aq, and the organic material was extracted 3 times with EtOAc. Drying ($MgSO_4$), filtering and evaporation of the solvent, left an oil which crystallized under light petroleum (40–60°). The product was purified by filtration through deactivated neutral alumina (75 g + 8 ml MeOH) and elution with benzene; m.p. 86–87°C; yield: 11·6 gr (80%). IR($CHCl_3$): 3435, 2955, 2837, 1748, 1675, 1603, 1582, 1483, 1438, 1349, 1083 cm^{-1}; NMR ($CDCl_3$): 8·06–7·72 (m, 2H, arom), 7·68–7·27 (m, 3H, arom, +1H, NH), 5·81 (d, 1H, CH), 3·83 (s, 3H, OCH_3), 3·54 (s, 3H, OCH_3).

Methyl α - methoxy - N - benzyloxycarbonylglycinate (**4b**). Using the procedure described above, **2b** (11·27 g, 0·05 mol) afforded 11·60 g (91·5%) of the colorless solid **4b**, m.p. 76–78°. IR (KBr): 3310, 3025, 2948, 2849, 1755, 1689, 1432, 1360, 1261, 1223, 1101, 981, 813, 738 cm^{-1}; NMR ($CDCl_3$): δ 7·37 (s, 5H, arom), 5·98 (broad s, 1H, NH), 5·35 (d, 1H, CH), 5·17 (s, 2H, CH_2Ph), 3·81 (s, 3H, CO_2CH_3), 3·47 (s, 3H, OCH_3). (Found: C, 56·76; H, 5·88; N, 5·63. $C_{12}H_{15}NO_5$ requires: C, 56·91; H, 5·97; N, 5·53%).

*Both the methyl ester (**5e**) and the pure acid (**3a**) were used in the reaction is produce **9**. As the ester hydrolyses to the acid under the reaction conditions, **9** is described in the Experimental as coming direct from the acid.

Amidoalkylation of mercaptans

Procedure (A). To a stirred suspension of **2a** or **2b** (0·05 mol) and the mercaptan to be amidoalkylated (0·2 mol; 4 equivs) in glacial AcOH (50 ml) at ice bath temp, was added conc H_2SO_4 (Merck 96%, 5 ml), followed by stirring at room temp for 2 days. The mixture was poured into ice and the organic material extracted with EtOAc. The EtOAc soln was washed with water (to remove the excess AcOH) followed by extraction with 5% $NaHCO_3$ aq. The separated aqueous layer was washed with ethyl ether and then acidified with conc HCl. Extraction of the acidified soln with EtOAc, drying ($MgSO_4$), filtering and removal of the solvent under reduced pressure gave the crude, i.e. **3a–e**. Trituration with light petroleum (b.p. 40–60°) followed by filtration gave colourless solids which were pure enough for further synthetic procedures. Analytical samples were obtained by recrystallization from ether–light petroleum.

Procedures (B). (used only with the high boiling mercaptans). A soln of **4a** or **4b** (0·05 mol), the mercaptan (0·055 mol benzyl mercaptan and 0·15 mol with the more volatile alkyl mercaptans), and 2-naphthalenesulfonic acid as a catalyst (0·20 g), was refluxed (24 hr for benzyl mercaptan and 2 days for the alkyl mercaptans) in dry 1,2-dichloroethane (200 ml). The organic soln was washed with water, dried ($MgSO_4$) and the solvent evaporated under reduced pressure.

α-Methylthiohyppuric acid (**3a**). This compound was prepared from **2a** and methyl mercaptan in 84% yield by procedure A; IR(KBr): 3350, 3160–2370, 1700, 1637, 1575, 1511 cm^{-1}; NMR (DMSO-d_6): δ 9·08 (d, 1H, NH), 8·16–7·25 (m, 5H, arom.), 5·60 (d, 1H, J = 8·5 c/s, CH), 2·21 (s, 3H, SCH_3). MS: *m/e* 225 (M^+), 207, 179, 120, 103, 77. (Found: C, 53·45; H, 4·93; N, 6·16; S, 13·98. $C_{10}H_{11}NO_3S$ requires: C, 53·32; H, 4·92; N, 6·22; S, 14·23%).

α-Isopropylthiohyppuric acid (**3b**). This compound was prepared from **2a** and isopropylmercaptan in 87·5% yield by procedure A. It melted at 143–144°. IR (KBr): 3255, 2947, 1700, 1637, 1510 cm^{-1}; NMR ($CDCl_3$): δ 9·31 (broad s, 1H, CO_2H), 8·02–7·34 (m, 5H); 7·11 (d, 1H), 5·85 (d, 1H J = 8·5 c/s), 3·37 (m, 1H), 1·41 (d, 3H, J = 7 c/s), 1·37 (d, 3H; J = 7 c/s). MS: *m/e* 253 (M^+), 235, 211, 209, 178, 148, 133, 105, 103, 77. (Found: C, 57·15; H, 5·97; N, 5·46; S, 12·65. $C_{12}H_{15}NO_3S$ requires: C, 56·90; H, 5·96; N, 5·53; S, 12·66%).

α-Benzythiohyppuric acid (**3d**). This compound was prepared from **2a** and benzylmercaptan in 73% yield by method A; m.p. 172–173° (lit.[5] m.p. 170–171°). IR (KBr): 3360, 3200–2250, 1716, 1628, 1521, 1491 cm^{-1}; NMR (DMSO-d_6): δ 9·3 (d, 1H), 8·17–7·20 (*m*, 10H), 5·67 (d, 1H; J = 8·5 c/s), 4·02 (s, 2H).

α - Methylthio - N - benzyloxycarbonylglycine (**3e**). This compound was prepared from **2b** and methylmercaptan in 72% yield by procedure A; m.p. 112–114°. IR(KBr): 3340, 3080–2400, 1710, 1655, 1512, 1401 cm^{-1}; NMR ($CDCl_3$): δ 9·25 (s, 1H), 7·35 (s, 5H), 5·70 (very br. s, 1H), 5·33 (d, 1H, J = 8·5 c/s), 5·17 (s, 2H), 2·17 (s, 3H). (Found: C, 51·84; H, 5·14; N, 6·06; S, 12·48. $C_{11}H_{13}NO_4S$ requires: C, 51·75; H, 5·13; N, 5·49; S, 12·56%).

Methyl α-isopropylthiohyppurate (**5a**). This oily compound was prepared from **4a** and isopropylmercaptan in 92% yield by procedure B. IR ($CHCl_3$): 3420, 1737, 1665, 1602, 1582, 1474 cm^{-1}; NMR ($CDCl_3$): δ 7·99–7·32 (m, 5H), 7·24 (d, 1H) 5·88 (d, 1H; J = 8·5 c/s), 3·83 (s, 3H), 3·59–2·96 (m, 1H), 1·40 (d, 3H; J = 7 c/s), 1·33 (d, 3H; J = 7 c/s). MS: *m/e* 235 (M–MeOH), 224, 208, 193, 162, 147, 136, 133, 121, 117, 105, 89, 77, 59. The ester was hydrolysed with sodium hydroxide to give an acid identical with **3b**.

Methyl α-butylthiohyppurate (**5b**). This oily compound was prepared from **4a** and n-butylmercaptan in 89% yield by procedure B. IR ($CHCl_3$): 3415, 1741, 1662, 1602, 1582 cm^{-1}; NMR ($CDCl_3$): δ 8·02–7·06 (m, 5H, arom. +1H, NH), 5·86 (d, 1H; J = 8·5 c/s), 3·82 (s, 3H), 2·76 (t, 2H); 1·92–1·13 (m, 4H) 0·89 (t, 3H); MS: *m/e* 381 (M^+), 249, 222, 192, 176, 161, 135, 133, 121, 105, 77, 59, 43. The ester was hydrolysed to the corresponding acid (see below).

Methyl α-benzylthiohyppurate (**5c**). This compound was prepared from **4a** and benzylmercaptan in 68% yield by procedure B; it melted at 67–69° after crystallization from EtOH. IR(KBr): 3336, 3023, 1731, 1698, 1601, 1580, 1516, 1489; NMR ($CDCl_3$): δ 7·79–7·12 (m, 10H) 6·85 (br. s, 1H), 5·78 (d, 1H; J = 8·5 c/s), 3·97 (s, 2H), 3·77 (s, 3H); MS: *m/e* 256 ($M-CO_2Me$), 224, 193, 164, 161, 121, 105, 92, 77. Found: C, 64·62; H, 5·36; N, 4·59; S, 10·05. $C_{17}H_{17}NO_3S$: requires: C, 64·74; H, 5·43; N, 4·44; S, 10·17%).

Methyl α - benzylthio - N - benzyloxycarbonylglycine (**5d**). This compound was prepared from **4b** and benzylmercaptan in 88% yield by procedure B; m.p. 48–50° (lit.[3] oil). IR (KBr): 3325, 3020 1733, 1688, 1503 cm^{-1}; NMR ($CDCl_3$): δ 7·37 (s, 5H), 8·33, (s, 5H), 5·71 (d, 1H), 5·35 (d, 1H; J = 9 c/s), 5·13 (s, 2H), 3·91 (s, 2H), 3·71 (s, 3H); MS: *m/e* 286 ($M-CO_2Me$), 246, 223, 214, 198, 194, 181, 162, 150, 129, 123, 115, 107, 105, 91, 77. (Found: C, 62·76; H, 5·45; N, 4·18; S, 9·50. $C_{18}H_{19}NO_4S$ requires: C, 62·59; H, 5·56; N, 4·06; S, 9·28%).

Esterification of α-alkylthio (or benzylthio)-hippuric acids and N-benzyloxycarbonylglycine. To the stirred soln of the acid **3**, (0·01 mol) in abs MeOH (25 ml), was added conc H_2SO_4 (96%, 0·3 ml). The mixture was stirred at room temp for 3 hr and was then poured into ice-saturated $NaHCO_3$ aq. Extraction with EtOAc, drying ($MgSO_4$), filtration and removal of the solvent under reduced pressure, afforded the desired esters in 80–90%, yield.

Methyl α-methylthiohyppurate (**5e**). This compound was prepared in 81% yield by the esterification procedure described above; m.p. 75–76° (EtOAc–light petroleum). IR (KBr): 3320, 2955, 1734, 1636, 1510 cm^{-1}; NMR ($CDCl_3$): δ 8·02–7·36 (m, 5H) 7·16 (d, 1H broad), 5·79 (d, 1H, J = 8·5 cps), 3·88 (S, 3H), 2·26 (S, 3H). (Found: C, 55·43 H. 5·37 N, 6·03 S, 13·64 $C_{11}H_{13}NO_3S$: requires: C, 55·21 H, 5·48 N, 5·85 S, 13·40%).

Hydrolysis of esters

α-Buthylthiohyppuric acid. Compound **5b** (0·845 g, 3 mmol) was refluxed overnight in MeOH aq (15 ml, 1:9) containing KOH (0·20 g, 1·2 eq). Water was then added, and the aqueous soln was washed with ether, followed by acidification with conc HCl. The acidified soln was extracted with EtOAc. Drying ($MgSO_4$), filtration and evaporation, afforded the colorless **3c** (0·741 g, 92·4%) which was further purified by trituration with light petroleum (40–60°) and filtration. An analytical sample was obtained by recrystallization from ether–light petroleum; m.p. 111–112·5°. IR ($CHCl_3$): 3410, 1722, 1665, 1603, 1580, 1476, 1314; NMR ($CDCl_3$): δ 9·49 (s, 1H), 8·09–6·92 (m, 5H, arom. +1H, NH), 5·81 (d., 1H; J = 8·5 c/s), 3·13–2·50 (t, 2H), 1·90–1·12 (m, 4H), 1·07–0·69 (m, 3H); MS: *m/e* 267 (M^+), 266 (M–H), 249 ($M-H_2O$), 222, 210, 179, 162, 135, 121, 117, 106, 105, 90, 77, 57. (Found: C, 58·46; H, 6·10; N, 5·32; S, 11·80. $C_{14}H_{17}NO_3S$ requires: C, 58·42; H, 6·41; N, 5·28; S, 11·99%).

Oxidation of α-alkylthio- and benzylthiohyppurates to the corresponding sulfoxides and sulfones

Sulfoxides **6**. In an ice bath, to a cooled and stirred soln of methyl α-alkylthio- or benzythio-hippurate (5–10 mmol) in anhydrous ethyl ether (35–70 ml), was added dropwise MPCA (Fluka >85%, 1·043–2·09 g, approx. 1 equiv +10% excess) in ethyl ether (25–50 ml) over a period of 20 min. After stirring for 30 min with cooling, the mixture was allowed to stir an additional 5 hr at room temp. Filtration afforded the essentially pure sulfoxides in good to high yields.

Methyl α-methyl sulfoxyhyppurate (**6a**). This compound was prepared in 91% yield by the general procedure described above; m.p. 108–110° (methylene chloride–hexane). IR (KBr): 3245, 1746, 1640, 1511, 1320, 1210, 1028 cm^{-1}; NMR ($CDCl_3$): δ 8·14–7·29 (5H, arom. +1H NH), 5·82 (d, 1H; J = 9 c/s), 3·93 (s, 3H), 2·61 (s, 3H);

MS: *m/e* 239 (M–O), 237, 192, 180, 150, 134, 126, 121, 105, 94, 93, 77, 63, 59. (Found: C, 51·67; H, 5·22; N, 5·40; S, 12·28. $C_{11}H_{13}NO_4S$ requires: C, 51·75; H, 5·13; N, 5·49; S, 12·56%).

Methyl α-isopropylsulfoxyhyppurate (**6b**). This compound was prepared in 64% yield by the above general procedure; m.p. 98–100° (EtOH aq). IR (KBr) 3230, 1727, 1663, 1603, 1535, 1312, 1288, 1037 cm^{-1}; NMR ($CDCl_3$): δ 8·10–7·23 (5H arom. +1H NH). 5·94 (d, 1H; J = 10 c/s), 3·92 (s, 3H), 2·98 (d, 1H; J = 7 c/s), 1·32 (d, 6H; J = 7 c/s); MS: *m/e* 267 (m-O), 224, 208, 192, 161, 150, 121, 105, 92, 77, 59. (Found: C, 54·98; H, 6·05; N, 5·13. $C_{13}H_{17}NO_4S$ requires: C, 55·11; H, 6·05; N, 4·94; S, 11·32%).

Methyl α-benzylsulfoxyhyppurate (**6c**). This compound was prepared in 64% yield by the general procedure described above; m.p. 142–143° (EtOH). IR (KBr): 3330, 1735, 1648, 1600, 1528, 1488, 1280, 1240, 1043 cm^{-1}; NMR ($CDCl_3$): δ 8·18–7·18 (m, 5H, arom. +1H, NH), 7·43 (s, 5H) 5·91 (d, 1H; J = 10 c/s), 4·11 (s, 1H), 4·08 (s, 1H), 3·83 (s, 3H); MS: *m/e* 314 (M–OH), 282, 213, 192, 180, 161, 140, 121, 105, 91, 77. (Found: C, 61·44; H, 5·16; N, 4·09; S, 9·48. $C_{17}H_{17}NO_4S$ requires: C, 61·62; H, 5·17; N, 4·23; S, 9·67%).

Methyl α-methylsulfonylhyppurate (**7a**). This compound was prepared in 87% yield by the procedure described above for the synthesis of the sulfoxides except that 3 equivs of MCPA were used and the time was extended to 2 days. The sulfone was filtered and crystallized from 95% EtOH; m.p. 158–160°. IR (KBr): 3340, 1740, 1649, 1600, 1507, 1337, 1307, 1168, 1124 cm^{-1}; NMR ($CDCl_3$): 8·15–7·27 (m, 5H, arom. +1H, NH), 6·17 (d, 1H; J = 9·5 c/s), 3·97 (s, 3H), 3·12 (s, 3H); MS: *m/e* 194 (M–Ph), 193, 159, 157, 142, 140, 114, 112, 107, 106, 79, 78, 77, 64. (Found C, 48·85; H, 4·87; N, 5·04; S, 11·89. $C_{11}H_{13}NO_5S$ requires: C, 48·70; H, 4·83; N, 5·16; S, 11·78%).

Methyl α-benzylsulfonylhyppurate (**7b**). This compound was prepared in 88% yield by the procedure described above for the synthesis of the sulfoxides, except that 3 equivs of MCPA were used and the mixture stirred at room temp for 2 days; m.p. 167–168°. IR (KBr): 3323, 3038, 1760, 1664, 1601, 1581, 1516, 1490, 1329, 1315, 1191, 1123 cm^{-1}; NMR ($CDCl_3$): δ 8·04–7·17 (m, 1OH, arom. +1H NH), 6·14 (d, 1H; J = 9 c/s), 4·51 (s, 2H). 3·89 (s, 3H); MS: *m/e* 329 ($M-H_2O$), 316, 283, 224, 192, 162, 134, 121, 105, 91, 77, 59. (Found: C, 58·57; H, 4·89; N, 3·79; S, 9·21. $C_{17}H_{17}NO_5S$ requires: C, 58·78; H, 4·93; N, 4·03; S, 9·23%).

Cleavage of the C–S *bond in alkylthio- (or benzylthio-hippurates through sulfur oxidation*

(a) *With NBS.* To a stirred solution of methyl α-benzylthiohippurate (315·4 mg, 0·001 mol) in abs. MeOH (7·5 ml) at acetone–dry ice temp, was added in one portion N-bromosuccinimide (267 mg, 0·0015 mol). The mixture was stirred for 3 hr, letting the temp gradually reach room temp. The MeOH was evaporated and water was added. Extraction with EtOAc, drying, filtration and removal of the solvent afforded crude **4a** in quantitative yield. The spectral data of **4a** thus obtained, was identical with that of an authentic sample.

(b) *With Chlorine: Methyl α-chlorohippurate* **8**. To a stirred soln of **5e** 1·196 g, 0·005 mol) in CCl_4 (40 ml) at ice-bath temp, was added Cl_2 (0·71 g, 0·01 mol) in CCl_4 (10 ml). The mixture was stirred at room temp. for 2 days. Evaporation of the solvent under reduced pressure followed by trituration of the crude product with light petroleum (40–60°) afforded the somewhat labile **8** as a white solid (1·049 g, 92·2%), m.p. 62–67° (somewhat dependent on the rate of heating since most probably HCl is being evolved). IR ($CHCl_3$): 3410, 1750, 1676, 1603, 1581, 1477, 1343 cm^{-1}; NMR ($CDCl_3$): δ 8·06–7·75 (m, 2H, arom.), 7·73–7·32 (m, 3H, arom, +1H, NH), 6·57 (d, 1H; J = 10 c/s, CH), 3·94 (s, 3H, CH_3) MS: *m/e* 192 (M–Cl), 170, 164, 150, (M–Ph), 135, 121, 105, 88, 77, 59. The compound **8** is quite sensitive to moisture by which it is hydrolysed to the corresponding hydroxy-compound.

Amidoalkylation of benzene with α-methylthiohippuric acid to N-benzoyl - 2 - phenylglycine **9**

A stirred soln of **3a** (1 g, 0·0044 mol) in conc. H_2SO_4 (Merck 96%, 5 ml) at ice-bath temp, was treated with benzene (2 ml). The mixture was allowed to stir at room temp for 3 days, and then poured into ice-saturated $NaHCO_3$ aq. Extraction with EtOAC, drying ($MqSO_4$) and filtration followed by evaporation of the solvent gave the expected crude **9** in almost quantitative yield. The IR, NMR and MS spectra of **9** showed it to be identical with authentic sample (m.p. 165°) prepared by an alternative route. The crude acid **9** was esterified by the procedure previously described to yield the expected methylester **9a**; m.p. 105–107°. The methyl ester was also identical with the ester of the authentic sample **9**.

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