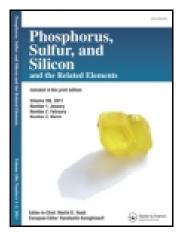
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A Comparative Study on Some Diaryl Azines Amino Acid Derivatives

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A Comparative Study on Some Diaryl Azines Amino Acid Derivatives

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Benzaldehydeazines, p-anisaldehydeazines, and thiophene-2-carboxaldehyde azines react with excess chlorosulfonic acid to give corresponding disulfonyl chlorides 1,13, and 24. These were condensed with nucleophiles to give disulfonyl amino acid derivatives, 2–4, 14–16, and 25–27. Some of the corresponding methyl esters were prepared: 5–6, 17–18, and 28–29. Hydrazinolysis of these methyl esters yielded hydrazides 7–8, 19–20, and 30–31. Coupling reactions of some amino acid derivatives, in THF-Et₃N medium using the dicyclohexylcarbodiimide method DCC, furnished dipeptide methyl esters 9–12, 21–23, and 32–34. Attemped chlorosulfonation of furan-2-carboxaldehyde azine were unsuccessful. Some spectra data are briefly discussed.

Keywords Benzaldehyde azines; chlorosulfonation of diarylazines; p-anisaldehyde azines; thiophene-2-carboxyaldehyde azines; and their reactions with essential amino acids

INTRODUCTION

The work reported here is a continuation of our general program on the chemistry and reactivity of aryl sulfonyl derivatives as candidate pesticides, which are found to possess hypoglycemic, antipyretic, analgesic diuretic, bacteriostatic, and other pharmacological activities. The compounds mentioned were found to have these activities.¹⁻¹²

Diarylazines are known¹³ to be readly formed by condensation of the appropriate aryl aldehyde and hydrazine hydrate. However, the chlorosulfonation of these compounds has been previously reported. In view of the known ability of diaryl azines to undergo 1,3-dipolar cycloaddition reactions with maleic acid derivatives.

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Sulfonyl chlorides 1,13, and 24 by condensation with nucleophiles, e.g., amino acids residue, can be converted into sulfonylamino acid derivatives for biological evaluation as candidate biocides.

DISCUSSION

In diaryl azines, the C=N group is a deactivating substituent with regard to electrophilic substitution. In agreement, (Comp. 1, R = X =H) were prepared by reaction of chlorosulfonic acid with benzaldehyde azine in a 68% yield.

The N–N bond does not undergo fission under the reaction conditions adopted, and the imino group was deactivated to electrophilic attack. The ¹H NMR spectrum contained an unsymmetrical aromatic region.

Other azines were treated with chlorosulfonic acid, p-anisaldehyde azines, and (Comp. **13**, R = P-OMe, X = H) accured under milder conditions than for benzaldehyde azine (Comp. **1**, R = X = H). In thiophene carboxaldehyde azines, (Comp. **24**, Y = S, X = H) the more electron rich azines react with chlorosulfonic acid, the greater reactivity of the thiophene ring as a result from electron donation from the hetero sulfur atom, which is known.¹⁴ Generally, an electron–donner substituent gives direct electrophilic substition at 5-position of the thiophene ring. The ¹H NMR spectrum of disulfonylamino acids derivatives showed an AB pattern in the aromatic resonance at (δ **7.8**, **7.7**).

In the case of furan-2-carboxyladehydeazines (Comp. **35**, Y = O, X = H) powerful electron donation from the hetero oxygen atom. The ¹**H NMR** spectrum showed a complex series of aromatic resonace at (δ **7.3–6.8**).

Furan is well known¹⁵, to decompose with highly acidic sulfonation reagents, chlorosulfonic and sulfuric acid; the electron-withdrawing C=N group might sufficiently stabilize the furan ring to allow sulfonation, as was observed with furan-2-carboxamide,¹⁶ and carboxanilide.¹⁷

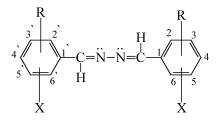
EXPERIMENTAL

Melting points were taken on a Griffin melting point apparatus and are uncorrected. Infrared solid samples were run as a KBr disc on a Schimadzu model 440 spectrophotometer. ¹H NMR spectra were measured in DMSO-d₆ as a solvent unless otherwise stated using Fx 90 Q Furier Transform ¹HNMR. Mass spectra were obtained using a Schimadzu (Japan). GC. M.S. QP 1000 Ex spectrometer using the direct inlet system. TLC analyses were carried out on Merek silica gel plates and developed with n-butanol-acetic acid-water (4:1:1) using iodine, ninhydrin, and benzidine as spraying agents.

Diaryl azines disulfonyl chloride **1,13**, and **24** were prepared according to the procedure described earlier.¹⁸

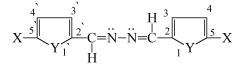
Coupling Reaction 2–4, 14–16, and (25–27): General Procedure

To an amino acid (0.2 mol) in a water (25 mL) THF (15 mL) mixture was added triethylamine (5 mL), followed by the portionwise addition of disulfonyl chlorides (0.11 mol) during 30 min. The temperature of the reaction mixture during the process of addition was kept at 10° C. Stirring continued for 4 h at 20° C. Tetrahydrofuran was removed by concentration of the reaction mixture under reduced pressure, and water (50 mL) was added and acidified with 2M HCl to pH₅. The crude products were filtered and recrystallized (ethanol-water). All products



Parent azines 1,13

| Comp. 1, $R = H$, | X = 3, | 3 SO ₂ Cl |
|---------------------------------|--------|----------------------|
| Comp. 13 , $R = 4$ -OMe, | X = 3, | 3 SO ₂ Cl |



Parent azines 24

| Comp. 24 , $Y = S$, | X = 5,5 SO ₂ Cl | |
|-----------------------------|----------------------------|----------------|
| Comp. 35 , Y = O, | X = 5,5 SO ₂ Cl | (Unsuccessful) |

CHART 1 (Continued)

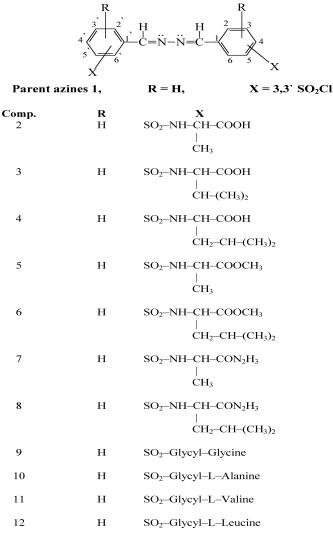
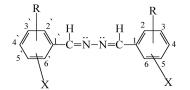


CHART 1 (Continued)

2–4, **14–16**, and **25–27** were chromatographically homogeneous by iodine and benzidine development (cf. Charts 1, 2, and 3 and Table I).

| IR of 2 : | ν 3350 cm ⁻¹ (NH), ν 1660 cm ⁻¹ (C=O), ν 1580 cm ⁻¹ |
|--------------------------|--|
| | (C=N), ν 1600 cm ⁻¹ (Ar–C=C), ν 1380, 1170 cm ⁻¹ |
| | (SO_2) |
| IR of 14 : | ν 3270 cm ⁻¹ (NH), ν 1640 cm ⁻¹ (Co), ν 1590 cm ⁻¹ |
| | $(SO_2), \nu 1270, 1030 \text{ cm}^{-1} (Ar-O-CH_3)$ |



| Parent azine | s 3 and 13 | R = P-OMe, | X = 3,3 SO ₂ Cl |
|--------------------|-------------------|---|----------------------------|
| Comp. 14 | R 4–OMe | X SO ₂ NHCHCOOH CH ₃ | |
| 15 | 4–OMe | SO ₂ –NH–CH–COOH CH–(CH ₃) ₂ | |
| 16 | 4–OMe | SO ₂ –NH–CH–COOH CH ₂ –CH–(CH ₃) | 2 |
| 17 | 4–OMe | SO ₂ –NH–CH–COOCH ₃ CH ₃ | |
| 18 | 4–OMe | SO ₂ –NH–CH–COOCH ₃ CH ₂ –CH–(CH ₃) | 2 |
| 19 | 4–OMe | SO ₂ –NH–CH–CON ₂ H ₃ CH ₃ | |
| 20 | 4–OMe | SO ₂ –NH–CH–CON ₂ H ₃ CH–(CH ₃) ₂ | |
| 21 | 4–OMe | SO ₂ -Glycyl-Glycine | |
| 22 | 4–OMe | SO ₂ -Glycyl-L-Alanine | |
| 23 | 4–OMe | SO ₂ -Glycyl-L-Valine | |

CHART 2

| | $X \xrightarrow{3}$ | $\frac{1}{1}$ $\frac{1}{5}$ H $C=$ | $= N - N = C - \frac{H^{3}}{1} \frac{4}{2}$ | -X |
|--|---------------------|--------------------------------------|--|----------------|
| Parent azines 24. Parent azines 35. | | Y = S, Y = O, | X = 5,5 SO ₂ Cl X = 5,5 SO ₂ Cl | (Unsuccessful) |
| Comp. 25 | Y S | SO_2 | X 2-NH-CH-COOH CH3 | |
| 26 | S | SO_2 | 2-NH-CH-COOH CH-(CH ₃)2 | |
| 27 | S | SO_2 | 2-NH-CH-COOH CH2-CH-(CH3 |)2 |
| 28 | S | SO_2 | 2-NH-CH-COOCH3 CH3 | |
| 29 | S | SO ₂ | 2-NH-CH-COOCH ₃ CH-(CH ₃) ₂ | |
| 30 | S | SO ₂ | 2-NH-CH-CON ₂ H ₃ CH ₃ | |
| 31 | S | SO ₂ | 2-NH-CH-CON ₂ H ₃ CH-(CH ₃) ₂ | |
| 32 | S | SO ₂ | 2-Glycyl-Glycine | |
| 33 | S | SO2 | 2–Glycyl–L–Alanine | |
| 34 CHART 3 | S | SO_2 | -Glycyl-L-Valine | |

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|---|----------------|-------------------|-----------|------------|------------------|---|-------|--------------------------|------------------------|-----------|
| motion X M.P.°C Yield % R_1 formula % C % DL-Ala $268-270$ 71 0.81 $C_{20}H_{22}N_4O_8S_2$ 47.06 4.2 L-Val $268-270$ 71 0.81 $C_{20}H_{22}N_4O_8S_2$ 50.78 5.5 L-Val $310-312$ 74 0.80 $C_{24}H_{30}N_4O_8S_2$ 50.78 5.5 L-Ueu $268-210$ 64 0.76 $C_{24}H_{30}N_4O_8S_2$ 50.73 5.50 $5.50.73$ $5.50.73$ $5.50.73$ $5.50.73$ $5.51.50$ $5.50.73$ $5.50.73$ $5.50.73$ $5.50.73$ $5.50.73$ $5.50.73$ $5.50.73$ $5.52.50$ $5.50.73$ $5.52.50$ $5.50.73$ $5.52.50$ $5.50.73$ $5.52.50$ $5.50.73$ $5.52.50$ $5.50.73$ $5.52.50$ $5.50.73$ $5.52.50$ $5.52.50$ $5.52.50$ $5.52.50$ $5.52.50$ $5.52.50$ $5.52.50$ $5.52.50$ $5.52.50$ $5.52.50$ $5.52.50$ $5.52.50$ $5.52.50$ $5.50.16$ $5.50.$ | Compound | | | | | Molecular | E | llemental a Calculate | analysis % ed/found | |
| DL-Ala $268-270$ 71 0.81 $C_{20}H_{22}N_4O_8S_2$ 4700 4.1 L-Val $310-312$ 74 0.80 $C_{24}H_{30}N_4O_8S_2$ 50.88 5.5 L-Leu $310-312$ 74 0.80 $C_{24}H_{30}N_4O_8S_2$ 50.78 5.5 L-Leu $263-265$ 68 0.76 $C_{24}H_{36}N_4O_8S_2$ 52.53 5.54 5.52 5.52 5.52 5.52 | nupound no. | Х | M.P.°C | Yield $\%$ | $\mathrm{R_{f}}$ | formula | % C | Н % | N % | % S |
| L-Val 310-312 74 0.80 $C_{24}H_{30}N_4O_8S_2$ 50.73 51.73 51.73 51.73 51.73 52.53 55.73 55.73 55.73 55.73 55.73 55.73 55.73 55.54 50.00 48.7 49.00 48.7 49.00 48.7 49.00 56.6 60.16 56.001 66.1 66.1 66.7 66.7 48.50 56.001 66.1 66.7 66.7 66.7 66.7 66.7 66.7 66.7 66.7 66.7 66.7 66.7 66.7 66.7 <td>2</td> <td>DLAla</td> <td>268 - 270</td> <td>71</td> <td>0.81</td> <td>${ m C}_{20}{ m H}_{22}{ m N}_4{ m O}_8{ m S}_2$</td> <td>47.06</td> <td>4.31</td> <td>10.98</td> <td>12.55</td> | 2 | DLAla | 268 - 270 | 71 | 0.81 | ${ m C}_{20}{ m H}_{22}{ m N}_4{ m O}_8{ m S}_2$ | 47.06 | 4.31 | 10.98 | 12.55 |
| L-Val 310-312 74 0.80 $C_{24}H_{30}N_4O_8S_2$ 50.88 5.5 L-Leu 263-265 68 0.76 $C_{26}H_{34}N_4O_8S_2$ 50.73 55.60 56.73 DL-Ala-OMe 208-210 64 0.76 $C_{26}H_{34}N_4O_8S_2$ 50.88 55.60 56.6 DL-Ala-OMe 100-112 79 0.76 $C_{28}H_{38}N_4O_8S_2$ 54.02 61. DL-Ala-N2H3 194-196 60 0.61 $C_{20}H_{26}N_8O_6S_2$ 54.02 61. DL-Heu-N2H3 165-167 54 0.69 $C_{26}H_{38}N_8O_6S_2$ 54.02 61. Gly-Gly-OMe 183-185 80 0.84 $C_{24}H_{28}N_6O_{10}S_2$ 54.02 61.1 Gly-Gly-OMe 183-185 80 0.84 $C_{26}H_{38}N_6O_6S_2$ 44.61 44.61 Gly-LHau-OMe 187-189 76 0.88 $C_{26}H_{38}N_6O_{10}S_2$ 50.16 66. Gly-L-Leu-OMe 187-189 76 0.88 $C_{26}H_{28}N_6O_{10}S_2$ 46.11 47.77 | | | | | | | 47.00 | 4.22 | 10.91 | 12.41 |
| L-Leu $263-265$ 68 0.76 $C_{26}H_{34}N_4O_8S_2$ 50.73 55.3 DL-Ala-OMe $208-210$ 64 0.76 $C_{22}H_{26}N_4O_8S_2$ 54.00 56.7 DL-Ala-OMe $110-112$ 79 0.79 $C_{28}H_{38}N_4O_8S_2$ 54.00 61.7 L-Leu-OMe $110-112$ 79 0.79 $C_{26}H_{38}N_4O_8S_2$ 54.00 61.7 DL-Ala-N_2H_3 $194-196$ 60 0.61 $C_{26}H_{38}N_8O_6S_2$ 54.00 61.7 DL-Ala-N_2H_3 $165-167$ 54 0.69 $C_{26}H_{38}N_8O_6S_2$ 54.00 61.7 Cily-Gly-OMe $183-185$ 80 0.84 $C_{24}H_{28}N_6O_5S_2$ 44.61 44.61 Cily-Gly-OMe $183-185$ 80 0.84 $C_{24}H_{28}N_6O_1S_2$ 56.10 61.7 Gly-L-Ma-OMe $187-189$ 76 0.88 $C_{26}H_{32}N_6O_1S_2$ 46.15 44.61 44.61 Gly-L-Vala-OMe $187-189$ 76 0.88 $C_{26}H_{32}N_6O_1S_2$ 50.16 60.01 Gly-L-Vala-OMe $177-180$ 0.88 $C_{26}H_{32}N_6O_1S_2$ 56.01 60.01 Gly-L-Vala-OMe $177-180$ 77 0.88 $C_{26}H_{32}N_6O_1S_2$ 56.01 60.01 Gly-L-Vala-OMe $187-189$ 76 0.88 $C_{26}H_{32}N_6O_1S_2$ 50.01 60.01 Gly-L-Vala $205-207$ 71 0.90 $C_{22}H_{36}N_4O_1S_2$ 50.85 56.00 DL-Ala $218-220$ 70 0.70 0.70 $C_$ | 0 | L-Val | 310 - 312 | 74 | 0.80 | ${ m C}_{24}{ m H}_{30}{ m N}_4{ m O}_8{ m S}_2$ | 50.88 | 5.30 | 9.89 | 11.31 |
| L-Leu $263-265$ 68 0.76 $C_{26}H_{34}N_4O_8S_2$ 52.53 5.7 DL-Ala-OMe $208-210$ 64 0.76 $C_{26}H_{36}N_4O_8S_2$ 54.00 4.8 L-Leu-OMe $110-112$ 79 0.76 $C_{28}H_{38}N_4O_8S_2$ 54.00 4.8 L-Leu-OMe $110-112$ 79 0.79 $C_{26}H_{38}N_4O_8S_2$ 54.00 6.6 DL-Ala-N ₂ H ₃ $194-196$ 60 0.61 $C_{20}H_{26}N_8O_6S_2$ 44.61 4.8 U-Cleu-N ₂ H ₃ $165-167$ 54 0.69 $C_{26}H_{38}N_8O_6S_2$ 51.00 6.6 Gly-Cly-OMe $183-185$ 80 0.84 $C_{24}H_{28}N_6O_{10}S_2$ 50.11 6.6 Gly-L-Val-OMe $187-189$ 76 0.86 $C_{26}H_{38}N_6O_{10}S_2$ 50.16 6.6 Gly-L-Val-OMe $187-189$ 76 0.86 $C_{30}H_{40}N_6O_{10}S_2$ 46.11 4.77 Gly-L-Leu-OMe $177-175$ 74 0.86 $C_{30}H_{40}N_6O$ | | | | | | | 50.73 | 5.21 | 9.81 | 11.22 |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$ | 4 | L-Leu | 263 - 265 | 68 | 0.76 | ${ m C}_{26}{ m H}_{34}{ m N}_4{ m O}_8{ m S}_2$ | 52.53 | 5.72 | 9.43 | 10.77 |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$ | | | | | | | 52.50 | 5.63 | 9.40 | 10.60 |
| L-Leu-OMe 110-112 79 0.79 $C_{28}H_{38}N_4O_8S_2$ 54.00 43.61 DL-Ala-N ₂ H ₃ 194-196 60 0.61 $C_{20}H_{26}N_8O_6S_2$ 44.61 44.53 L-Leu-N ₂ H ₃ 165-167 54 0.69 $C_{26}H_{38}N_8O_6S_2$ 54.00 6.0 Gly-Gly-OMe 183-185 80 0.69 $C_{26}H_{38}N_6O_6S_2$ 44.61 44.53 Gly-Gly-OMe 187-189 76 0.84 $C_{24}H_{28}N_6O_{10}S_2$ 50.16 6.0 Gly-DL-Ala-OMe 187-189 76 0.88 $C_{24}H_{28}N_6O_{10}S_2$ 46.11 44.53 Gly-DL-Ala-OMe 187-189 76 0.88 $C_{30}H_{40}N_6O_{10}S_2$ 46.11 46.15 Gly-L-Val-OMe 173-175 74 0.88 $C_{30}H_{40}N_6O_{10}S_2$ 50.01 65.6 Gly-L-Leu-OMe 205-207 71 0.90 $C_{32}H_{44}N_6O_{10}S_2$ 50.85 55.6 DL-Ala 218-220 70 0.70 $C_{32}H_{26}N_4O_{10}S_2$ 50.85 55.17 55.17 55.17 55.17 55.17 55.17 55.17 55.17 | 0 | DL-Ala-OMe | 208 - 210 | 64 | 0.76 | ${ m C}_{22}{ m H}_{26}{ m N}_4{ m O}_8{ m S}_2$ | 49.07 | 4.83 | 10.41 | 11.90 |
| L-Leu-OMe 110-112 79 0.79 $C_{28}H_{38}N_4O_8S_2$ 54.02 6.1 DL-Ala-N ₂ H ₃ 194-196 60 0.61 $C_{20}H_{26}N_8O_6S_2$ 44.61 4.8 DL-Leu-N ₂ H ₃ 165-167 54 0.69 $C_{26}H_{38}N_8O_6S_2$ 54.00 6.6 Gly-Gly-OMe 183-185 80 0.84 $C_{24}H_{28}N_6O_{10}S_2$ 50.16 6.1 Gly-H2n-OMe 187-189 76 0.84 $C_{24}H_{28}N_6O_{10}S_2$ 50.16 6.1 Gly-DL-Ala-OMe 187-189 76 0.84 $C_{24}H_{28}N_6O_{10}S_2$ 46.11 4.5 Gly-DL-Ala-OMe 187-189 76 0.86 $C_{26}H_{32}N_6O_{10}S_2$ 46.15 4.5 Gly-L-Val-OMe 173-175 74 0.88 $C_{30}H_{40}N_6O_{10}S_2$ 50.80 5.6 Gly-L-Leu-OMe $2173-175$ 74 0.98 $C_{30}H_{40}N_6O_{10}S_2$ 50.80 5.6 Gly-L-Leu-OMe $2173-175$ 52 $62.01A_{40}N_6O_{10}S_2$ 52.177 52 62.00 62.6 62.80 62.6 | | | | | | | 49.00 | 4.81 | 10.33 | 11.83 |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$ | 9 | L-Leu-OMe | 110 - 112 | 79 | 0.79 | ${ m C}_{28}{ m H}_{38}{ m N}_4{ m O}_8{ m S}_2$ | 54.02 | 6.11 | 9.00 | 10.29 |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$ | | | | | | | 54.00 | 6.00 | 8.91 | 10.21 |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$ | 7 | $DL-Ala-N_2H_3$ | 194 - 196 | 60 | 0.61 | ${ m C}_{20}{ m H}_{26}{ m N}_8{ m O}_6{ m S}_2$ | 44.61 | 4.83 | 20.82 | 11.90 |
| L-Leu-N ₂ H ₃ 165-167 54 0.69 $C_{26}H_{38}N_8O_6S_2$ 50.16 6.1 Gly-Gly-OMe 183-185 80 0.84 $C_{24}H_{28}N_6O_{10}S_2$ 46.15 4.4 Gly-DL-Ala-OMe 187-189 76 0.86 $C_{26}H_{32}N_6O_{10}S_2$ 46.11 4.4 Gly-DL-Ala-OMe 187-189 76 0.86 $C_{26}H_{32}N_6O_{10}S_2$ 47.77 4.8 Gly-L-Val-OMe 173-175 74 0.88 $C_{30}H_{40}N_6O_{10}S_2$ 50.85 5.6 Gly-L-Val-OMe 173-175 74 0.88 $C_{30}H_{40}N_6O_{10}S_2$ 50.80 5.6 Gly-L-Leu-OMe 205-207 71 0.90 $C_{32}H_{44}N_6O_{10}S_2$ 50.80 5.6 DL-Ala 218-220 70 0.70 $C_{22}H_{26}N_4O_{10}S_2$ 52.17 5.2 DL-Ala 218-220 70 0.70 $C_{22}H_{26}N_4O_{10}S_2$ 46.32 4.5 | | | | | | | 44.53 | 4.75 | 20.78 | 11.88 |
| Gly-Gly-OMe 183-185 80 0.84 $C_{24}H_{28}N_6O_{10}S_2$ 50.01 6.0 Gly-DL-Ala-OMe 187-189 76 0.86 $C_{26}H_{32}N_6O_{10}S_2$ 46.11 4.5 Gly-DL-Ala-OMe 187-189 76 0.86 $C_{26}H_{32}N_6O_{10}S_2$ 47.35 4.5 Gly-L-Val-OMe 173-175 74 0.88 $C_{30}H_{40}N_6O_{10}S_2$ 50.85 5.6 Gly-L-Leu-OMe $205-207$ 71 0.90 $C_{32}H_{44}N_6O_{10}S_2$ 50.80 5.6 Gly-L-Leu-OMe $205-207$ 71 0.90 $C_{32}H_{44}N_6O_{10}S_2$ 50.80 5.6 DL-Ala $218-220$ 70 0.70 $C_{22}H_{26}N_4O_{10}S_2$ 46.32 4.5 | 8 | $ m L-Leu-N_2H_3$ | 165 - 167 | 54 | 0.69 | ${ m C}_{26}{ m H}_{38}{ m N}_8{ m O}_6{ m S}_2$ | 50.16 | 6.11 | 18.00 | 10.29 |
| Gly-Gly-OMe 183-185 80 0.84 $C_{24}H_{28}N_6O_{10}S_2$ 46.11 4.5 Gly-DL-Ala-OMe 187-189 76 0.86 $C_{26}H_{32}N_6O_{10}S_2$ 47.37 4.5 Gly-LL-Val-OMe 173-175 74 0.88 $C_{30}H_{40}N_6O_{10}S_2$ 50.85 5.6 Gly-L-Val-OMe 173-175 74 0.88 $C_{30}H_{40}N_6O_{10}S_2$ 50.85 5.6 Gly-L-Leu-OMe $205-207$ 71 0.90 $C_{32}H_{44}N_6O_{10}S_2$ 50.80 5.6 Gly-L-Leu-OMe $205-207$ 71 0.90 $C_{32}H_{44}N_6O_{10}S_2$ 52.17 5.5 DL-Ala $218-220$ 70 0.70 $C_{22}H_{26}N_4O_{10}S_2$ 46.32 4.5 | | | | | | | 50.01 | 6.01 | 17.90 | 10.18 |
| Gly-DL-Ala-OMe 187-189 76 0.86 $C_{26}H_{32}N_6O_{10}S_2$ 46.11 $4.6.11$ $4.6.11$ $4.6.11$ $4.6.11$ $4.6.11$ $4.6.11$ $4.6.11$ $4.6.11$ $4.6.11$ $4.6.11$ $4.6.11$ $4.6.11$ $4.6.11$ $4.6.11$ $4.6.11$ $4.7.77$ 4.8 $6.914_{10}N_6O_{10}S_2$ 50.85 5.6 6.685 5.6 6.86 5.6 6.86 5.6 6.86 5.6 6.86 5.6 6.86 5.6 6.86 5.6 6.86 5.6 6.86 5.6 6.86 5.6 6.80 6.6 $6.80_{10}N_{10}S_2$ 50.80 5.6 | 6 | Gly-Gly-OMe | 183 - 185 | 80 | 0.84 | ${ m C}_{24}{ m H}_{28}{ m N}_{6}{ m O}_{10}{ m S}_{2}$ | 46.15 | 4.49 | 13.46 | 10.26 |
| Gly-DL-Ala-OMe $187-189$ 76 0.86 $C_{26}H_{32}N_6O_{10}S_2$ 47.85 4.6 Gly-L-Val-OMe $173-175$ 74 0.88 $C_{30}H_{40}N_6O_{10}S_2$ 50.85 5.6 Gly-L-Ual-OMe $173-175$ 74 0.88 $C_{30}H_{40}N_6O_{10}S_2$ 50.85 5.6 Gly-L-Leu-OMe $205-207$ 71 0.90 $C_{32}H_{44}N_6O_{10}S_2$ 52.17 5.6 DL-Ala $218-220$ 70 0.70 $C_{22}H_{26}N_4O_{10}S_2$ 46.32 4.6 | | | | | | | 46.11 | 4.40 | 13.38 | 10.10 |
| Gly-L-Val-OMe 173-175 74 0.88 $C_{30}H_{40}N_6O_{10}S_2$ 50.85 5.6 Gly-L-Leu-OMe $205-207$ 71 0.90 $C_{32}H_{44}N_6O_{10}S_2$ 52.17 5.6 Gly-L-Leu-OMe $205-207$ 71 0.90 $C_{32}H_{44}N_6O_{10}S_2$ 52.17 5.5 DL-Ala $218-220$ 70 0.70 $C_{22}H_{26}N_4O_{10}S_2$ 46.32 4.5 | 10 | Gly–DL–Ala–OMe | 187 - 189 | 76 | 0.86 | ${ m C}_{26}{ m H}_{32}{ m N}_{6}{ m O}_{10}{ m S}_{2}$ | 47.85 | 4.91 | 12.88 | 9.82 |
| Gly-L-Val-OMe 173-175 74 0.88 $C_{30}H_{40}N_6O_{10}S_2$ 50.85 5.6 Gly-L-Leu-OMe $205-207$ 71 0.90 $C_{32}H_{44}N_6O_{10}S_2$ 52.17 5.5 Gly-L-Leu-OMe $205-207$ 71 0.90 $C_{32}H_{44}N_6O_{10}S_2$ 52.17 5.5 DL-Ala $218-220$ 70 0.70 $C_{22}H_{26}N_4O_{10}S_2$ 46.32 4.5 DL-Ala $218-220$ 70 0.70 $C_{22}H_{26}N_4O_{10}S_2$ 46.32 4.5 | | | | | | | 47.77 | 4.88 | 12.80 | 9.70 |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 11 | Gly–L–Val–OMe | 173 - 175 | 74 | 0.88 | $ m C_{30}H_{40}N_6O_{10}S_2$ | 50.85 | 5.65 | 11.86 | 9.04 |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | | | | | | | 50.80 | 5.60 | 11.83 | 9.00 |
| 52.00 $5.8218-220 70 0.70 C_{22}H_{26}N_4O_{10}S_2 46.32 4.546.20$ 4.4 | 12 | Gly–L–Leu–OMe | 205 - 207 | 71 | 0.90 | $ m C_{32}H_{44}N_6O_{10}S_2$ | 52.17 | 5.98 | 11.41 | 8.70 |
| $218-220$ 70 0.70 $C_{22}H_{26}N_4O_{10}S_2$ 46.32 4.5 4.5 | | | | | | | 52.00 | 5.81 | 11.40 | 8.70 |
| 4.4 | 14 | DL-Ala | 218 - 220 | 70 | 0.70 | $ m C_{22}H_{26}N_4O_{10}S_2$ | 46.32 | 4.56 | 9.82 | 11.23 |
| (Continued on next page | | | | | | | 46.20 | 4.44 | 9.75 | 11.10 |
| | | | | | | | | (Con) | tinued on r | ext page) |

TABLE I Physical Data for Diarylazines Derivatives 2-12, 14-23, and 25-34

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 $\begin{array}{c} 10.22\\ 9.79\\ 9.79\\ 10.01\\ 10.70\\ 10.7$ % SElemental analysis % Calculated /Found $\begin{array}{c} 12.28\\ 12.01\\ 11.80\\ 11.63\\ 11.63\\ 10.94\\ 10.73\\ 10.73\\ 10.61\\ 9.69\\ 9.61\\ 9.24\\ 9.24\end{array}$ 9.218.568.4118.7318.71 17.13 17.00 10.18 8.95 8.95 8.56 8.49 9.369.10z 8 Η $\begin{array}{c} 5.43 \\ 5.33 \\ 5.81 \\ 5.78 \\ 5.02 \\ 5.00 \end{array}$ $\begin{array}{c} 5.78\\ 5.02\\ 5.02\\ 5.81\\ 5.81\\ 5.63\\ 5.73\\ 5.73\\ 5.06\\ 5.06\\ 5.00\\ 5.73\\ 5.60\\ 3.45\\ 3.41\\ 3.41\end{array}$ 5.81 4.50 4.44 4.95 4.95 4.81 4.00 3.92 3.92 8 47.71 47.62 49.84 49.70 51.3851.3048.1648.0051.38 $51.30 \\ 44.20$ 44.1045.61 45.52 47.19 47.00 50.00 49.85 36.78 36.66 41.5241.5043.5643.51 39.27 39.11 C 8 $\rm C_{26}H_{34}N_4O_{10}S_2$ $\rm C_{28}H_{38}N_4O_{10}S_2$ $\rm C_{24}H_{30}N_4O_{10}S_2$ $\rm C_{28}H_{38}N_4O_{10}S_2$ $\rm C_{26}H_{32}N_6O_{12}S_2$ $C_{28}H_{36}N_6O_{12}S_2$ $\rm C_{26}H_{38}N_8O_8S_2$ $C_{32}H_{44}N_6O_{12}S_4$ $\rm C_{22}H_{30}N_8O_8S_2$ $\rm C_{16}H_{18}N_4O_8S_4$ $C_{20}H_{26}N_4O_8S_4$ $C_{22}H_{30}N_4O_8S_4$ $C_{18}H_{22}N_4O_8S_4$ Molecular formula 0.830.770.640.830.630.690.750.630.660.840.730.860.82Å Yield % 7573 83 86 68 585465 67 77 48 5471 208-210 170-172 110-112 205-207 212 - 214M.P.°C 237-239 183-185 138 - 140178-180 128 - 13061-77 80-82 95 - 97Gly-L-Ala-OMe Gly-L-Val-OMe $DL-Ala-N_2H_3$ Gly-Gly-OMe DL-Ala-OMe DL-Ala-OMe $L-Val-N_2H_3$ L-Val-OMe × DL-Ala L-Leu L-Leu L-Val L-Val Compound no. 15 16 17 18 19 22 32 2627 28 20 33 21

TABLE I Physical Data for Diarylazines Derivatives 2–12, 14–23, and 25–34 (Continued)

| 29 | L-Val-OMe | 178 - 180 | 42 | 0.75 | ${ m C}_{22}{ m H}_{30}{ m N}_4{ m O}_8{ m S}_4$ | 43.56 | 4.95 | 9.24 | 21.12 |
|----|-----------------|-----------|----|------|---|-------|------|-------|-------|
| | | | | | | 43.44 | 4.81 | 9.10 | 21.01 |
| 30 | $DL-Ala-N_2H_3$ | 122 - 124 | 60 | 0.77 | $ m C_{16}H_{22}N_8O_6S_4$ | 34.91 | 4.00 | 20.36 | 23.27 |
| | | | | | | 34.90 | 3.94 | 20.11 | 23.11 |
| 31 | $L-Val-N_2H_3$ | 154 - 156 | 64 | 0.79 | ${ m C}_{20}{ m H}_{30}{ m N}_8{ m O}_6{ m S}_4$ | 39.60 | 4.95 | 18.48 | 21.12 |
| | | | | | | 39.56 | 4.81 | 18.33 | 21.00 |
| 32 | Gly-Gly-OMe | 133 - 135 | 61 | 0.80 | ${ m C}_{20}{ m H}_{24}{ m N}_{6}{ m O}_{10}{ m S}_{4}$ | 37.74 | 3.77 | 13.21 | 20.13 |
| | | | | | | 37.63 | 3.71 | 13.10 | 20.00 |
| 33 | Gly–L–Ala–OMe | 120 - 122 | 70 | 0.84 | ${ m C}_{22}{ m H}_{28}{ m N}_{6}{ m O}_{10}{ m S}_{4}$ | 39.76 | 4.22 | 12.65 | 19.28 |
| | | | | | | 39.66 | 4.20 | 12.55 | 19.10 |
| 34 | Gly-L-Val-OMe | 143 - 145 | 73 | 0.87 | ${ m C}_{26}{ m H}_{36}{ m N}_{6}{ m O}_{10}{ m S}_{4}$ | 43.33 | 5.00 | 11.67 | 17.79 |
| | | | | | | 43.10 | 4.91 | 11.61 | 17.66 |

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 $\label{eq:hyperbolic} \begin{array}{ll} {}^{1}\textbf{H}\ \textbf{NMR}\ of\ \textbf{26}: & (DMSO-d_{6}): \delta\ 4.1\ [s,\ 2H,\ 2C\underline{H}], \delta\ 4.5\ (s,\ 4H,\ 2\underline{CH}_{2}), \\ & \delta\ 4.0\ (s,\ 6H,\ 2O-CH_{3}), \delta\ 7.8-7.7\ (s,\ 4H,\ 2\ thiphene), \\ & \delta\ 8.3-7.17\ (s,\ 6H,\ 2Ar-H), \delta\ 8.68\ (s,\ 2H,\ 2CH=N), \delta \\ & 11.3\ (s,\ 2H,\ 2COOH),\ MS\ of\ 27\ :\ m/z\ 606\ (M^+) \end{array}$

Synthesis of Disulfonylamino Acid Methyl Esters 5, 6, 17, 18, 28, and 29: General Procedure

A suspension of coupling reaction products **2–4**, **17**, **18**, and **28** and **29** (0.2 mole) in absolute methanol (100 mL) was cooled to -10° C, and pure thionyl chloride (2.2 mL) was added dropwise during 1 h. The reaction mixture was stirred for an additional 3–4 h at r.t. It was kept overnight, and the solvent was removed by vacuum distillation. The residual solid material was recrystallized (methanol-water) (cf. Table I, and Charts 1, 2, and 3).

| IR of 17 : | ν 3460cm ⁻¹ (NH), ν 3250, 1370, 1170 cm ⁻¹ |
|---------------------------|--|
| | (SO ₂ -NH), ν 1445, 1360 cm ⁻¹ (COOCH ₃), |
| | ν 2960 cm ⁻¹ (O–CH ₃), ν 1760 cm ⁻¹ (<u>Co</u>), ν 1310, |
| | $1160 \text{ cm}^{-1} (\text{SO}_2)$ |
| ¹ H NMR of 18: | $(DMSO-d_6): \delta 8.34-7.17 (s, 8H, Ar-H), \delta 3.81-3.87$ |
| | (s, 6H, $2COOCH_3$), and disappear of OH protons, |
| | and other peaks in support of their structures. |

Synthesis of Disulfonylamino Acid Hydrazides 7, 8, 19, 20 and 30, 31: General Procedure

The methyl esters **5**, **6**, **17**, **18** and **28**, **29**, (0.2 mol) were dissolved in ethanol (100 ml) and hydrazine hydrate 85% (0.2 mol) was added. The reaction mixture was stirred for 3 h at 20°C and left 24 h at room temperature. The crystalline products **7**, **8**, **19**, **20** and **30**, **31** were filtered off, washed with water and recrystallized (ethanol-water).

The hydrazides **7**, **8**, **19**, **20**, **30** and **31** were shown to be chromoatographically to be homogeneous. cf. Table 1, Chart 1, 2 and 3.

| IR of 7 : | ν 3340, 3125 cm ⁻¹ (NH), ν 1640, cm ⁻¹ (Co), ν 1600, 1550 cm ⁻¹ (Ar–C=C), ν 1340, 1180 cm ⁻¹ (SO ₂) |
|--|---|
| ¹ H NMR of 20 : | $(DMSO-d_6): \delta 9(s, \underline{H}, SO_2N\underline{H}), \delta 8.2-7.5 (Ar-H), \delta 5.52 (s, 2N\underline{H}), \delta 5.61 (s, 4H, 2NH_2)$ |

Synthesis of Disulfonyl Dipeptide Methyl Esters 9–12, 21–23, and 32–34: General Procedure

To a solution of amino acid methyl ester hydrochloride (0.01 mol) in THF (100 mL) was added triethylamine (5 mL). The solution was stirred at

 20° C for 30 min and cooled to 0° C, where the disulfonyl amino acid (0.005 mol) and dicyclohexylcarbodiimide **DCC** (1.62 g) were added to the above mixture. The reaction mixture was stirred for 2 h at 0° C and for another 2 h at r.t. The precipitated dicyclohexylurea was filtered off, and acetic acid (2 mL) was added to the solution and was left standing overnight. The precipitate was filtered off, and the remaining solution was distilled under vacuum. The remaining solid was recrystallized from ethanol-water. The products were to be chromatographically homogeneous.

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